Studies in Environmental Science 32

PESTICIDE CHEMISTRY

by

Gy. Matolcsy
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Pesticide Chemistry

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Pesticide Chemistry

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Preface

Several excellent books on the chemistry of pesticides have been published in the last decade. Nevertheless, we consider that events of recent years justify the writing of a further book on a similar theme. Developments in this field have been quite rapid, and it thus seems desirable to publish a book which includes coverage of the latest achievements.

The thematic treatment in this book differs somewhat from that of other works on this subject, and thus may serve as a supplement to other books. Our object was not to write an encyclopedic work on pesticides and their characteristics. Rather, we discuss mainly those active substances in pesticides which are of practical significance, may be of possible future importance, or represent research results and interesting trends. With regard to the latter, compounds are also discussed which are not on the market but represent promising new types. Ample space has been devoted to alternative methods of plant protection, e.g., insect growth regulators, sterilants and pheromones, which show promise for control of insect pests.

An attempt has been made to give an overview of all chemical aspects of plant protection, with the exception of analytical chemistry. We are fully aware that the designation "chemistry of pesticides" does not cover an unequivocally defined, uniform branch of science, because the fundamental sciences on which it is built, particularly organic chemistry and biochemistry, have maintained their independence and their original scope also within the frame of this special field. The chemistry of pesticides integrates these fundamental sciences only functionally, and not with respect to their methods. Our book attempts to achieve this functional unity. In the discussion of individual compounds and types of compound our aim has been to cover preparative and organic chemical and biochemical aspects, metabolism, activity–structure relationships, fields of application, and environmental and toxicological problems.

We have tried to emphasise characteristic features indicating trends of development, omitting what is irrelevant or repetitive. Accordingly, physical constants are given only if they carry essential information. Thus, for example, the unusually high melting point of dechloran, 485°C, is given, because it is connected with the remarkably high degree of symmetry of the molecule, and is an indicator of the high chemical stability of the compound. The preparation of phosphorus ester insecticides, which follows the same route and with known methods, has not been described for each pesticide, but ample space is devoted to synthetic routes developed individually for particular compounds, reflecting organic chemical creativity.

Pesticide compounds are generally cited under their common names. Trade names are given only for preparations of outstanding importance or of historical interest, or in cases where they are needed for a better understanding of relationships.

We have tried to organise the book along historical lines, demonstrating chronological order, in the hope of highlighting trends, and thereby providing a prognosis of further development.

The Authors

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Introduction

The publication "Man and Hunger" of the Food and Agricultural Organisation of the United Nations reported that more than half the population of the Earth is in a state of famine. The situation is aggravated because food-shortage is greatest where increase in population is highest: in the countries of the third world. Baade writes in his book "Der Wettlauf zum Jahre 2000" that at the turn of the millennium two-thirds of mankind (according to the forecast of demographers about 4.5 thousand million people) will live in areas where even today food is scarce. The world food problem is the key issue also in a study by Professor Tinbergen, written for the Club of Rome, the international scientific society which answers to the fundamental problems of mankind. Indeed, the menace of diminishing food production has become a permanent factor in the considerations and recommendations of experts studying the future of mankind.

According to reliable estimates, biotic factors, i. e., animal pests, microorganisms and weeds, diminish the yield of agricultural produce by 35%. Even in the past, mankind could not accept a loss of 35%, and will be able to afford it still less in the future. The saving of perishable agricultural produce is no longer an economic, but a fundamental humanitarian problem.

The spectrum of crop pests is very broad. The pathogens of plant diseases are microorganisms — microfungi, bacteria and viruses. Proliferating within the host plant and interacting with the host, they act mainly by producing toxic substances which inhibit the activity of essential enzymes of the host, or the pathogens themselves produce enzymes able to degrade important components of the host. Animal pests, particularly insects of the highest economic importance, damage the host plant either directly by feeding on it, or indirectly by spreading viral diseases. Weeds compete on arable land, thereby depriving crops of sunlight, air, water, soil and nourishment.

However, loss reduction is not the sole aim of plant protection. Certain rust and smut fungi not only damage crops, but also produce metabolites toxic to human beings and domestic animals. The chitin shield of the grain weevil contains carcinogenic compounds, quinones, which may appear in the flour prepared from the infested cereal.

Industrialisation and the ensuing massive rural exodus result in shortage of agricultural labour; hence, herbicide application with large-scale technology has become the only possible way of killing weeds.

Attempts to combat pests with chemicals were made several thousand years ago. In China as early as 3000 B. C. a mixture of lime, woods ash and chalk was used to

kill insects damaging stored produce. Sulfur dioxide, burning sulfur, was applied for the same purpose. Leonardo da Vinci noted that harmful insects can be destroyed with arsenic, and in England, as early as the beginning of the 19th century, lime-sulfur solution, made by boiling sulfur, lime and water was applied to fruit trees to protect them against powdery mildew.

However, the development of modern organic pesticides was not the outcome of these sporadic observations, but of the research work started in the middle of the last century in organic chemical laboratories. As a result of the rapid development of organic chemical research, ever more new organic compounds were amassed on laboratory shelves, but this however, was the final result of research at that time. It was only in the 20th century that organic chemistry became an applied science, interacting with biology, biochemistry, medical sciences and, last but not least, with agriculture. In the nineteen-thirties the insecticidal action of DDT, BHC and organophosphorus esters, and the herbicidal properties of phenoxyacetic acid derivatives, were discovered almost simultaneously, and the first modern organic pesticides were introduced. This was the beginning of far-reaching developments and although fundamental changes have taken place since then in the field of chemical plant protection, the importance of these accomplishments is still to be seen in modern research and application.

Pesticides can be classified in several ways. The clearest and most widely used classification is based on the practical purpose of application. Thus, pesticides are classified as microbicides against microbial pests, zoocides against animal pests and herbicides against weeds.

Of the microbes, fungi cause the heaviest agricultural losses and consequently, fungicides form the most important group of microbicides. Plant diseases caused by bacteria are of considerably less importance, although their spread directs the attention of pesticide research to an as yet unattained objective, the development of efficient bactericides for plant protection.

Because, of all animal pests, insects cause the greatest losses in agriculture, anti-insect agents are the most important zoocides. These agents can be divided into two groups: insecticides in the conventional sense and novel anti-insect agents with specific action.

The further classification of conventional insecticides, acting chiefly on the insect nervous system, is a chemical one: compounds of natural origin, arsenic compounds, chlorinated hydrocarbons, organophosphorus compounds, carbamates, and other compounds.

Novel anti-insect agents are classified according to their mode of action, but this biological subdivision at the same time represents a chemical grouping. The most important categories are insect growth regulators, chemosterilants, pheromones and antifeeding agents.

Further representatives of zoocides, although of lesser economic importance, are mite killers (acaricides), nematode killers (nematocides) and rodent killers (rodenticides).

Weed-killers (herbicides) are the chemical tools for controlling weeds harmful to crops. They include a great variety of types both in the chemical sense and with respect to their mode of action. According to their mode of application, we may distinguish foliar herbicides and soil herbicides, and according to the time of application, pre- and postemergent herbicides.

Pesticide research and development is a long process and one which requires the coordinated efforts of several branches of science. The first step is to design the compound to be made. However, we still know little on the molecular level about the processes which occur in the living organism between the biologically active compound and the receptor group at the reaction site, and which are the basis of biological activity. Insufficient knowledge in this field makes it impossible to design new compounds with the desired action in a rational way. Therefore, even today, empirical work based on trial and error dominates in pesticide research. In fact, it has been estimated that of forty thousand compounds prepared and biologically screened, generally only one meets the requirements for practical application.

This does not mean that the chemist has to rely entirely on serendipity in designing new pesticide families. Major innovations are increasingly the result of planned research. Knowledge of specific enzymes and their reactive groups, of metabolic pathways and of bioactive substances of natural origin may form the basis of various hypotheses in pesticide research.

If an active compound is detected by biological tests, then several of its derivates are prepared, in order to choose the one which shows the best biological characteristics. In this phase of research an opportunity offers itself even on the basis of our present knowledge to rate theoretical concepts into consideration. When a certain number of derivatives has been prepared, the computerised mathematical processing of data about them can reveal quantitative structure–activity relationships, on the basis of which the efficiency of compounds not yet prepared can be predicted with a high probability, and the compound which promises to be the most efficient can be selected. The rapid development of these mathematical molecule-design methods and the consequent increased success rate make it possible to work out the structure of effective compounds, and considerably fewer compounds have to be prepared than formerly.

In the initial testing step, the compounds prepared are subjected to a preliminary screening to establish whether they meet the minimal efficiency requirements as pesticides. Simultaneously their toxicity is tested in experiments with animals. As a result of this first screening about 90% of compounds are discarded because of low efficiency or high toxicity. In the next step, the promising compounds are subjected to more detailed biological assay, and compared with known pesticides of similar character. Analytical methods are developed for qualitative and quantitative analysis, for detection in the living organism and in soil. Toxicological tests include uptake by inhalation and through the skin.

The formulation which best suits the chemical and physico-chemical properties of the compound and satisfies the demands of application technology is then elaborated, i.e. by adding dispergents, surfactants, adhesion-increasing and other

auxiliary substances and by technological operations, the active ingredient is brought into a form suitable for spraying, dusting or granular application. Field experiments are initiated, first on small plots and then on experimental-field-plots of larger scale. In this period of development, toxicological tests include investigation of the effect of the active substance, administered continuously in small doses over a longer period (e.g. 2 years), on experimental animals of several species, including birds, fish and bees. A further problem to be elucidated is the metabolism of the pesticide in animals and plants. In the next test step, which on average only one in a thousand compounds survives, the scale of field experiments is substantially extended. The compounds which pass increasingly rigorous screening are tested on different crops and under different climatic conditions. Generally, large-scale manufacturing technology is developed during this period. Investigations of metabolism, begun earlier, are intensified, the chemical mechanism of degradation of the active substance in the living organism is elucidated, and residues in agricultural products are determined. Finally, in the last phase of development, the behaviour of the pesticide in the environment—its effect on surface waters and soil—is elucidated.

Eight to ten years pass from the first laboratory synthesis to the placing of the pesticide on the market, and the research and development costs of each new pesticide amount to about 20 million dollars. Nevertheless, as regulations become more rigorous, manufacturing companies have to spend more money and time on testing the safety aspects of pesticides, which leads to ever higher prices for new products. Increased research costs have created a paradoxical situation: modern toxicological and environmental demands would require the development either of pesticides with specific action for use in narrow areas of plant protection, or of pesticides which could be applied at low rates because of their high efficiency. However, due to the relatively low demand, such pesticides would not yield a profit proportional to the increased research costs. Thus, despite modern views, the interest of pesticide manufacturing companies dictates the development of broad-spectrum pesticides which can be sold in large quantities. Hence it would appear that environmental requirements and manufacturers' requirements are mutually exclusive. However, it is to be expected that in the long run these conflicting interests will be resolved so that a balance in the interrelations of crop, pest and environment may be established.

In the official registration of a new pesticide, residues in treated agricultural products represent the key issue. In this respect there are several ways in which conditions for safe application of the pesticide can be expressed numerically. The "no-effect" level is that quantity of the active ingredient in mg/kg body weight per day, which produces no observable reaction in experimental animals, even in long-term feeding tests of several months. The acceptable daily intake, also given in mg/kg body weight per day, is that quantity of the active ingredient, which, if ingested by human beings even throughout life, does not represent a hazard. It is calculated by dividing the "no-effect" level by a safety factor of at least 100. The maximal permissible residue is the highest tolerable quantity of the pesticide residue in

mg/kg, which is set down by the proper government authorities on the basis of daily intake and the actual residue quantities found in trials. Waiting time is the minimal period, in days, which must pass between the last treatment and harvest. It is established on the basis of the toxicity of the active substance and its degradation rate.

These values vary for different countries, different pesticides and different agricultural products, but they are always established with a large safety margin. Thus, for example, the residues actually permitted are only fractions of the acceptable daily intake, and a safety factor of 100 is generally allowed between the maximal permissible residue and the "no-effect" level.

World pesticide production shows a steeply increasing trend. In 1980 the value of world production was about US $ 7.5 thousand million, of which 46% represented herbicides, 32% insecticides, 19% fungicides and 3% other pesticides. In the last ten years application of pesticides has increased by a factor of 2.7. The increase has been highest for herbicides (a factor of 3.6), followed by fungicides (2.8) and insecticides (2). Eighty per cent of the total pesticide production of the world is contributed by 15 companies, distributed half-and-half between Western Europe and the United States.

Today the estimated number of pesticidally active substances on the market is about a thousand. This number seems rather high, but nevertheless, agriculture is far from the goal of using a separate pesticidally active substance for each individual crop, each individual plant disease, and, in general, for each individual risk/benefit situation. Thus, there are several problems still to be solved, and so it is understandable that pesticide manufacturers spend on average 2.5% of their returns on research.

One of the most important aims of research is to increase biological efficiency, which allows application rates to be reduced, thereby minimising both the loading of our environment with chemicals and the energy demand of pesticide manufacture.

The last ten years have seen important developments in this respect in the three most important families of pesticides: fungicides of the triazole group applied at about 100 g/ha, insecticides of the synthetic pyrethroid type at 20 g/ha and herbicides of the sulfonylurea type at 30 and even as little as 5 g/ha exert an effect which could be achieved with the pesticides of 15–20 years earlier only at rates of a few kilograms per hectare. These modern highly efficient preparations form only a small part of the selection of pesticides available today, but a rapid increase in their share of the total is to be expected as a result of purposeful research work. Another approach toward diminishing environmental contamination by chemicals is the development of new active substances which are less volatile, are degraded more rapidly or are more readily adsorbed by soil particles.

The problem of eliminating side-effects on nontarget organisms is most studied in insecticide research. This is partly because the recognition of specific biochemical and behavioural characteristics of insects has created a good theoretical basis for research, and partly because, of all pesticides, insecticides represent the greatest

hazard for other living organisms. Thus, in the immediate future, rapid advances are to be expected in the development of products with specific action killing exclusively harmful insects.

Pesticides have to be developed against pathogens, insects and weeds, which cannot be controlled adequately by the products available today. New demands are created by the acquired resistance of pests to various kinds of pesticides, by changes in the ecosystem arising from pesticide application, and by new agronomic techniques, such as new water management systems, erosion control, and zero tillage. All these demands set new research tasks.

The results of pesticide research, and the rapid development of fundamental sciences, particularly of organic chemistry, biochemistry and molecular biology, along with new demands raised by agriculture, will presumably bring about changes in the coming years, which will radically alter crop protection. On the basis of present trends it seems very likely that within one or two decades agriculture will be put in possession of pesticides in several fields of plant protection, which closely resemble ideal pesticides with respect to specificity of action (elimination of side-effects on nontarget organisms) and rapid degradation (no environmental contamination by residues). In the meantime, plant protection must work efficiently and safely with the imperfect pesticides of today, carefully balancing the aspects of maximal yield and maximal safety.

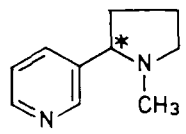
1. Anti-insect agents

1.1 Insecticides of natural origin

The application of natural insecticides, primarily of plant origin, for plant protection and hygiene, preceded by a long time that of synthetic insecticides. In certain parts of Europe, plants were sprayed with an extract of tobacco plants as early as 1690. In the period between 1900 and the 1940s only nicotine, anabasine, pyrethrins, rotenone and quassia were used in addition to inorganic insecticides, and their application virtually ceased on the discovery and large-scale economic production of synthetic insecticides. However, in recent decades, the importance of certain representatives of this group has increased again, partly because of their advantageous properties from the point of view of toxicology and environmental protection.

1.1.1 Nicotine, anabasine and related derivatives

The various *Nicotiana* species, particularly *N. rustica, N. tabacum, N. sylvestris* and *N. glauca,* contain different *Nicotiana* alkaloids in various proportions. The most important of these alkaloids are nicotine **(1),** nornicotine **(2)** and anabasine **(3).**



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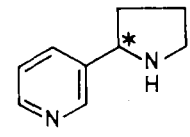

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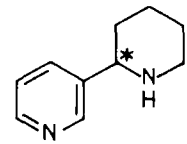

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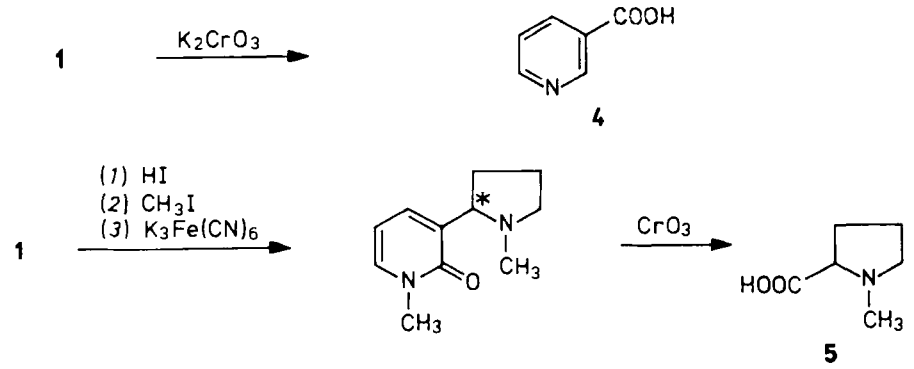
Although the French chemist Gohory prepared a raw tobacco product containing nicotine as early as 1571, the pure alkaloid was first isolated by Posselt and Reimann in 1828. The structure was proved by Pinner in 1893 by decomposition (Pinner, 1893a; 1893b), and later by Pictet and Rotschy (1904) by synthesis.

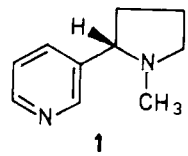
Nicotine is converted by oxidation with chromic acid or permanganate into nicotinic acid **(4),** and by quaternisation, methylation and subsequent oxidation



into N-methylpyrrolidine-2-carboxylic acid **(5)** (Karrer and Widmer, 1925; Griffith *et al.*, 1962).

These investigations, and also those of Pinner (1893a; 1893b) on the decomposition of the bromination products of nicotine, proved the presence of the pyridine and N-methylpyrrolidine moieties in the nicotine molecule.

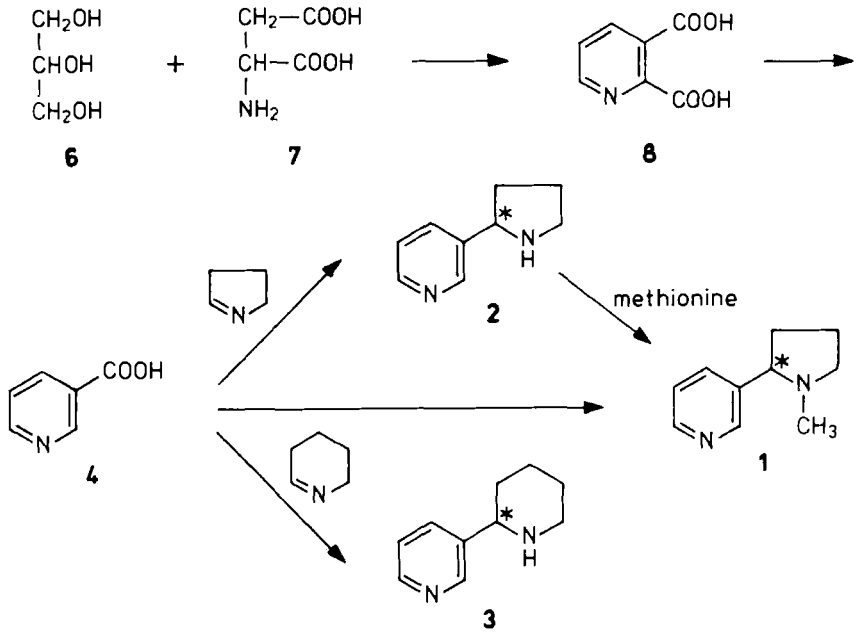
Investigations on the determination of the absolute configuration of nicotine showed that the nicotine molecule contains an asymmetric centre of *S*-configuration:



1

In the synthesis for the verification of the structure, Pictet and Rothschy (1904), in accordance with the general scheme of pyrrole synthesis, started from 3-aminopyridinium mucate. On heating, 2-(3'-pyridyl)pyrrole was formed, which on methylation and subsequent reduction gave *dl*-nicotine. The *l*-isomer obtained by resolution was identical with natural nicotine.

According to experimental evidence, obtained with radioactively labelled precursors, the pyridine ring of nicotine is formed by the condensation of a three-carbon-atom unit **(6)** with aspartic acid **(7)**. The partial decarboxylation of quinolinic acid **(8)** formed by condensation yields nicotinic acid **(4)**, which on reaction with 1-pyrroline formed from ornithine gives nornicotine **(2)**, and on reaction with 2,3,4,5-tetrahydropyridine formed from lysine gives anabasine **(3)**. Nornicotine is converted to nicotine by N-methylation effected by methionine. The new bond is formed with simultaneous decarboxylation at the site of the cleavage of the C—C bond (Flakker and Byerrum, 1965; 1967; Friedman and Leete, 1963; Griffith *et al.*, 1962; Gross *et al.*, 1963; Leete, 1958; 1965; Leete *et al.*, 1964; Mothes and Schütte, 1963; Wu and Byerrum, 1965; Yang *et al.*, 1965a,b), as shown in Scheme 1.1.



Scheme 1.1

Nicotine and anabasine are applied mostly in the form of their water-soluble sulfates in order to kill various insects and mites.

Nicotine is also a strong poison for warm-blooded animals and its acute oral LD_{50} value is 50–91 mg/kg for rats. Partly for this reason, its application has been greatly reduced with the increasing use of synthetic insecticides. Its volatility and rapid decomposition partly counterbalance the hazard due to its toxicity.

According to the investigations of Yamamoto *et al.* (1962; 1963), the structural requirements for insecticidal action in the group of *Nicotiana* alkaloids are the presence of a 3-pyridylmethylamino group, a pK value of the nitrogen atom outside the pyridine ring between 7.4 and 9, a distance of 0.42 nm between the two nitrogen atoms, neither of the two nitrogen atoms to be quaternary, and the pyridine ring not to contain a substituent in the α-position.

In accordance with the theory of Yamamoto *et al.*, nicotine acts in the organism of warm-blooded animals and insects as the mimic of acetylcholine. The nicotinium ion is attached through the positive charge of the pyrrolidine nitrogen atom to the anionic site of the acetylcholine receptor, and then nicotine penetrates in the form of the free base through the synaptic ion barrier. However, nicotine, in contrast to acetylcholine, is not subject to the hydrolytic action of acetylcholine esterase (Yamamoto, 1965; Hamilton, 1963).

In warm-blooded organisms, the metabolism of nicotine is characterised primarily by the oxidative decomposition of the pyrrolidine ring, and the

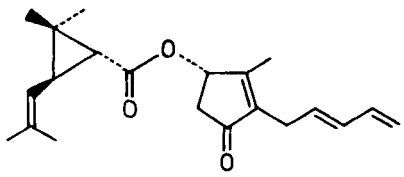
characteristic intermediate products of the conversion are γ-(3-pyridyl)-γ-oxobutyramide, γ-(3-pyridyl)-γ-hydroxybutyric acid and 3-pyridylacetic acid (McKennis *et al.*, 1964).

1.1.2 Pyrethrins and synthetic pyrethroids

Pyrethrum, the dried flower of *Chrysanthemum cinerariaefolium*, or its solvent extract, has been used for centuries in order to kill insects. The plant, originally native to the Near East, was introduced into Europe and America in the nineteenth century, and later into Japan and Africa. Its main regions of culture are Kenya and other African countries, Equador and Japan.

The active substances of pyrethrum (rethrins) are pyrethrin I **(9)** which is the (+)-3-penta-1,3-dienyl-2-methyl-4-oxo-cyclopent-2-en-1-yl ester of (+)-(1*R*, 3*R*)-(*E*)-chrysanthemic acid, pyrethrin II **(10)**, the (+)-3-penta-1,3-dienyl-2-methyl-4-oxo-cyclopent-2-en-1-yl ester of (+)-(1*R*, 3*R*)-(*E*)-pyrethric acid, cinerin I **(11)**, cinerin II **(12)**, the 3-but-2-enyl analogues, as well as jasmolin I **(13)** and jasmolin II **(14)**, the 3-pent-2-enyl analogues of **9** and **10**, respectively.

The elucidation of their structure was due primarily to Fujitani (1909), Yamamoto (1923), Staudinger and Ruzicka (1924a; 1924b), La Forge and Barthel (1944), Crombie and Harper (1949), Godin *et al.* (1964) and Cahn *et al.* (1966).



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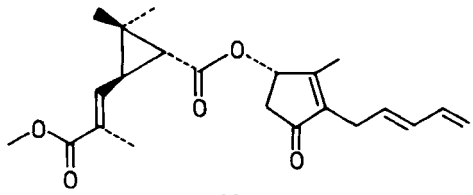

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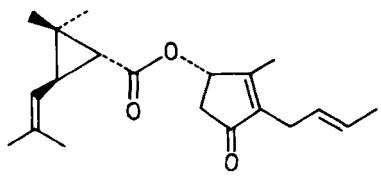

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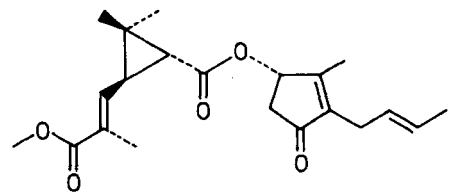

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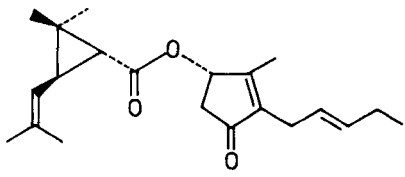

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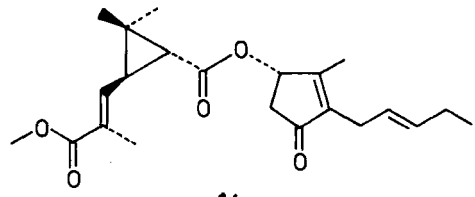
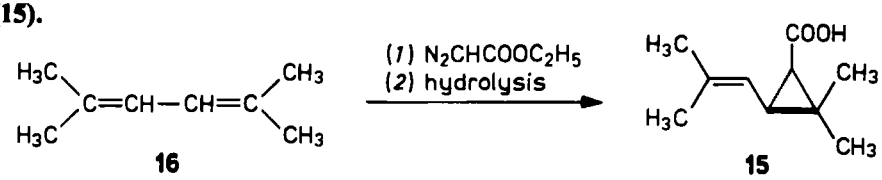


14

The esters are optically active, their absolute configuration being 1*R*, 3*R*, 4'*S*. The double bond in the alcoholic part possesses *Z*, while that in the carbonic acid part *E*-configuration.

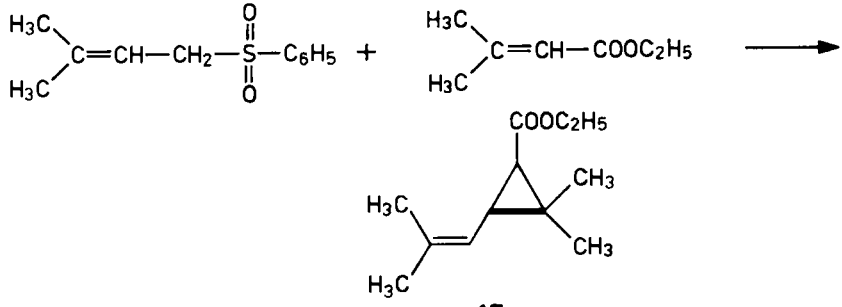
The synthesis of chrysanthemic acid **(15)**, the acid component of the esters **9**, **11** and **13**, was first solved by Staudinger *et al.* (1924). Starting from 2,5-dimethylhexa-2,4-diene **(16)** and ethyl diazoacetate, they obtained (±)-(*Z*)-chrysanthemic acid **(15)**.



16 **15**

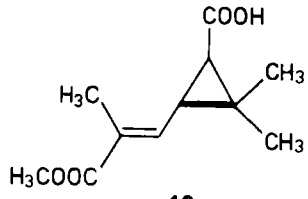
By modifying this process, Harper *et al.* (1951) obtained a mixture of the esters of the *Z* and *E* modifications, from which the active *E*-isomer could be recovered by crystallisation. According to the findings of Matsumoto *et al.* (1963), using the *t*-butyl ester of diazoacetic acid in the presence of copper dust, (*E*)-chrysanthemic acid is formed stereoselectively.

The stereoselective synthesis of (*E*)-ethyl chrysanthemate **(17)** has been achieved by Martel and Huyne (1967). The crucial step of their process is the addition of phenyl 3-methyl-2-butenyl sulfone to ethyl-3-methacrylate.



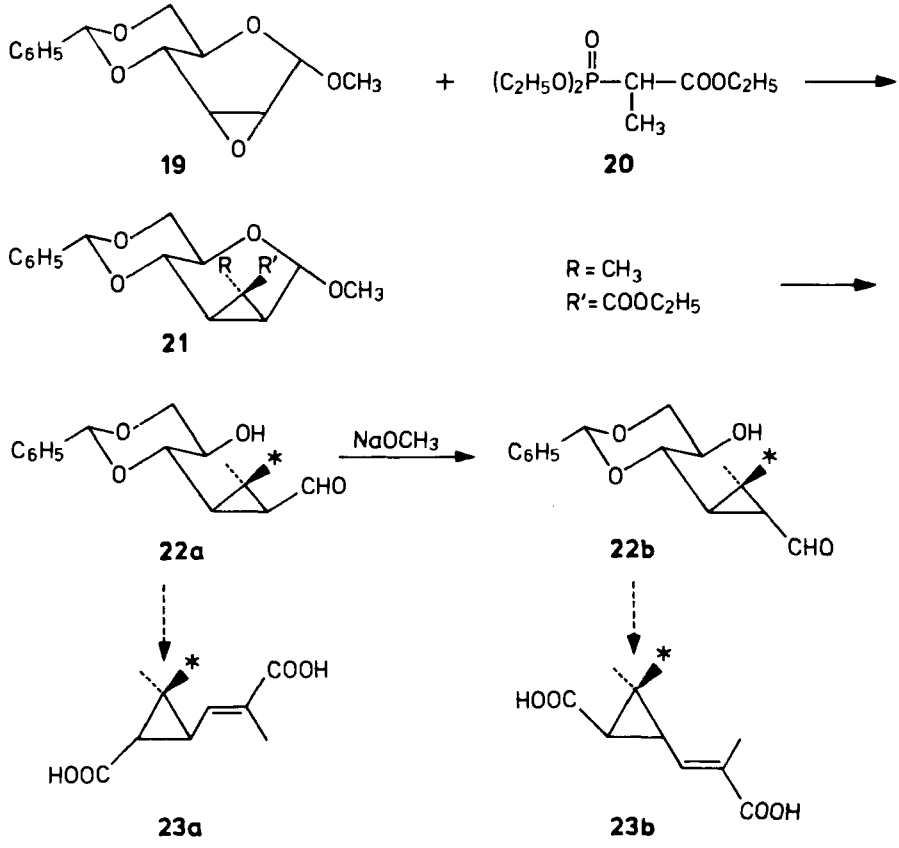
17

(±)-(*E*)-Pyrethric acid **(18)** and from this, by optical resolution, the pure (+)-isomer, forming the acid component of pyrethrin II **(10)**, cinerin II **(12)** and jasmolin II **(14)**, was prepared by Matsui and Yamada (1963) by the oxidation of (*E*)-chrysanthemic acid.



18

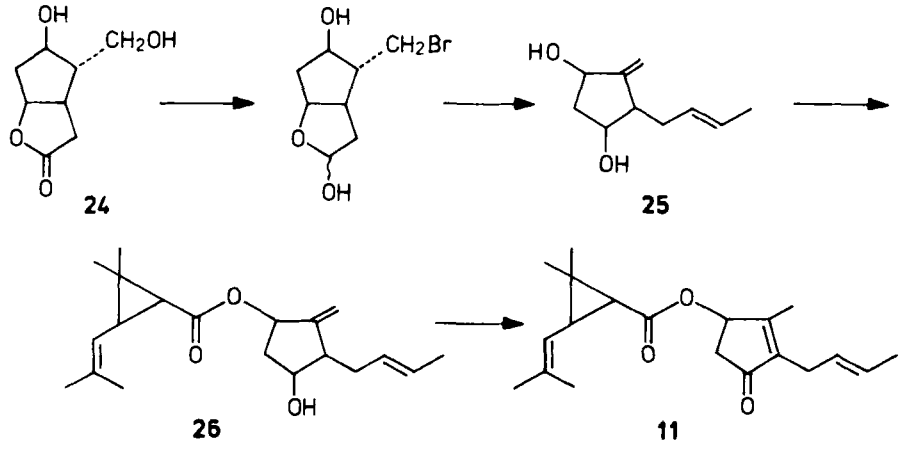
Fitzsimmons and Fraser-Reid (1979) described an enantiospecific synthesis of (+)- and (−)-chrysanthemdicarbonic acid from the same starting material. The pyranosid **19**, used as a a chiralic synthon, yielded on treatment with the propionate **20** the cyclopropane **21**. This was converted to the hydroxyaldehyde **22a** which could be epimerised to **22b** with sodium methoxide. As a result of several further steps, (+)-chrysanthemdicarbonic acid **(23a)** has been obtained from **22a** and (−)-chrysanthemdicarbonic acid **(23b)** from **22b**, as shown in Scheme 1.2.



Scheme 1.2

The synthesis of cinerin I (**11**), based on by-products of prostaglandin synthesis has been developed by Székely and co-workers (Székely *et al.*, 1976; 1980; Kovács, 1978). The lacton diol by-product **24**, the enantiomer of which has the natural prostaglandin chirality, has been used as the starting material in the synthesis route shown in Scheme 1.3. The key step of the synthesis is the oxidative conversion of the *exo*-methylene cyclopentanol **26** to **11** without affecting the ring chiralic centre.

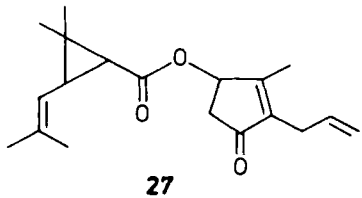
This method can also be used to synthesise pyrethrin I (**9**), jasmolin I (**13**) and allethrin (**27**) in optically pure forms using the proper phosphoranè in the Wittig reaction which yields the corresponding analogue of **25**.



Scheme 1.3

The excellent insecticidal properties of the substances present in natural pyrethrum, their sensitivity to light and oxygen, as well as achievements in the field of their synthesis brought about the need to prepare their synthetic analogues in order to obtain cheaper and less photosensitive products.

It soon became evident that the ester structure is necessary for their activity and both the acidic and the alcoholic hydrolysis products are inactive. Also the geminal methyl groups on the cyclopropane ring and the unsaturated side chains proved to favour insecticidal action. Based on these considerations Schechter *et al.* (1949) synthesised the (±)-3-allyl-2-methyl-4-oxo-cyclopent-2-en-1-yl ester of (±)-(*E,Z*)-chrysanthemic acid (**27**) which became known under the name allethrin.

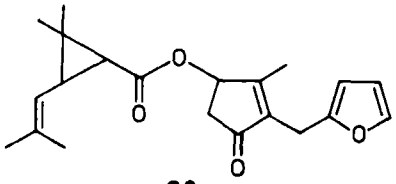


27

The commercial product is a mixture of isomers. The efficiency of the individual isomers varies greatly, demonstrating well the importance of the steric structure.

Early attempts to substitute pyrethrolone, the alcoholic part of the pyrethrin I molecule, for other alcohols usually resulted in a loss of activity (Staudinger and Ruzicka, 1924a, b; Crombie *et al.*, 1951). Great progress on this line was made by

the British research team led by Elliott and by researchers of the Sumitomo Company in Japan. Furethrin (**28**) and cyclethrin (**29**), the first significant products lacking the pyrethrolone moiety, differ from pyrethrin I in that they contain a 2-furylmethyl and a 2-cyclopentenylmethyl group, respectively, instead of the unsaturated side chain of the cyclopentenone ring.



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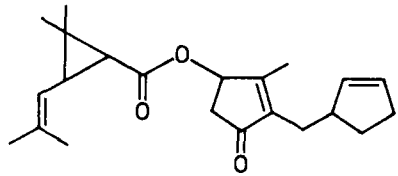

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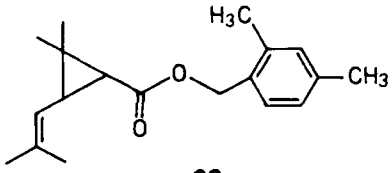
A more marked departure from the pyrethrin structure was represented by esters of chrysanthemic acid formed with substituted benzyl alcohols, such as 2,4-dimethylbenzyl alcohol (dimethrin, **30**), 2-chloro-4,5-methylenedioxybenzyl alcohol (barthrin, **31**), 2-benzyl-4-furylmethyl alcohol (resmethrin, **32**) and tetrahydrophthalimidomethyl alcohol (tetramethrin, **33**).



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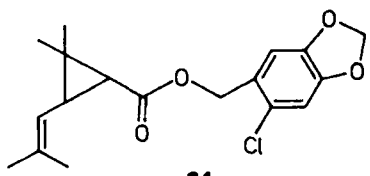

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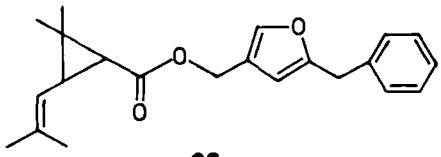

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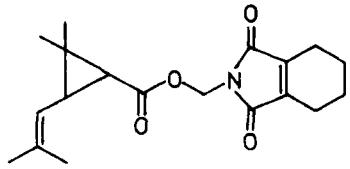


33

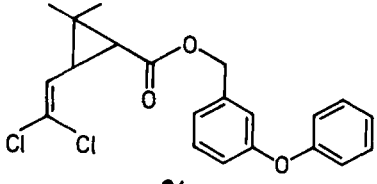
While the insecticidal efficiency of resmethrin and of tetramethrin is about twice that of allethrin, the benzyl derivatives **30** and **31** are of lower efficiency (Gersdorff and Piquett, 1958; Elliott *et al.*, 1965; 1967; Katsuda and Ogami, 1965; Katsuda *et al.*, 1967).

Bioresmethrin, an *E*-isomer prepared from (±)-(*E*)-chrysanthemic acid has an insecticidal activity on flies 50 times that of resmethrin (**32**), which is a mixture of the *Z*- and *E*-isomers.

Though most of these synthetic derivatives are more active insecticides than the natural pyrethrins, and also their synthesis is more simple, their photosensitivity prevented their abundant use. Research activity was directed first to exchange the isobutenyl moiety of chrysanthemic acid, regarded to serve as the site of

photosensitivity, to more stable groupings. These efforts resulted in a valuable combination of properties by scientists of the Rothamsted Experimental Station in 1972. 3-Phenoxybenzyl (1*R*, 1*S*)-(*Z*,*E*)-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylate (permethrin, **34**) proved to be highly active against various insects and revealed a greatly increased stability to oxygen and light (Elliott *et al.*, 1973).

(*S*)-α-cyano-3-phenoxybenzyl (1*R*, 3*R*)-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropanecarboxylate (decamethrin, **35**) represents a further improvement of practical properties such as rapid knockdown effect, low mammalian toxicity and high chemical stability (Elliott *et al.*, 1974). Its insecticidal activity to houseflies is 1700 times that of pyrethrin I and a dose as low as 10 g/ha is sufficient against insects damaging cotton.



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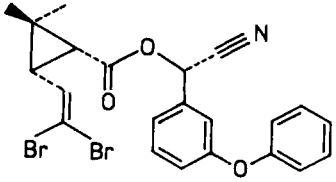
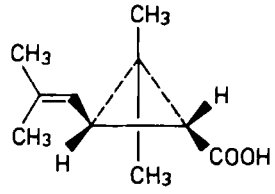


35

In comparative structure–activity relationship studies, (*S*)-α-cyano-3-phenoxybenzyl esters of dihalovinyl-cyclopropanecarboxylic acids were much more active while the (*R*)-α-isomers were generally much less active than the unsubstituted esters lacking the cyano group (Elliott *et al.*, 1978).

Based on former experimental findings, it was believed that the cyclopropanecarboxylic acid structure of chrysanthemic acid is an indispensable condition of activity. A complete break with this assumption has been effected by the Japanese researchers Ohno and co-workers (1974a,b), who demonstrated that the cyclopropanecarboxylic acid can be exchanged for 2-phenylalkanoic acids. Comparison of the absolute configuration of (1*R*, 3*R*)-(+)-chrysanthemic acid (**36**) with that of (*S*)-2-phenyl-3-methylbutyric acid (**37**) shows steric resemblance of the two acids. The corresponding groups attached to the α-carbon atom of the carboxylic acid moieties can overlap and substituents in position 3 and 4 at the phenyl group of compound **37** correspond to the isobutenyl group of chrysanthemic acid (**36**) (Ohno *et al.*, 1976).



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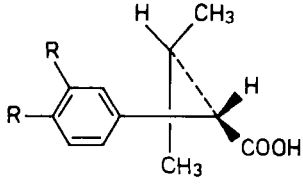
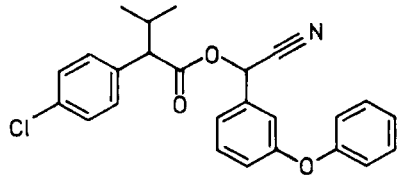


37

The major outcome that emerged from these considerations was the development of fenvalerate, (*R,S*)-α-cyano-3-phenoxybenzyl (*R,S*)-2-(4-chlorophenyl)-3-methylbutyrate (**38**).



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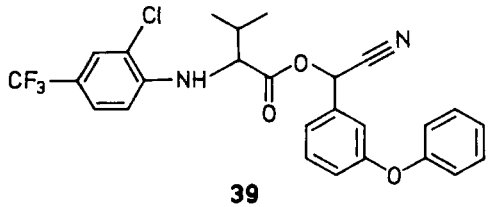
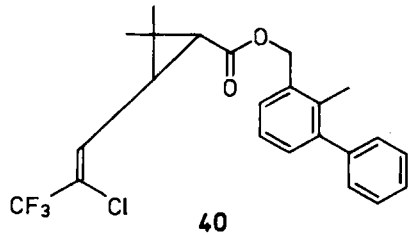
Fenvalerate is a highly active, broad spectrum insecticide used against a great variety of insects such as orthopterae, hemipterae and lepidopterae. It acts both as a contact and as a stomach poison, and is also effective against insects resistant to other pesticides. Its high stability has opened up the possibility of large-scale use.

Fluvalinate (**39**), developed by Henrick and co-workers (1980) is the first representative of pyrethroids possessing an amino acid moiety. Compounds of this type show good stability in air and light, and exhibit biological activities of a similar nature and potency to those of previously known synthetic pyrethroids. Esters of the (*R*)-2-anilino-3-methylbutyric acids are far more active than those obtained from the *S*-enantiomers. The *R*-configuration at C-2 of the acidic moiety is sterically equivalent to the active absolute configuration at the chiral carbon α to the carboxylate group in both the permethrin and the fenvalerate types of pyrethroids.



39

In contrast to earlier findings, suggesting the need of a bridging atom between the two centers of unsaturation in the alcoholic moiety, Engel and co-workers (Engel *et al.*, 1983; Plummer, 1984) have demonstrated that introduction of a single methyl group at C_2 of the phenyl-benzyl ring may induce a conformational effect similar to the bridging oxygen atom of the *m*-phenoxy-benzyl moiety. One of the most active members of this class was the 2-methyl-3-phenyl-benzyl derivative **40**, surpassing the activity of *cis*-permethrin. QSAR studies have indicated that the improved activities of the 2-methyl-pyrethroids is a direct function of the conformational preference for a twist angle between the two aromatic rings of about 50°C.



40

Pyrethrins and the synthetic pyrethroids are but slightly toxic to mammals. The acute oral LD_{50} of pyrethrin I is 330–720 mg/kg for mice and 200 mg/kg for rats. The corresponding values for allethrin are 300–650 and 680 mg/kg, respectively. Most of the other synthetic pyrethroids show similar toxicity values. However, pyrethrins and the synthetic pyrethroids are highly toxic to fish, necessitating caution in their application near rivers, lakes and watercourses. They have no adverse effects on soil microflora and microfauna and are rapidly degraded in soil.

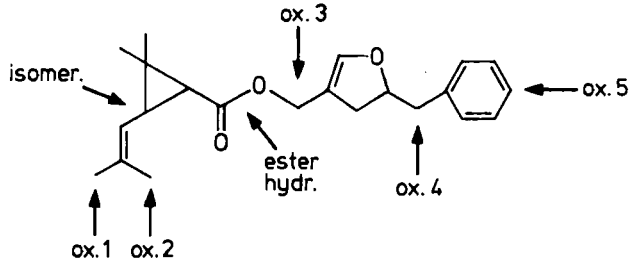
Their mode of action is not yet fully known, but it is certain that their point of attack is the nervous system. Initially, they have a stimulating effect on the nerve cells and nerve fibers, and this is then followed by a paralysing effect.

The most fundamental studies on their mode of action have been those of Narahashi who worked with giant fibre preparations. He proposed that pyrethroids modify axonal conduction within the central nervous system of insects by altering the permeability of the nerve membrane to sodium and potassium ions (Narahashi, 1965; 1974; 1976; Burt and Goodchild, 1977; Clements and May, 1977).

Structure–activity correlation studies have shown that polarity is not important for the toxicity of pyrethroids, while receptor–substrate interactions due to molecular size, shape and electronic effects are important and gave good correlation with bioactivity values (Briggs *et al.*, 1976; Lee, 1976).

Particularly characteristic of the metabolism of pyrethroids in the insects are oxidative conversions. Yamamoto *et al.* (1969) have shown that one of the two methyl groups of the isobutenyl side-chain is oxidised to a hydroxymethyl group.

According to the findings of Casida *et al.* (1974), the points of attack of oxidative enzymes in mammals are the methyl and methylene groups and the benzene ring of the resmethrin **(32)** molecule, the ester bond of esterases and the cyclopropane ring of isomerase:



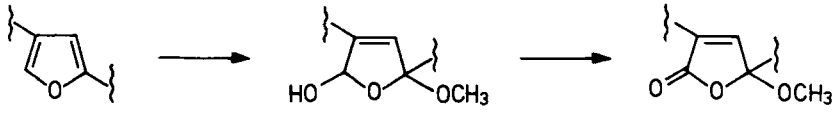
Also permethrin (**34**) is readily metabolised in the mammalian organisms and its metabolism pattern is similar to that of resmethrin (**32**) (Ruscoe, 1977; Gaughan *et al.*, 1977).

In plants permethrin (**34**) forms metabolites identical with those formed in mammals except for the nature of the conjugating moieties (Gaughan and Casida, 1978).

Photolysis of permethrin (**34**) in various solvents and on soil in sunlight resulted primarily in cyclopropane ring isomerisation and ester cleavage to yield 3-phenoxybenzyl alcohol and dichlorovinyl-dimethylcyclopropane carboxylic acid (Holmstead *et al.*, 1978).

The rapid hydrolytic and oxidative transformation is a decisive factor in the low toxicity of pyrethroids to mammals.

Photochemical decomposition of pyrethrins and synthetic analogues can be slowed down by the simultaneous use of antioxidants and photoscreens. In the course of decomposition, chrysanthemic acid, phenylacetic acid, benzyl alcohol, benzaldehyde and benzoic acid are formed from resmethrin (**32**) as decomposition products and, at the same time, the furan ring undergoes an oxidative transformation (Ueda *et al.*, 1974):



The effect of synergists in mixtures with pyrethroids is based on their inhibition of oxidases and esterases, thus increasing the insecticidal efficiency of the pyrethroids, and the duration of their action (Metcalf, 1967; Hewlett, 1960; Casida *et al.*, 1974; Jao and Casida, 1974).

Trans–cis isomerisation and other transformations caused by light often result in inactive products. Triplet quenchers have a stabilising effect in this respect by inhibiting rearrangements (Bullivant and Pattenden, 1974). Another means of stabilisation is the use of pyrethroids in the form of their 1 : 2 inclusion compounds formed with β-cyclodextrin (Yamamoto and Katsuda, 1974).

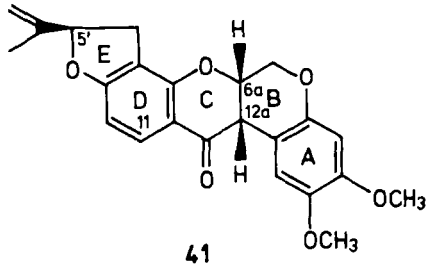
With a few notable exceptions all key pests are effectively controlled with pyrethroids. The extent to which economically important insects develop resistance to pyrethroids will profoundly influence their future application. The restricted use of photolabile pyrethroids mainly against medical and domestic pests resulted in low level of resistance, but the recent widespread application of photostable pyrethroids has exposed in some insects the potential to develop very strong resistance (Briggs *et al.*, 1984).

Though the price of the synthetic pyrethroids is higher than that of other types of insecticides, this disadvantage is counterbalanced by their increased insecticidal efficiency permitting the application of doses as low as 10–100 g/ha.

Structure–activity investigations to explore the potential of molecular modifications continue to provide the basis for new discoveries and to lead to a wider range of novel applications.

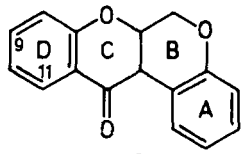
1.1.3 Rotenone and rotenoids

The insecticidal action of the roots of tropical plants belonging to the family of *Leguminosae*, thus of *Derris, Lonchocarpus, Milletia, Mundulea, Tephrosia* and other plant species, has been known for centuries. The active insecticidal component, the most important representative of the rotenoids, is rotenone (**41**). Pioneer work in the elucidation of its structure was done by Geoffroy (1896); Nagai (1912), Takei and Koide (1929), La Forge and Haller (1932), Butenandt and McCartney (1932), Robertson (1932), Takei *et al.* (1932), as well as Crombie and associates (Büchi *et al.*, 1960; 1961; Crombie and Lown, 1962; Adam *et al.*, 1966). According to the investigations of these authors, rotenone (**41**) is 6a,12a,4',5'-tetrahydro-2,3-dimethoxy-5'-isopropenylfurano-(3',2',8,9)-6H-rotoxen-12-one. The molecule contains three asymmetric carbon atoms, 5', 6a and 12a. The latter two arise from the thermodynamically stable *cis* fusion of rings B and C.



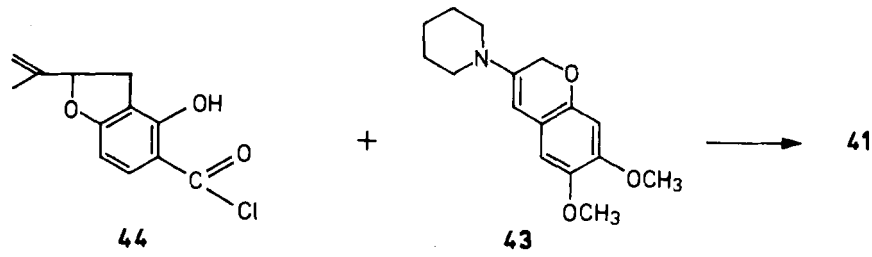
41

The common structural element of all rotenoids is the 6a,12a-dihydro-6H-rotoxen-12-one (**42**) skeleton, the various derivatives differing with respect to the groups attached to the rings A and D, and to carbon atom 11. Thus, sumatrol, for example, contains a methoxy group in place of the hydrogen atom at carbon 11, in deguelin a dimethyl-α-pyrano group is linked to the D ring, and in the munduserone molecule a methoxy group is similarly attached to carbon atom 9 of the D ring.

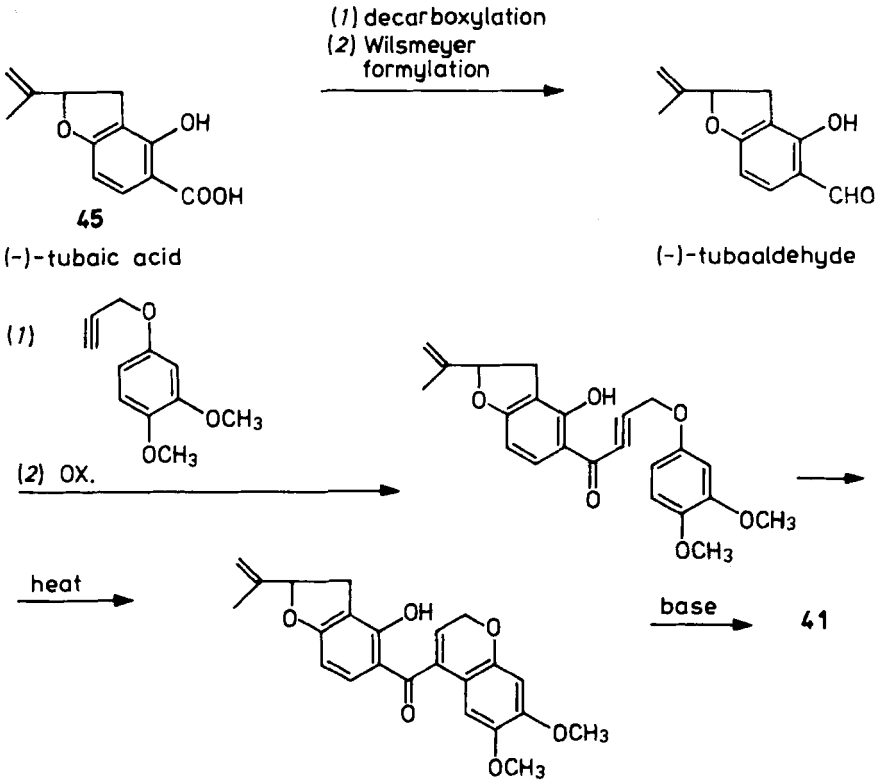


42

One of the most important methods of rotenoid synthesis is that of Miyano (1965), and further that of Uchiyama *et al.* (1966). The critical step is the reaction of 6,7-dimethoxychroman-3-one-pyrrolidyl enamine (**43**) with tubaic acid chloride (**44**).



The synthesis route developed by Sasaki and Yamashita (1979) starts from (−)-tubaic acid (**45**) as illustrated by Scheme 1.4.



Scheme 1.4

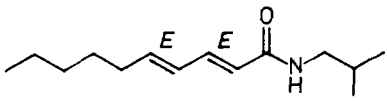
Owing to the structural similarity of rotenoids and isoflavonoides, Griesbach and Ollis (1961), and later Crombie and Thomas (1967), assumed a biogenetic relation between the two families of compounds. Gombos *et al.* (1974) were the first to isolate flavanones, the biointermediates of rotenoids.

Fukami *et al.* (1959) found a close relationship between the insecticidal efficiency of rotenoids and the degree of glutamate oxidation inhibition. The effect is accompanied by a substantial decrease in oxygen uptake. Lindahl and Öberg (1961) found that rotenone inhibits the aerobic oxidation of pyruvate. This effect can be counteracted with methylene blue, which permits the conclusion that rotenone inhibits mitochondrial respiration by reducing the activity of $NADH_2$-dehydrogenase. Hull and Whereat (1967) came to similar conclusions from their experimental results.

The toxicity of rotenoids to warm-blooded animals varies within wide limits and depends on the mode of application and on the species of the test animal. Similarly, great differences are observed with respect to insecticidal toxicity, depending on the insect species. The action develops slowly, which constitutes a practical disadvantage in the case of insects which chew rapidly.

1.1.4 Unsaturated isobutylamides

Some of the plants belonging to the families *Compositae* and *Rutaceae* contain the insecticidally active isobutylamides of unsaturated, straight-chain acids with 10–18 carbon atoms. Of these, the most important are pellitorine **(46)**, anacycline **(47)**, spilanthol **(48)**, herculine **(49)**, fagaramide **(50)** and piperlongumine **(51)**.



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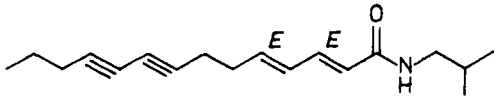

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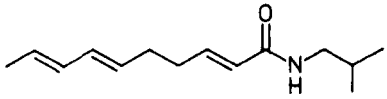

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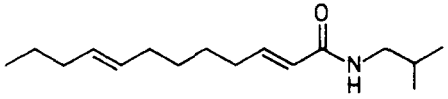

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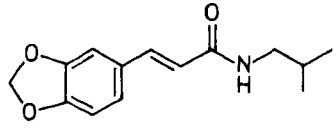

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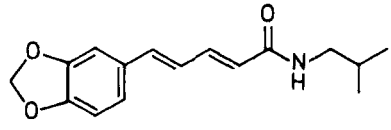


51

Early investigations of compounds of this type are linked with the names of Bucheim (1876), Dunstan and Garnett (1895) and Schneegans (1896). Using modern methods of structure investigation, Crombie *et al.* (Crombie and Harper, 1949; Crombie, 1952; 1955; Crombie and Manzoor-i-Khuda, 1956; 1957), Jacobson (1950; 1953), La Forge *et al.* 1942; La Forge and Barthel, 1944), Fish and Waterman (1972), Su and Horvat (1981), Oriowo (1982), as well as Kubo *et al.*

(1983a; 1983b) elucidated the structure of these compounds and confirmed them by synthesis.

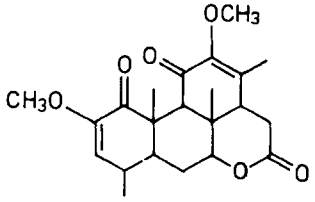
Their insecticidal action is manifested by a rapid knockdown effect, which is characteristic also of pyrethrines. A further property in common with pyrethrines is their pungency, which together with their unsatisfactory stability has prevented their general use in practice, in spite of their strong insecticidal action.

With the practical aim of eliminating these disadvantages whilst maintaining the strong insecticidal efficiency, several analogues of the unsaturated isobutylamides of plant origin have been synthesised. A few of the synthetic analogues exhibited strong insecticidal effects (Crombie and Manzoor-i-Khuda, 1957; Dominquez *et al.*, 1957; Meisters and Wailes, 1966), but the pungency was associated with the insecticidal efficiency in this case also, indicating a common mechanism for the two effects.

1.1.5 Quassia

Quassia amara and *Picrasma excelsa*, native species of the tropics, primarily of South America and the West Indies, and other shrubby trees contain bitter substances toxic to sucking insects. In plant protection practice an aqueous extract is prepared from *Quassia* chips ("quassia") at the site of application. Since the active substance decompose in water the aqueous extract is sprayed immediately after appropriate dilution.

The two insecticidally active substances of *Quassia* are quassin **(52)** and neoquassin **(53)** which are present in amounts of 0.2% in the wood.



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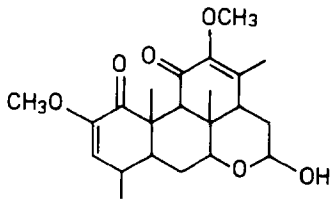


53

Elucidation of their structure is due to Clark (1937a; 1937b; 1938; 1942), Robertson and his co-workers (London *et al.*, 1950), Adams *et al.* (1950), Beer *et al.* (1954; 1956), Valenta *et al.* (1960; 1961; 1962) and Carman and Ward (1961; 1962).

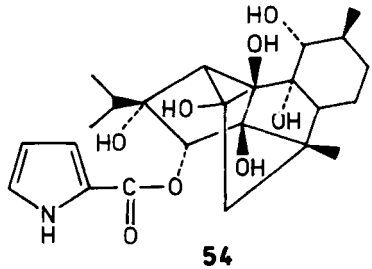
The effect of these active substances varies strongly, depending on the species of insects, and is directed primarily against larvae. They act as nerve poison, but the mode of action is not known. With the spread in the use of synthetic insecticides, the application of quassia in plant protection has lost its importance.

1.1.6 Ryana

Ryana species belonging to the family of *Flacourtiaceae*, such as *R. speciosa*, *R. tomentosa*, *R. sagotina* and others, contain insecticidally active substances. Their discovery is due to the search for insecticides of plant origin (Heal, 1949). The

powder of the dried roots, leaves and stems of the plant is used directly or in the form of its extract in water or alcohol.

The active substance of *Ryana* is ryanodin. Its structure has been investigated by Rogers *et al.* (Rogers *et al.*, 1948; Rogers, 1951), and Wiesner *et al.* (Kelly *et al.*, 1951; Babin *et al.*, 1960; Valenta and Wiesner, 1962; Santroch *et al.*, 1965; Wiesner *et al.*, 1967). Although not finally proved, its probable structure is **54**.



54

The insecticidal effect of *Ryana* surpasses that of the other insecticides of natural origin, as well as of a major part of chlorinated hydrocarbon insecticides (Clark and Laudani, 1953). Ryanodin entering the insect organism in 2–5 ppm quantities substantially reduces oxygen uptake, which results in paralysis.

Its persistency is low. Its price is relatively high and this, together with the competition of synthetic products has limited its use. However, the low persistency makes possible its application immediately before harvest, without a pre-harvest interval.

Although *Ryana* is hardly toxic to warm-blooded animals, ryanodin is a strong poison, one of its characteristic symptoms is irreversible muscle contraction.

1.1.7 Sabadilla

Sabadilla is the dry, ripe seed of the plant *Schoenocaulon officinale*, native in the mountains of Mid-America, of the family *Liliaceae*. Its insecticidal effect has been known since the sixteenth century, but its study by scientific methods began only in 1938 (Allen *et al.*, 1944).

Its active substances are polyol alkamines ("ceveratum alkaloids"), which can be classified with the veratrum alkaloids. Their common basic skeleton is a heterocyclic ring system each ring containing a nitrogen atom (Prelog and Jeger, 1953; Zeitler, 1965; Narayanan, 1962).

Similar to that of steroids, the biosynthesis of these polyol alkamines occurs through acetate and mevalonate (Goseva *et al.*, 1960).

1.1.8 Toxins of Bacillus thuringiensis

Japanese authors were the first to establish insect disease of bacterial origin, when discovering the pathogen of the epidemic disease of the silk worm (Ishida, 1901). Berliner (1911; 1915) found that the same bacterium, which he called *Bacillus*

thuringiensis, also causes the epidemic disease of flour moth. This discovery raised the possibility of using insect-pathogenic bacteria in plant protection, and extensive research on the biology and chemistry of *Bacillus thuringiensis* began. Environmental hazards caused by synthetic insecticides enhanced the importance of research in this direction. Toxins of various chemical nature and, consequently, of different biological activity have been isolated from the cultures of *Bacillus thuringiensis*.

In the course of its vegetative reproduction, the bacterium produces exoenzymes, with the aid of which exogenous nutrients are made available for assimilation. Principally the effect of certain phospholipases has been studied but, although their insecticidal effect has been established, experimental results do not permit an unequivocal elucidation of the nature of the action (Heimpel, 1955; Kushner and Heimpel, 1957; Rogoff, 1966).

Three exotoxins were isolated from the supernatant liquid of *Bacillus thuringiensis* cultures. Among these, β-exotoxin has been investigated most extensively. Its structure has not yet been established, but it is probably a nucleotide containing adenosine monophosphate (Heimpel, 1967; McConnel and Richards, 1959; De Barjac and Dedonder, 1965; Benz, 1966; Sebesta and Horská, 1968; Rogoff, 1966; Farkas *et al.*, 1969).

In the course of sporulation, protein crystals are formed by the side of the spores. The toxic effect of *Bacillus thuringiensis* can be traced back primarily to δ-endotoxin which constitutes these *para*-sporal formations. Endotoxin crystals consist of silicon-containing, nucleotide-free protein, which is a protomer of molecular weight 373 000, consisting of basic units of 25 000 molecular weight (Faust and Esters, 1966; Lecadet, 1965; Angus, 1956; Spencer, 1968; Akune *et al.*, 1971).

Of the toxic substances of various types in *Bacillus thuringiensis*, the effect of δ-endotoxin has been investigated most intensively. Its action is manifested by a lesion in the *epithelium* of the midgut, followed by a quick and extensive paralysis of the insect organism. Contradictory and not fully proven theories on the mechanism of action at the molecular level have been suggested. The theory of Angus (1968a; 1968b) seems to be best supported. According to this, crystalline endotoxin is transformed by the proteases of the insect gut into a smaller fragment which acts as an ionophore, altering the selective permeability of the *epithelium* for potassium ions.

The action of β-exotoxin induces a group of phenomena completely different from that of endotoxin, proceeded according to a different mechanism. The effect is manifested by teratological phenomena, inhibited pupation, mortality after moulting, and malformation. Therefore, the assumption of several authors seemed to be justified that β-exotoxin affects the activity of formation of hormones regulating the metamorphosis of insects. On the other hand, the nucleotide structure indicates that β-exotoxin exerts its action as a nucleic acid antimetabolite (Benz, 1966; Grebelsky and Kandybin, 1974).

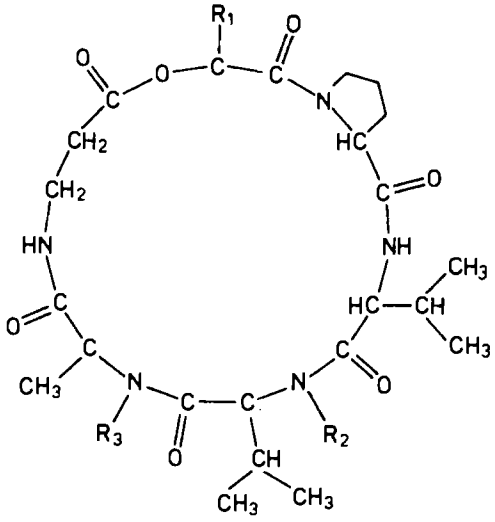
The commercial preparations are *Bacillus thuringiensis* cultures prepared on semi-solid or liquid culture medium. An important requirement is the maintenance

of the vitality of the spores and prevention of denaturation of the toxic protein. Its advantage over insecticides obtained by chemical means is that it can also be used at harvest time because it leaves no harmful residue. It is not harmful to warm-blooded animals so that its use does not require strict sanitation regulations.

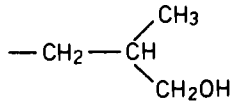
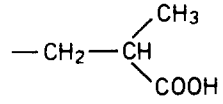
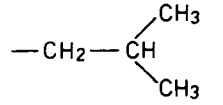
1.1.9 Insecticidal compounds produced by fungi

Kodaira (1961), then later Tamura and his associates (Tamura *et al.*, 1964; Suzuki *et al.*, 1970), isolated from the culture filtrate of *Metharrhizium anisoplias* the depsipeptides with insecticidal action which cause muscardine disease in various insects as a result of fungal infection.

The derivatives isolated so far are named destruxins after the earlier name of the fungus (*Oospora destructor*). The common basic skeleton of the destruxins is a 19 membered depsipeptide ring, and the various derivatives differ from each other with respect to their side chains (**55–60**).



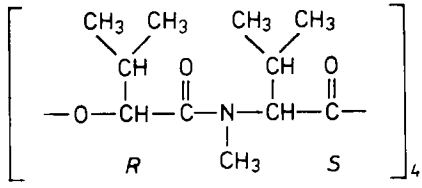
		R_1	R_2	R_3
prodestruxin	**55**	$-CH_2-CH(CH_3)_2$	—H	—H
destruxin A	**56**	$-CH_2-CH=CH_2$	$-CH_3$	$-CH_3$
destruxin B	**57**	$-CH_2-CH(CH_3)_2$	$-CH_3$	$-CH_3$

destruxin C	**58**		—CH_3	—CH_3
destruxin D	**59**		—CH_3	—CH_3
desmethyl-destruxin	**60**		—H	—CH_3

Bassianolide **(61)**, a further insecticidal cyclodepsipeptide has been isolated from two entomopathogenic fungi, *Bauveriana bassiana* and *Verticillium lecanii* by Kanaoka *et al.* (1977, 1978)

Destruxins and bassianolide have no importance in practical plant protection because their recovery is cumbersome, they are highly toxic to warm-blooded animals and, moreover, they are not contact poisons. Their activity as a stomach poison is greatly limited by their antifeedant effect. They are primarily products of theoretical interest, and it is to be hoped that study of them will clarify relationships concerning the mechanism of the insecticidal and antifeedant effects, and will help elucidate the biological effect of cyclodepsipeptide antibiotics of similar structure.

The isolation of piercidine A and piercidine B from *Streptomyces mobaraensis* cultures, obtained from soil samples, is also linked with the name of Tamura and co-workers (Tamura *et al.*, 1963; Takahashi *et al.*, 1965; 1967; Suzuki *et al.*, 1966; Yoshida *et al.*, 1977). Piercidine A **(62)** has a pyridine ring containing several substituents including an unsaturated side chain with seventeen carbon atoms. Piercidine B **(63)** contains a methoxy substituent instead of a hydroxy group at carbon atom 10 of the side chain.



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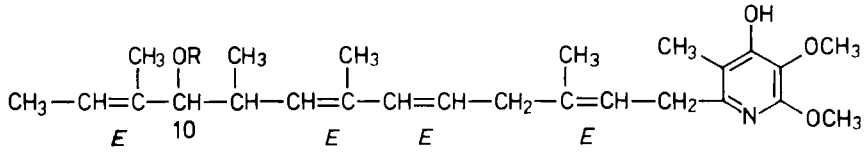


R = H piercidine A

62

R = CH_3 piercidine B

63

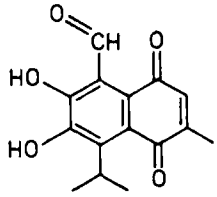
Based on the structural similarity between the piercidines and co-enzyme Q, several research groups presumed and supported experimentally that the effect of the piercidines is based on competitive inhibition of the mitochondrial electron-transport systems (Hall *et al.*, 1966; Jeng *et al.*, 1968; Horgan *et al.*, 1968; Horgan and Singer, 1967; Mitsui *et al.*, 1969). Both piercidine A and piercidine B inhibit respiration at very low concentrations (Tamura *et al.*, 1963).

Further piercidines produced by *Streptomyces pactum* have been isolated by Yoshida *et al.* (1977a,b).

1.1.10 Insecticidal terpenoids

The increased resistance of some primitive and wild strains of cotton to bollworms and tobacco budworms has been attributed to certain terpenoids. Some of these were isolated from flower bud extracts and have been identified as hemigossypolone **(64)**, heliocide H_2 **(65)**, heliocide H_3 **(66)**, heliocide H_1 **(67)** and heliocide H_4 **(68)**.

The structures of the isolated compounds have also been confirmed by synthesis (Gray *et al.*, 1976; Stipanovic *et al.*, 1978).



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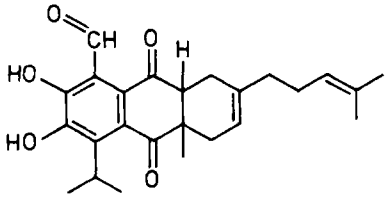

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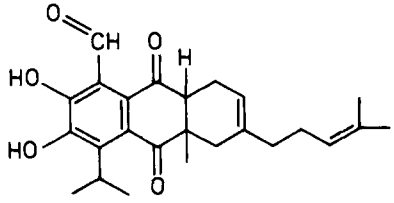

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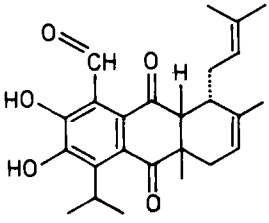

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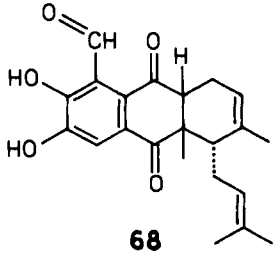

68

Heliocide H_1 proved to be four or five times as toxic to insects as hemigossypolone or heliocide H_2. This indicates that the insecticidal activity within this class is highly dependent on the stereochemistry of the products. According to Stipanovic *et al.* (1978), it should be possible to breed cotton varieties that contain the most effective mixture of heliocides.

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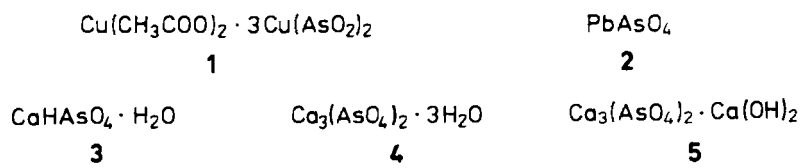
1.2 Arsenic compounds

The poisonous effect of arsenic has been known since ancient times and its application against insects was recommended as early as the seventeenth century in a book by John Worlidge (Munro, 1946). The use of various inorganic preparations for plant protection increased to several hundred million tons per year by the 1940s, but since then they have been replaced to a considerable extent by chlorinated hydrocarbon insecticides.

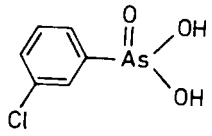
Paris green is copper(II) acetate metaarsenite (**1**). In addition to its toxicity to haematotherma, characteristic in general of arsenic compounds, it has the disadvantage of being strongly phytotoxic. This effect is due primarily to the fact that it decomposes in water to form arsenic trioxide, which is very injurious to cells. This detrimental property could be overcome by using lead arsenate. Of the various salts of lead formed with arsenic acid, lead (II) hydrogen arsenate (**2**) is the most widely used in plant protection. It is almost insoluble in water, and is therefore free of phytotoxic side-effects. Damage to plants sprayed with it usually occurs when water containing a large amount of metal HCO_3^- salts is used, because soluble arsenic compounds are then formed.

Smith (1907) recommended the use of calcium arsenate instead of lead arsenate. Of the calcium salts of arsenic acid, mainly the acid salt of structure **3**, and to a lesser extent the neutral salt of structure **4** and the basic salt of structure **5**, have been applied in protection against insect pests in orchards, cotton and other plants.



Roark (1942) prepared several modifications of Paris green in which the acetate radical was exchanged for other organic acid radicals. Of these, the oleate and stearate analogues, owing to their lipophilic character, were readily miscible with preparations of oily spray-type compounds. However, they did not find wide practical application.

The experiments of Yun Fan (1947) were similarly aimed at the enhancement of lipid solubility. In these experiments, the insecticidal action of phenylarsonic acid and its derivatives substituted in the ring was investigated. Of this type of insecticide *m*-chlorophenylarsonic acid (**6**) proved to be the most efficient.



6

Preparations containing arsenic cannot strictly be considered as insecticides, as they are more or less toxic to all living organisms. In fact they had also been used as raticides and fungicides. Their use has been decreased owing to continuing improvements in human hygiene and environmental protection.

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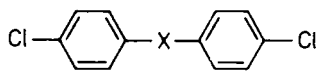
1.3 Chlorinated hydrocarbons

1.3.1 DDT and its related derivatives

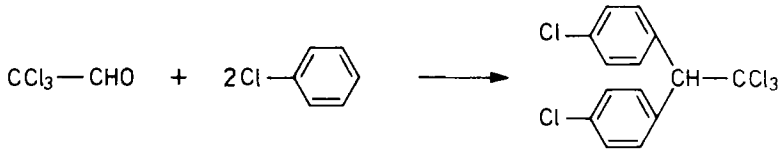
The aim of Paul Müller's research work, begun in 1935 was to develop contact insecticide compounds to be used primarily against clothes-moth. In 1939 he established the insecticidal efficiency of those compounds in which two *p*-chloro-substituted benzene rings are linked together by a central bivalent radical (Müller, 1940; 1955):



X = O, S, NH, SO or SO_2.

Based on these earlier, promising results, Müller in the course of his later work extended his investigations to the study of dichlorodiphenyltrichloroethane (DDT, **1**), with the trichloromethylmethylene group as the central bivalent radical in the general concept given above.

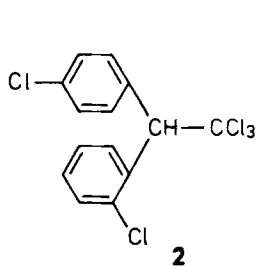
The compound was already described by Zeidler in 1873 (Zeidler, 1873; Baeyer *et al.*, 1974). It was prepared by the reaction of chloral with chlorobenzene in the presence of sulfuric acid as condensing agent:



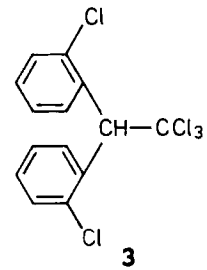
1

DDT exhibited a high insecticidal efficiency. It was marketed in 1942 under the name Gesarol® in the crop protection field, and under the name Neocid® in the field of human hygiene. The discovery was of immense importance in both fields, and marked the beginning of the application of modern synthetic products in plant protection.

The industrial manufacture of DDT is based on the synthesis described by Zeidler. Chloral, chloral alcoholate or chloral hydrate is reacted with chlorobenzene in the presence of sulfuric acid, oleum or chlorosulfonic acid (Rueggeberg and Torrance, 1946). The technical product thus obtained contains several impurities, including the *ortho–para* (**2**) and *ortho–ortho* (**3**) isomers, 2,2-bis-(*p*-chlorophenyl)-1,1-dichloroethane (*p,p'*-DDD, **4**), its *ortho–para* isomer (*o,p'*-DDD, **5**), in addition to the *para–para*-DDT (**1**) which presents about 70% of the product.



2



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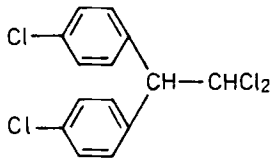

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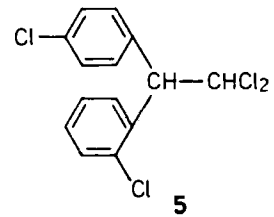
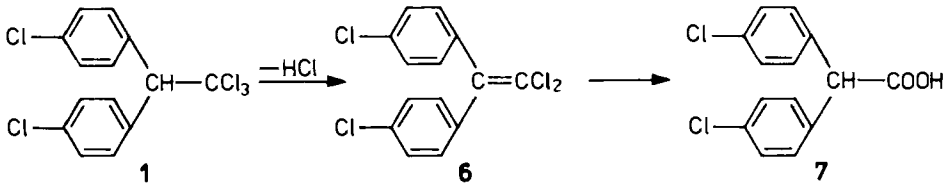


5

p,p'-DDT is resistant to light, atmospheric oxygen and weak inorganic acids, but is rapidly decomposed to the biologically inactive 2,2-bis(*p*-chlorophenyl)-1,1-dichloroethylene (*p,p'*-DDE, **6**) and 2,2-bis(*p*-chlorophenyl)acetic acid (*p,p'*-DDA, **7**) by the action of high temperature or strong ultraviolet light with consequent elimination of hydrochloric acid. *o,p'*-DDT **(2)** is similarly converted to *o,p'*-DDE. In an alcoholic–basic medium, by the action of light, *p,p'*-DDT undergoes partial reductive dechlorination by loss of ionic chlorine. In this photochemical reaction alcohol is the reducing agent (Matsui *et al.*, 1973).



1 6 7

o,p'-DDT **(2)** is 7.5 times more volatile than *p,p'*-DDT **(1)**. Similarly, *p,p'*-DDE **(6)** formed primarily as a decomposition product is more volatile than *p,p'*-DDT. This is why the airlayer above the surface treated with technical DDT contains mainly *o,p'*-DDT, *o,p'*-DDE and *p,p'*-DDE; while the proportion of *p,p'*-DDT present is only 8% (Spencer and Cliath, 1972). The high volatility of *o,p'*-DDT and *p,p'*-DDE means that they quickly disappear from treated surfaces. This has certain advantages from an environmental protection point of view as *o,p'*-DDT caused harmful oestrogenic effects and, according to some authors, *o,p'*-DDE has an adverse effect on bird reproduction. Conversely, the higher volatility of these detrimental products increases the possibility of the contamination of untreated areas. Organic soil colloids strongly reduce the volatility of DDT (Porter and Beard, 1968).

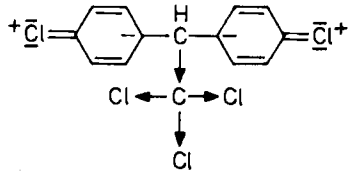
DDT has been and is also today a widely used insecticide, strongly toxic to many species of agricultural insect pests, with the exception of mites and plantlice.

Early theories concerning the mode of action of DDT on insects followed two main directions. One of these was the theory of Läuger, Martin and Müller (1944), according to which the lipoid solubility of the compound, and consequently its penetration into the cuticle are due to the trichloromethyl moiety of the DDT molecule, while the two *p*-chlorophenyl moieties are those responsible for biologic action. However, according to the opinion of Martin and Wain (1944), the lipoid solubility can be traced back to the *p*-chlorophenyl groups, while the toxic action is exerted by the trichloromethyl moiety which, by dehydrochlorination, releases hydrochloric acid into the vital centres of the organism. If this latter theory is valid, there should be a positive relationship between the dehydrochlorinability of the various DDT-analogues and their toxic efficiency. Cristol (1945) and Oettingen and Sharpless (1946) extensively investigated the dehydrochlorinability of numerous DDT-analogues, but the data obtained showed no relationship with toxicity values. According to Martin, this does not disprove the theory of action based on the

liberation of hydrochloric acid, because absorbability and permeability factors may be predominant over dehydrochlorinability.

A futher counter-argument to the theory of release of hydrochloric acid was that the toxic effect is also exerted by compounds for which the liberation of hydrochloric acid is excluded *a priori*.

These inconsistencies seem to be surmounted by the more general formulation of Campbell and West (1945), according to which the mode of action of DDT and similar derivatives is very complex, and the liberation of hydrochloric acid is only a secondary consequence of the electronic structure, but which also influences activity in other ways. The effect of the chlorine atoms can also be traced back to steric factors. The fact that the presence of three chlorine atoms at the methyl group results in maximal efficiency is indicative of the fact that this structure provides the steric orientation desired. Owing to the strong electron-withdrawing ($-I$) effect of the three chlorine atoms of the trichloromethyl moiety, the central carbon atom acquires a positive charge, and the molecule can take the following border case structure:



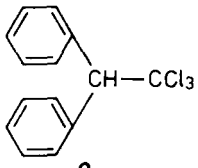
Sternburg and Kearns (1952) detected the formation of an unknown neuroactive substance in the blood of insects poisoned with DDT. Tashiro *et al.* (1972) established later that this neuroactive substance is L-leucine. Using L-leucine labelled with ^3H, they found that, under the action of DDT, the nerve fibre of the insects releases more L-leucine than normal. On the basis of their experimental results they assumed that L-leucine is converted to isoamylamine, the ultimate neurotransmitting agent, by the action of the decarboxylase enzyme (Tashiro *et al.*, 1974).

Mullins (1955) defined the site of action of the DDT molecule as the interstices of cylindrical lipoprotein strands of the nerve axon. Based on this concept, Holan (1969; 1971) has developed a theory suggesting that the molecule of DDT fits into the membrane of the nerve axon in such a way that the trichloromethyl group acts as a "molecular wedge", propping open the sodium gate, which then results in a continuous influx of Na^+ ions.

According to the theory of Matsumura and Patil (1969), based on their experimental findings, DDT acts by inhibiting the Na^+, K^+ and Mg^{2+} ATP'-ases.

Attempts to elucidate the structural requirements of bioactivity of DDT type compounds and to improve the properties of the parent molecule were initiated soon after the discovery of the insecticidal action of DDT. Early studies of Müller (1946) showed that a high degree of lipophilicity is desirable. On the basis of the relationship between the action of numerous DDT-analogues and their structures,

Riemschneider (1948; 1958) stated that active derivatives can be derived from four basic compounds. He called these contactophores: 2,2-diphenyl-1,1,1-trichloroethane **(8)**, 1,1-dichloro-2,2-diphenylethane **(9)**, 2,2-diphenyl-1,1,2-trichloroethane **(10)** and 3,3-diphenyl-1,1,2-trichloropropylene **(11)**.



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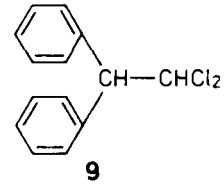

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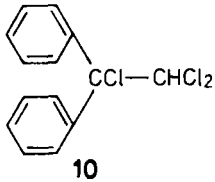

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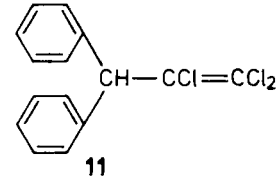


11

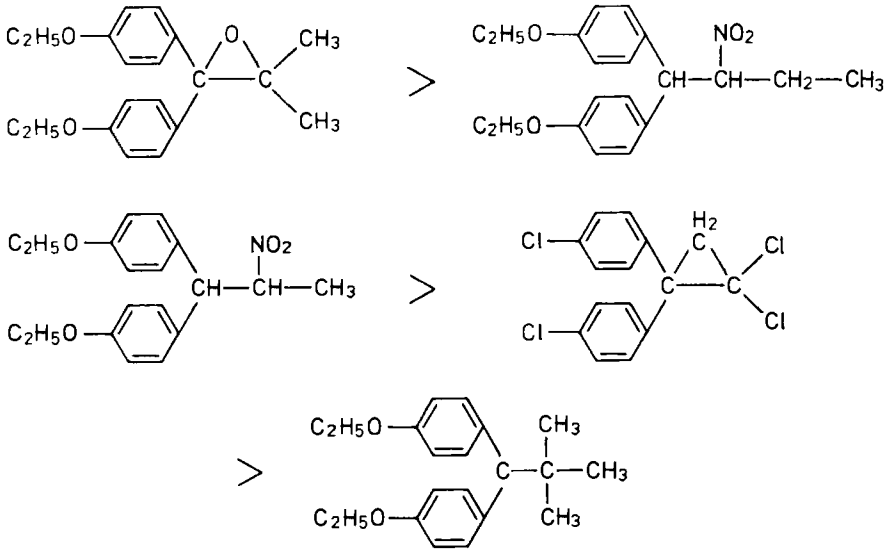
The substitution at the benzene ring in definite positions may enhance or reduce the effect of the parent compound, depending on the nature of the substituent. Positive auxocontacts increasing the effect are: $—CH_3$, $—C_2H_5$, —F, —Cl, —Br, $—OCH_3$, $—OC_2H_5$; while negative auxocontacts decreasing efficiency are: $—C_4H_9$, $—C_6H_5$, —OH, —COOH, $—NH_2$, $—NO_2$. Among the derivatives with positive auxocontact substituents, those with substitutions in the *p,p'*-position are the most efficient. A transfer of the substituent(s) to the *m*-position slightly decreases the efficiency, the transfer of the substituents at one of the benzene rings to the *o*-position strongly decreases efficiency while, in the case of *ortho*-substitution at both benzene rings, a completely inactive compound is obtained. Experiments with Stuart-Briegleb's molecule models showed a definite correlation between the insecticidal efficiency and the free rotability of the benzene rings. Because of their steric position, substituents in the *ortho*-position suspend the possibility of free rotation of the benzene rings and, consequently, also the bioactivity.

Fujita and co-workers (1964) concluded from their quantitative structure activity relationship studies that moieties with relatively large π-values such as hydroxyl, furyl, carboxyl or amino render a DDT type molecule nontoxic probably due to the poor penetration through the cuticle or through the lipid sheath of the nerve.

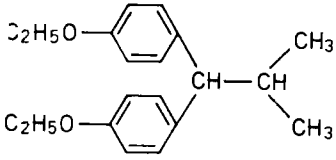
Fahmy *et al.* (1973) found a close relationship between the log LD_{50} values of various DDT analogues and their steric substituent constants, E_s demonstrating that E_s is the most relevant parameter for the correlation of bioactivity with structure.

Holan and Spurling (1974) determined by molecular orbital calculations the charge distribution of DDT analogues selected on the basis of steric criteria. They

found good agreement between the calculated charge on the apex of molecules and the LD_{50} values measured. The insecticide efficiency and, at the same time, the calculated charge of the compounds investigated decreased in the following order:



Coats *et al.* (1977) prepared a series of new DDT analogues with altered aliphatic moieties. The ratio of mouse LD_{50} to housefly LD_{50} was the poorest for trichloroethane and dichloroethane compounds when the aromatic substitution was diethoxy or ethoxy-propoxy. The gradual replacement of chlorine atoms in the aliphatic group with methyl groups yielded compounds with a wider safety margin. Several of the compounds prepared, such as **12** and **13**, show promise also as practical insecticides.



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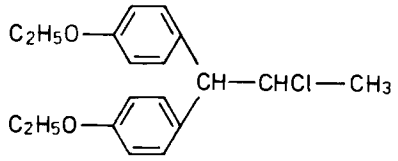
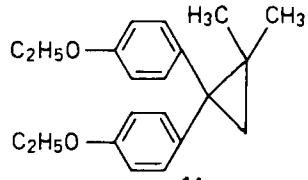


13

Plotting the insect toxicity values against the van der Waals volumes, the authors revealed that a sharply defined minimum volume is required. Steric interaction is apparent between the aliphatic and aromatic substituents, suggesting that the molecule must fit into a tridimensional elastic sac to induce toxicity.

Holan and associates (1978) described the synthesis of 1,1-bis(4-ethoxyphenyl)-2,2-dimethylcyclopropane (**14**), which is isosteric with DDT but also contains the dimethylcyclopropane moiety of the pyrethroids.



14

This compound exhibits a central nervous system action in insects like the pyrethroids, but its peripheral action on sensory nerve structures is different from that of other DDT analogues.

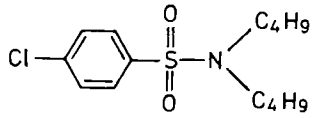
Some years after the world-wide introduction of DDT an unforeseen disadvantage manifested itself: in the course of the prolonged use of DDT, certain insect strains became resistant to the original doses, so that the effect of the originally applied dose could only be attained by substantially raised doses. A more thorough study of this phenomenon, and its later extension to other types of compounds showed that an acquired resistance is characteristic not only of DDT but also of several other types of insecticides, such as BHC, cyclodienes and organophosphorus pesticides. Resistance developed in a certain member of single groups (strains or populations) generally extended to the other members of the same group, but not to other groups. This type of resistance indicates an identical resistance-mechanism within a group. The reasons for this acquired resistance are the sublethal amounts of insecticide introduced into the insect organism over a long period, while its chemical basis is, in the case of DDT, primarily the DDT-dehydrochlorinase enzyme. It was shown by Perry and Hoskins (1951) that the detoxification mechanism has an enzymatic character. The enzyme was described by Sternburg *et al.* (1954), and later isolated from the organism of fly strains resistant to DDT and some DDT analogues by Lipke and Kearns (1959). DDT is decomposed by DDT-dehydrochlorinase, to 2,2-bis(*p*-chlorophenyl)-1,1-dichloroethylene (*p,p'*-DDE, **6**) whereby hydrochloric acid is eliminated, that is, it undergoes the same changes as under *in vitro* conditions by the action of alkali, high temperature or ultraviolet radiation.

Heinman *et al.* (1970) concluded from their experiments that DDT inhibits pyruvate oxidation and phosphorylation reactions in the mitochondria of the insects. In the natural DDT resistance of certain insect species, the resistance of mitochondrial oxidative phosphorylation to DDT may be significant. According to Sestovic and Peric (1974), the resistant strains of Colorado potato beetle metabolise DDT considerably faster than the strains susceptible to DDT.

Summerford *et al.* (1951), March (1952) and Speroni (1952) showed that certain derivatives structurally related to DDT but inactive themselves can increase the effect of DDT on DDT-resistant flies. However, the same compounds are unable to enhance the effect on fly strains sensitive to DDT. These observations support the assumption that compounds known as DDT-synergists act by inhibiting the DDT-dehydrochlorinase enzyme. Various benzene sulfamide derivatives can also

potentiate the effect of DDT on resistant flies and, at the same time, under *in vitro* conditions, inhibit the DDT-dehydrochlorinase enzyme.

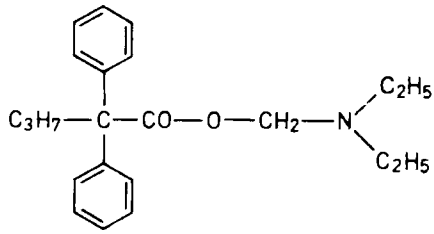
The best known example of anti-resistant compounds of the benzene sulfonamide type is N,N-di-*n*-butyl-4-chlorobenzene sulfonamide **(15)**, introduced under the name WARF anti-resistant (Fales and Bodenstein, 1961; Pittai *et al.*, 1963).



15

DDT-dehydrochlorinase is only one of the enzymes causing detoxification of DDT. Also important in this respect are those mixed function oxydases which decrease the effect of DDT by inducing oxidative degradation. In his experiments carried out on *Heliothis* species, Plapp (1973) showed that the development of resistance to DDT can be traced back to oxidative enzymes. The field of action of these enzymes involves a wide range of insecticides. Accordingly, the effect of those anti-resistant compounds — the action of which is based on the inhibition of oxydases — is more general and concerns almost all types of insecticides.

β-Diethylaminoethyl-2,2-diphenylvalerate **(16)**, known as SKF 525 A, may also be considered as one of these anti-resistant compounds (Fine *et al.*, 1966; Morello, 1964; Dyte *et al.*, 1965; 1966; Lloyd, 1969).



16

In general this compound is known as the inhibitor of various hydroxylation reactions and, as such, as a non-specific synergist of several biologically active compounds (Axelrod *et al.*, 1954; Veldstra, 1956; Gillette, 1966).

DDT is a nerve poison for warm-blooded organisms, that is, also to humans. Its acute oral toxicity (LD_{50}) value for male rats is about 110 mg/kg, and its percutaneous LD_{50} value, applied as a solution in xylene, is 2500 mg/kg. The large difference between the two values shows that absorption through the skin is slight, while that through the gastro-intestinal tract is much greater, depending on the particle size, the solvent and the content of the gastro-intestinal tract. According to the investigations of Bordás (1962), the toxicity of DDT preparations is also strongly influenced by the mode of formulation. The toxicity of dust preparations is

lower than it would be expected on the basis of the percentage active substance content because DDT adsorbed on the carrier dust is resorbed to a much lesser extent in the intestines.

DDT attacks the central nervous system. Acute poisoning is manifested by vertigo (imbalance) which may be followed by spasms and nausea. In the case of grave and prolonged poisoning, myocardial, hepatic and renal lesions may occur.

However, compared to its relatively moderate acute toxicity, a decidedly more dangerous property of DDT is its ability to cumulate in several organisms, including human; this is connected on the one hand with its lipoid solubility, and on the other hand with its chemical stability. Unchanged DDT or its metabolites may pass through the food chain into the body tissues. Owing to its mentioned lipoid solubility, it accumulates mainly in the fatty tissues. In cases when the organism is forced to utilise its fat reserves, accumulated DDT may cause intoxication. DDT may also accumulate in various organs, primarily in the adrenal glands, the spleen and the liver (Kavadia and Phillips, 1972; Kovaleva and Talanov, 1972). Measurements carried out in the period from 1965 to 1970 in various countries showed that human fat contained the following amounts of *p,p'*-DDT (mg/kg): New Zealand 0, The Netherlands 0.32, UK 0.52, Denmark 0.60, FRG 1.10, Italy 1.46, Canada 1.56, Australia 2.50, USA 2.30–4.8, Hungary 5.57, Israel 8.20 (Abbot *et al.*, 1972).

Fitzhugh and Nelson (1947), Kemény and Tarján (1966), Innes *et al.* (1969) published data on the carcinogenic effect of DDT and its metabolites. However, these results were not supported by thorough checking tests (Tomatis *et al.*, 1972; Jukes, 1970).

The chemical stability of DDT and the established, alleged or expected drawbacks arising from its application have resulted in extensive and often excited discussions between supporters and opponents of the restriction in the use of DDT. Those defending restriction see considerable danger in the contamination of the human environment and in the disturbance of the balance of nature, as well as the direct toxicological misgivings already mentioned. DDT passes through the food-chain into the organisms of the carnivores, being at the peak of the food pyramid, endangering the reproduction of animals, especially of birds. DDT accumulates in ocean waters, reducing the photosynthesising ability of algae, and thereby the oxygen content of the atmosphere (Hickey and Anderson, 1968; Wurster, 1968; Porter and Wiemeyer, 1969; Bitman *et al.*, 1969; Risebrough *et al.*, 1968; Woodwell *et al.*, 1971; Lee *et al.*, 1976).

According to Kenaga (1972) the degree of bioconcentration of DDT and its stable transformation products depends on the temporary equilibrium of residue concentration reached initially by adsorption on organisms in competition with parts of the environment, and by redistribution, partitioning and elimination.

Opponents of DDT restriction counter these arguments by stressing the sanitarian and dietetic importance of DDT, and their reservations with respect to test methods and evaluation of the results (Jukes, 1974; Claus and Bolander, 1974). The experiments of Waibel (1972) and others seem to refute earlier publications

according to which DDT causes thin egg-shells of birds and other disturbances of reproduction. Melnikov (1974) found that though DDT is toxic to fish, its saturated aqueous solution contains only 0.001 mg/l of DDT, which is less than the toxic concentration. According to Wilson *et al.* (1970) the half-life of *p,p'*-DDT in seawater is 17 days and, in 40 days, DDT and its decomposition products practically disappear.

Nevertheless, reservations against excessive application of DDT are justified. The mere presence of DDT and its metabolites in the organism may be considered as a potential source of later chronic effects and genetic harm. Therefore, efforts and legal measures to keep the use of DDT within rational limits dictated by absolute necessity are justified. One manifestation of this concept is that the use of DDT against parasites of lactating animals and flies in stables is prohibited in several countries because DDT, as mentioned, is secreted in milk. Similarly, DDT may be present in the eggs, meat or fat of poultry which have been treated perorally against endoparasites. These reasons induced the authorities of several countries — among the first those of Sweden and Hungary — to ban or greatly restrict the use of DDT and other chlorinated hydrocarbon insecticides. In the Federal Republic of Germany following the prohibition of the use of DDT in vegetable culture in 1971, the residue of the substance in the soil diminished to about one-tenth of that present in 1969 (Fricke, 1972). In Hungary, during the five years following the restriction of the use of DDT, DDT residues disappeared completely from foods of plant origin. However, at the end of the same period, the DDT content of foods of animal origin still amounted to one-fifth to one-third of the earlier quantity (Cieleszky and Soós, 1974) which is not easy to explain.

In warm-blooded organisms, *p,p'*-DDT is metabolised to *p,p'*-DDD **(4)** by the microflora of the gastro-intestinal tract (Braunberg and Beck, 1968; Guenzi and Beard, 1967; Johnson *et al.*, 1967; Fries *et al.*, 1969). The conversion is mostly a single step reductive dechlorination without the intermediate formation of DDE **(6)** (Plimmer *et al.*, 1968). In warm-blooded organisms, DDD is further metabolised to 2,2-bis(*p*-chlorophenyl)acetic acid **(7)** and its glycine and alanine conjugates. Owing to their water solubility these compounds are partly excreted with urine, and partly converted to the metabolite 2,2-bis(*p*-chlorophenyl)ketone, which is insoluble in water (Jukes, 1972; Wallcave *et al.*, 1974).

A similar degradation by the action of soil bacteria and other microorganisms has also been observed (Focht and Alexander, 1970; Smith and Parr, 1972; Glass, 1972).

The metabolic stability of DDT is mainly due to the two chlorine atoms in the *para*-position. In the absence of either one or both of the chlorine atoms, the aromatic ring is oxidatively broken by aerobic microbial action (Focht and Alexander, 1971).

In the case of technical DDT, allowance has to be made for the oestrogen activity of the *o,p'*-isomer **(2)** present as an impurity. The geometrical similarity of the structure of compounds of the DDT type and that of synthetic oestrogens made it obvious that a similarity of action should also be investigated (Bitman *et al.*, 1968;

Welch *et al.*, 1969; Cecil *et al.*, 1971). After the discovery of the oestrogen action of *o,p'*-DDT, Bitman and Cecil (1970) established in their comparative investigations that those diphenylmethane and diphenylethane derivatives have an oestrogen action in which at least one of the two *p*-positions is unsubstituted or carries a hydroxy or a methoxy substituent. A further factor connected with bioactivity is that *o,p'*-DDT has two enantiomeric forms (McBlain *et al.*, 1976; 1977).

In the organism of chickens, *o,p'*-DDT is converted to metabolites in which the benzene ring containing the *o*-chlorine atom also contains a hydroxy or methoxy group in position 3 and/or 4 (Feil *et al.*, 1975).

The tolerance values for DDT, i.e. the maximum residue quantities in ppm concentrations for the application of various insecticides, thus also of DDT, have been fixed in the form of statutory decrees or recommendations.

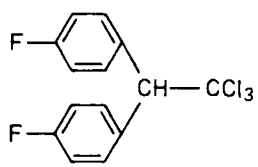
The tolerance values for DDT, i. e. the maximum residue quantities in ppm permissible in food, vary in different countries, ranging in general between 0 and 7 ppm.

The pre-harvest interval, i. e. the minimum period to be observed between treatment and harvest, is very long in various countries, owing to the high chemical stability of DDT. For example the prescribed pre-harvest interval in the UK is 14 days, in Austria 35 days, in Belgium 28 days, in the USA for fruit 30 days and for greenhouse vegetables 5 days, in The Netherlands 28 days, in Hungary, in general, 30 days but for vegetables 21 days, and for cherries 14 days. These differences show that there is great diversity of opinion. In spite of its toxicological and environmental hazards, DDT remained one of the most important insecticides against vectors of many tropical diseases, such as malaria, yellow fever, spotted typhus and others.

Since the discovery of DDT several hundreds of related derivatives have been prepared, partly to clarify the relationship between action and structure and partly to develop compounds with more advantageous properties. However, none of these compounds were found to have a real advantage over DDT that would justify attaching to it a similar importance. Therefore, their application remained limited.

The compound 2,2-bis(*p*-fluorophenyl)-1,1,1-trichloroethane (DFDT, **17**) prepared by the condensation of chloral and fluorobenzene is, like DDT, a compound of high lipoid solubility. It is rarely used in plant protection, but rather against flies and lice. Its use is rather restricted, mainly owing to the high price of fluorobenzene (Bradlow and Vanderwerf, 1947).

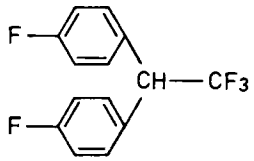
If the chlorine atoms of the trichloromethyl group are gradually exchanged by fluorine atoms, the lipoid solubility of the compound and, at the same time, its



17

insecticide efficiency decrease, so that 2,2-bis(*p*-fluorophenyl)-1,1,1-trifluoroethane (fluor-DDT, **18**) is, in practice, already an inactive compound.

2,2-bis(*p*-methoxyphenyl)-1,1,1-trichloroethane (DMDT, methoxychlor, **19**), prepared by the condensation of chloral and anisole, attained somewhat greater importance. It was developed by Läuger, Martin and Müller (1944). Its advantage over DDT is its lower toxicity to warm-blooded organisms. Moreover, it does not accumulate in these organisms because it is metabolised both in warm-blooded organisms and in insects under O-demethylation to the hydrophilic *p,p'*-bis-hydroxy derivative possessing an LD_{50} 5000–7000 mg/kg for rats. Its lower toxicity and reduced chemical stability, compared to DDT, allowed the tolerance of higher residue values (in general, 10–14 ppm) and shorter pre-harvest intervals (7–14 days). Its insecticide efficiency is lower than that of DDT (Martin and Wain, 1944; Siegler and Gertler, 1944; Prill *et al.*, 1945; Kapoor *et al.*, 1970).



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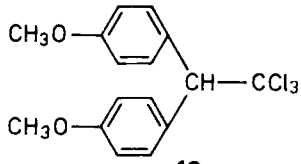
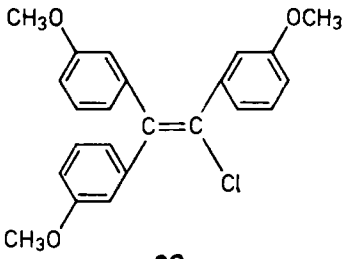


19

The commercial product contains hydrocarbon-type impurities due to further Friedel–Crafts arylation of methoxychlor during manufacture such as **20** and **21.** Photo closure of **21** yields the phenantrene **22,** which on further oxidative closure gives the dibenzochrysene **23** (Mitchell and West, 1978).



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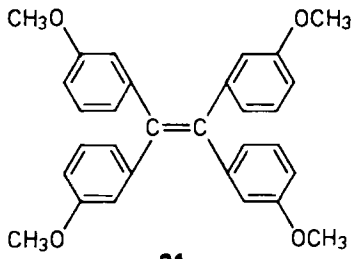

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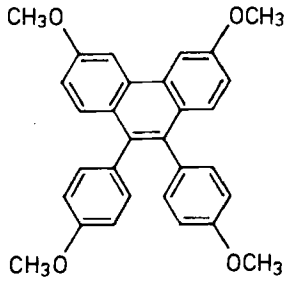

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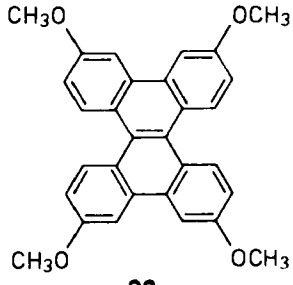
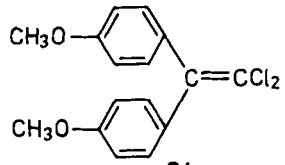


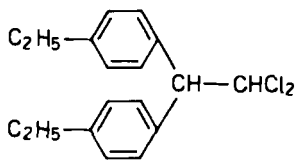
23

Zepp and co-workers (1976) found that photolysis of methoxychlor, although much more rapid than that of DDT, is still a very slow environmental process. The major product of light-induced transformation is 1,1-bis(*p*-methoxyphenyl)-2,2-dichloroethylene (DMDE, **24**). This product is subject to rapid photodegradation in both aqueous and hydrocarbon media.



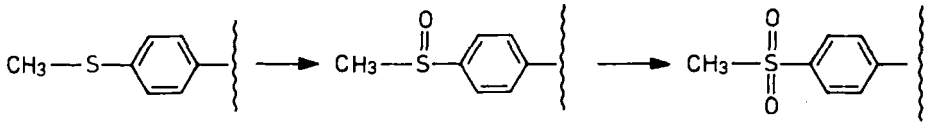
24

The compound 2,2-bis(*p*-ethylphenyl)-1,1-dichloroethane (perthane, **25**) obtained by the condensation of ethylbenzene with dichloroacetaldehyde is also characterised by its low toxicity to warm-blooded organisms (Anonym, 1953). $LD_{50} = 8170$ mg/kg for rats.



25

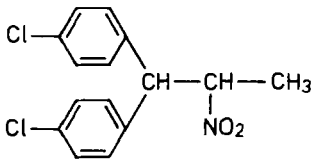
In order to investigate biodegradability, Kapoor, Metcalf and their co-workers (Kapoor *et al.*, 1970; 1972; 1973; Metcalf *et al.*, 1971) prepared several symmetrically and asymmetrically substituted DDT analogues which contain methyl, methoxy, ethoxy and methylmercapto groups in the *para*-position of the aromatic rings. Compared to DDT, all derivatives revealed a high biodegradability; the highest being those containing methylmercapto groups. The rapid detoxification and excretion of these derivatives is caused by the fact that the methylmercapto group is oxidised first to the sulfoxide, then to the sulfon group:



Thus, the methoxy groups of methoxychlor **(19)**, the two ethyl groups of perthane **(25)** and the methylmercapto groups of the derivatives mentioned above, are vulnerable groups, exposed to biodegradation (degradophores). In the course of their enzymatic oxidation, they are converted to hydroxy, carboxy and sulfo-groups, respectively, and due to their higher water-solubility these polar,

hydrophilic metabolites are easily excreted (Dahn, 1957; Riemschneider, 1958; Ariëns, 1971; Kapoor *et al.*, 1973).

The product known as Dilan is a 1 : 2 mixture of 2,2-bis(*p*-chlorophenyl)-1-nitropropane (DNP, prolan, **26**) and 2,2-bis(*p*-chlorophenyl)-1-nitrobutane (DNB, bulan, **27**), and is very sensitive to alkaline and oxidative actions. It is prepared by condensation of *p*-chlorobenzaldehyde and the corresponding nitroalkane (Hass and Blickenstaff, 1950).



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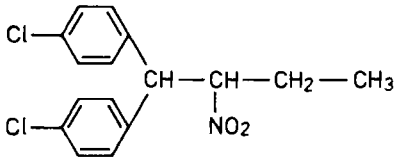
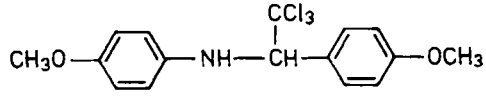


27

As may be concluded from their structure, prolan and bulan are not sensitive to the DDT-dehydrochlorinase enzyme.

Hirwe *et al.* (1972) and Miller *et al.* (1974), giving an ingenious example for molecule modification based on theory, attempted to reduce the persistence of DDT type insecticides. They based their investigations on the fact that aromatic amines, excited by light absorption, may cause photochemical decomposition of organo-chlorine compounds. According to their findings, DDT decomposes under the action of light of 310 nm wavelength in the presence of diethylaniline as photosensitiser. Incorporating the photosensitising group in the methoxychlor **(19)** molecule, they prepared N-(α-trichloromethyl-*p*-methoxybenzyl)-*p*-methoxyaniline **(28)**, which proved to have a similar effect as DDT, but less persistent. During its photochemical conversion, the degradation products as well as, e.g. the 2-hydroxyamide of structure **29** and the 2-oxoamide of structure **30** are formed.



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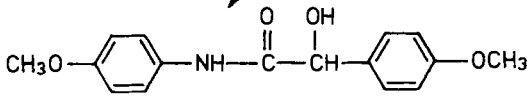

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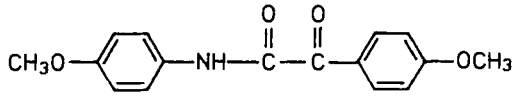
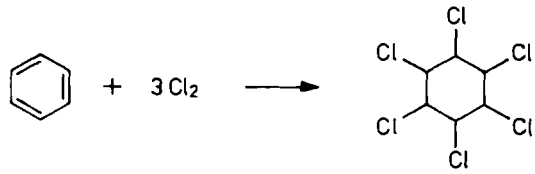


30

1.3.2 Hexachlorocyclohexane

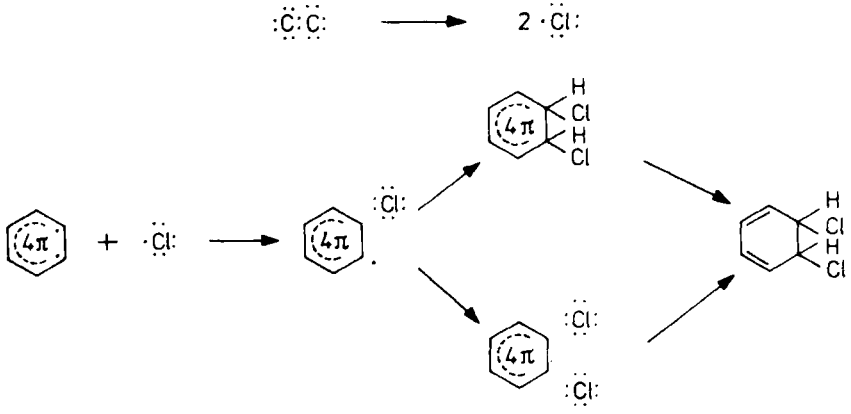
As early as 1825 Faraday prepared the addition product of benzene and three molecules of chlorine, formed in sunlight. From this product, which contains various isomers of hexachlorocyclohexane (benzenehexachloride, BHC, **31**), Linden was the first to isolate the single isomers in 1912. In 1936, Bender discovered the insecticidal properties of hexachlorocyclohexane and took out a patent. However, his important discovery attracted little attention at the time, so that rediscovery of the insecticidal properties of hexachlorocyclohexane, and its application as an insecticide took place only at the beginning of the 1940s, and was the work of several research groups working independently (Dupire and Rancourt, 1943; Slade, 1945; Haller and Bowen, 1947). The important discovery that, among the various isomers formed, the γ-isomer of BHC (**31a**) is the carrier of insecticidal properties is linked with the name of Thomas (Slade, 1945).



31

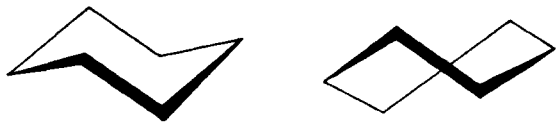
A number of different methods for the manufacture of BHC are known, all of them being based on an additive chlorination of benzene under the influence of ultraviolet light or in the presence of a chemical activator.

Free radicals formed in the cleavage of unstable compounds (e.g. sodium hypochlorite, boron trichloride and organic peroxides) may serve as chemical activators. Ultraviolet light used in photocatalytic processes and the chemical activators are used to shift the chlorination reaction from substitution to addition, and ultimately to furnish the energy necessary for homolysis of the chlorine



molecule. The chlorine atom thus formed disrupts the π-electron sextet of the benzene ring to form a common orbital with its own electron. The free chlorophenyl radical then either collides with another chlorine atom or initiates a chain reaction by homolysis of another chlorine molecule. Dichlorocyclohexadiene—which is already more easily activated than benzene with its π-electron sextet—is formed, so that additive chlorination proceeds according to the previous reaction mechanism, but already considerably accelerated, until the formation of BHC (Schwabe and Rammelt, 1955).

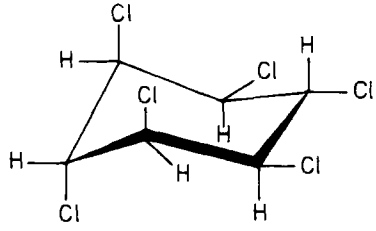
The unsubstituted cyclohexane has two strainless conformations: the chair (*C*) and the twisted boat (*TB*) forms (Barton, 1970). The chair form possesses the higher stability, due to the absence of both Baeyer tension and Pitzer tension.



chair form twisted boat form

*cyclo*hexane conformers

Considering these two modifications, hexachlorocyclohexane could have 17 stereoisomer forms, depending on the position of the chlorine atoms. However, owing to the high steric requirement of the chlorine atoms and for energetic reasons, only the chair conformation is stable, so that the number of possible isomers is restricted to eight (Hassel and Ottar, 1942; 1950; Orloff, 1954). In technical BHC, from these eight isomers five are present in detectable quantities. In the biologically mostly active γ-isomer **(31a)**, formed in the isomer mixture at a ratio of about 8–15%, three of its six chlorine atoms have an axial (*a*), and three an equatorial (*e*) orientation (*aaaeee*).



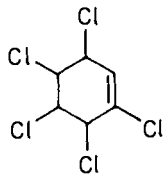
31a

The configurations of the additional isomers are as follows:

β-isomer:	*eeeeee*	ε-isomer:	*aeeaee*
δ-isomer:	*aeeeee*	η-isomer:	*aaeaee*
α-isomer:	*aaeeee*	ζ-isomer:	*aeaeae*
ϑ-isomer:	*aeaeee*		

In addition to the hexachlorocyclohexane isomers, technical BHC also contains hepta- and octachlorocyclohexane isomers as a result of the additive chlorination of monochlorobenzene and dichlorobenzenes, formed as by-products in the reaction.

The technical BHC isomer mixture is a grey or brownish amorphous product. It melts gradually at temperatures above 65°C. Owing to its pungent taste and penetrating, mouldy odour, the odour and taste of products originating from treated areas are adversely affected. Presumably, these changes are not caused by the BHC isomers, but by their decomposition products, primarily pentachlorocyclohexene **(32)** and tetrachlorocyclohexadiene **(33)**, formed by the loss of hydrochloric acid.



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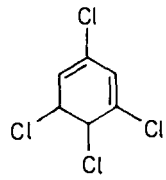


33

The single BHC isomers differ substantially from one another with respect to their solubility in organic solvents. This enables their separation by fractional crystallisation and fractional extraction. Subsequent determination of the structure of the isomers was established by X-ray diffraction, electron diffraction and spectrophotometric methods, on the basis of differences in their dipole moments and chemical reactions, and by theoretical considerations (Orloff, 1954; Bastiansen and Hassel, 1947; Whitney and Corvin, 1949; Bastiansen *et al.*, 1949; Hassel and Ottar, 1950; Hughes *et al.*, 1953).

Table 1.1 shows the percentage composition of technical BHC based on the investigations of Slade (1945), Ramsey and Patterson (1946), and Riemschneider (1952).

Table 1.1
Percentage composition of technical BHC

Compound	Melting point, °C	Composition % according to		
		Ramsey and Patterson	Slade	Riemschneider
α-hexachlorocyclohexane	159–160	65–70	up to 70	55–80
β-hexachlorocyclohexane	309–310	5–6	5	5–14
γ-hexachlorocyclohexane	112–113	13	10–12	8–15
δ-hexachlorocyclohexane	138–139	6	7	2–16
ε-hexachlorocyclohexane	219–220	0	0	3–5
heptachlorocyclohexane	85–86	4	—	—
octachlorocyclohexane	147–149	0.6	—	—

Comparative studies of the individual isomers on various insects revealed that the γ-isomer is 50–10 000 times as active as the α- and δ-isomer, depending on the insect species, while the β- and ε-isomers are practically inactive.

Much effort has been made to substitute the BHC isomer mixture, revealing a number of undesirable side effects, for the γ-isomer which was to be almost or completely free from other isomers. These attempts were not only made because in practice, among the isomers contained in the raw product only the γ-isomer is active, but also because the lowest rate of by-products causing changes in taste are formed from this isomer. Separation of the γ-isomer is also important from the viewpoint of human toxicology because on the one hand it considerably decreases the total quantity of BHC used, and on the other hand, the β-isomer, which is without insecticidal effect, accumulates most easily in various organisms (Rosival and Szokolay, 1974). According to the investigations of Kido and Watanabe (1979), among BHC isomers absorbed in the body of silkworm larvae, the β-isomer reached the highest concentration in all tissues and also the highest rate of concentration in tissues versus concentration in the haemolymph.

Separation of the γ-isomer, the so-called gamma-enrichment, can be achieved in various ways based on multistep extraction with methanol. The α- and β-isomers form the largest part of technical BHC and are almost insoluble in methanol. The γ-isomer can be separated from the isomers remaining in the methanolic solution and purified by recrystallisation from chloroform. Obtaining a gamma-concentrate containing 50–60% of γ-isomer is relatively simple, while the preparation of a product of 99% purity (lindane) requires a more elaborate purifying operation.

The BHC γ-isomer is an odourless, crystalline compound. At room temperature its solubility in water is 10 ppm; it is slightly soluble in mineral oils, and readily soluble in acetone, aromatic and chlorinated solvents. It is not attacked by mineral acids but is sensitive to alkaline action and is converted by elimination of 3 molecules of hydrochloric acid to 1,3,4-trichlorobenzene.

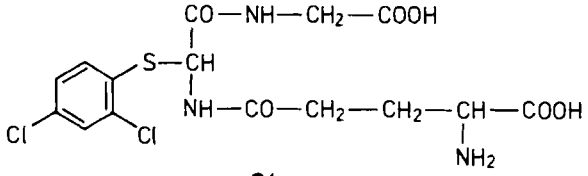
As with DDT, poisoning caused by BHC is manifested in insects by tremor, ataxia and spasms, followed by paralysis. However, these effects occur more rapidly than in the case of DDT because of the great volatility of lindane, and the gas effect connected with it. Initially, respiration is greatly augmented, up to five times the normal rate, but then decreases gradually with the onset of paralysis. γ-BHC taken up by the insect organism is translocated first through the heamolymphs, and secondly through the nerve tissues.

Its mode of action is unknown. The theory of Slade (1945) according to which the γ-isomer exerts its action as the antimetabolite of hexahydroxycyclohexane (*meso*-inositol) of identical steric structure, present in the organism of certain microorganisms and mammals, could not be upheld in the light of recent experimental results. It has been made clear by recent structural investigations that the steric structure of *meso*-inositol is not identical with that presumed earlier. Its presence in the insect organism is of no importance and, moreover, the effect of BHC cannot be counteracted by the administration of *meso*-inositol.

From the results of molecular orbital calculations, Block and Newland (1974) established that among the various isomers of BHC, the most bioactive γ-isomer is also the best electron acceptor. It may be assumed, therefore, that biological activity can be explained on the basis of disruption of electron transfers taking place in the metabolic process of mitochondria.

The spectrum of insecticidal action of BHC is very wide as it includes almost all insects, whether sucking or chewing. It acts both as a contact and a stomach poison, and owing to its volatility also as a fumigant.

Houseflies can metabolise γ-BHC. In the case of resistant fly strains this metabolism is more rapid than it is for susceptible ones. In the first step of metabolism 2,3,4,5,6-pentachlorocyclohex-1-ene **(32)** is formed, which is then converted to conjugates. S-2,4-Dichlorophenyl-glutathione **(34)**, formed in the course of the dehydrochlorination of a conjugate, could be isolated from treated insects. Other metabolites are 1,2,3-trichlorobenzene, 1,2,4,5- and 1,2,3,4-tetrachlorobenzene and pentachlorobenzene (Oppenoorth, 1954; Bradburg and Standen, 1959; Clark *et al.*, 1966; Reed and Forgash, 1968; 1969; 1970).



34

The vapour tension of γ-BHC is high, compared to that of other chlorinated hydrocarbon insecticides, being $4.45 \cdot 10^{-3}$ Pa at 20°C (Spencer and Cliath, 1970). When used as a spray or powder, this high volatility gives a high knockdown effect but might be disadvantageous because it results in a short-duration action. Therefore, BHC is often combined with DDT because the potent and rapid effect of BHC and the weaker but longer lasting action of DDT are complementary.

At the same time, the volatility of BHC makes this compound ideal for use as a soil insecticide against such soil pests as may-beetle larvae and wireworms. When incorporated into the soil, BHC not only acts by direct contact with soil pests, but also in the air space among the soil particles.

γ-BHC is moderately phytotoxic. Bogdarina (1961) investigated its effect on plants and found that it decreased the photosynthesis of young wheat plants by 25%. However, after 18 days, the intensity of photosynthesis increased to twice that of the control. The carbohydrate metabolism of plants is also changed by treatment with BHC, and is largely manifested in an increase in monosaccharide content.

For humans and warm-blooded animals technical BHC is a weaker, and the γ-isomer a stronger poison than DDT. The oral LD_{50} value of γ-BHC for rats is 150–230 mg/kg (Riemschneider, 1958). The acute oral LD_{50} value of the technical BHC-isomer mixture for mammals is, in general, about 100 mg/kg. Values for the

single isomers measured in rats are as follows: α 500, $\beta > 6000$, γ 125, δ 1000 mg/kg (Lehman, 1948; Barnes, 1953). It can also be resorbed through the skin where it causes inflammation. When swallowed, it induces headache and nausea. Acute poisoning may be manifested by disturbance of senses, vertigo and tremor, in graver cases by convulsions, unconciousness, pulmonary oedema and paralysis of the nervous system. Important are the numerous later observations about the selective cumulation and different chronic effects of the BHC isomers in warm-blooded animals and thus as potential environment polluting factors.

In warm-blooded organisms, usually the metabolites isolated from insects and 2,3,5- and 2,4,5-trichlorophenol and their conjugates appear after treatment with γ-BHC. The enzymes which catalyse the degradation of BHC, and which can be activated with glutathione, seem to be identical with those catalysing the dehydrochlorination of DDT (Woodard *et al.*, 1948; Bridges, 1959; Grover and Sims, 1965; Ishida and Dahm, 1965).

As BHC is toxic to fish, its application in the vicinity of open waters (i.e. rivers and lakes) is regulated in several countries.

The BHC content of vegetables treated with BHC can be substantially decreased by boiling in water or in 1% acetic acid (Visweswariah and Jayaram, 1972).

1.3.3 Chlorinated terpenes

On chlorinating camphene (**35**) to a chlorine content of 67–69%, a yellowish, waxy product is obtained; it has a slight odour of terpene and melts at 65–90°C. The product of the elementary composition $C_{10}H_{10}Cl_8$ (**36**) became known as an insecticide under the name toxaphene.

35 **36**

According to Parker and Beacher (1947), toxaphene is a mixture of the isomers of octachlorocamphene. Investigations by Casida *et al.* (1974) revealed that the product is a mixture of at least 175 polychlorobornanes, each containing 6, 7, 8 or 9 chlorine atoms. Using ^{36}Cl and ^{14}C labelled toxaphene, it has been proved that about half of the carbon–chlorine bonds are metabolically labile and that most of the components contain biodegradable sites.

The volatility of toxaphene is low, its vapour tension being $1.33 \cdot 10^{-4}$ Pa. Under the influence of alkalies, continuous light, or temperatures above 155°C, it loses one molecule of hydrochloric acid and forms a product devoid of insecticidal activity.

In the insect organism toxaphene is translocated primarily by the haemolymphs. It affects cardiac function and oxygen consumption and acts as a stomach and contact poison; its effect is of long duration.

From the ecological point of view, an important property of toxaphene is that of the insecticides used at present, it is the least toxic to bees. Additionally, its terpene-like odour is repellent to bees, so that it is recognised as a substance which does them little harm and can thus be used on plants in bloom.

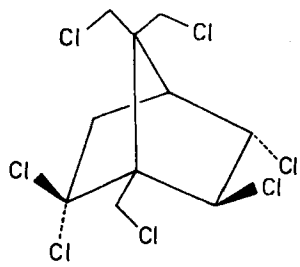
Initially, it strongly increases the carbon dioxide production of plants, but subsequently the intensity of respiration gradually returns to normal.

Toxaphene is a moderate poison to warm-blooded organisms. Its LD_{50} value, measured in male rats on oral administration is 69 mg/kg and on dermal administration 1075 mg/kg. It is absorbed through the epidermis and has a local irritating effect. The poisoning pattern following peroral application is similar to that of other chlorinated hydrocarbon insecticides, manifesting itself in convulsive and tetanic spasms and in symptoms similar to those of epilepsy. As in DDT, it accumulates in the fatty tissues and it is secreted in milk (Gruch and Steiner, 1960).

According to Casida *et al.* (1974), the toxicity to warm-blooded organisms can presumably be attributed mainly to two components: one is 2,5-*endo*-2,6-*exo*-8,9,10-heptachlorobornane (**37**), and the other an octachlorobornane of an as yet unidentified structure. According to these authors, these two components are responsible for the neurotoxic action of toxaphene, as the relative steric positions of the chlorine atoms meet the structural requirements of this effect.

Toxaphene is one of the chlorinated hydrocarbon insecticides most toxic to fish. A concentration of 0.0056 ppm in a goldfish pond killed 70% of the fish.

In rats it undergoes reductive dechlorination resulting in a cleavage on one of the two chlorine atoms of the geminal dichloro group (Saleh and Casida, 1978).



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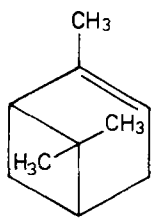


39

$\longrightarrow$ $C_{10}H_{11}Cl_7$

38

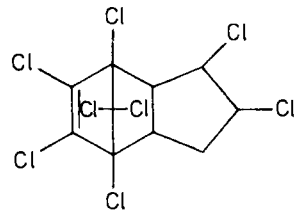
A product strobane, **38** similar to toxaphene is formed when camphene **(35)** and pinene **(39)**, forming the main component of turpentine oil, are chlorinated to a chlorine content of 66%. The empirical formula of this product is $C_{10}H_{11}Cl_7$.

Strobane is a waxy, yellowish product with a weak aromatic smell. It is practically insoluble in water and readily soluble in most of the organic solvents. However, it is not decomposed by boiling water and is sensitive to alkali reagents.

1.3.4 Cyclodiene derivatives

One of the most important groups of chlorinated hydrocarbon insecticides is formed by the compounds belonging to the diene group. These compounds can be prepared by the diene synthesis linked with the names of Diels and Alder (1928). In the synthesis of the diene insecticides, hexachlorocyclopentadiene **(40)** is used as the 1,3-diene partner, and various ring systems as the dienophylic partner, the single members of the group differing from one another in relation to this latter partner.

The first member of the group to be developed was chlordane **(41)** which has been synthesised simultaneously in the USA and in the FRG (Riemschneider and Kühnl, 1948; Hyman, 1945; Riemschneider, 1950; Kearns *et al.*, 1954).

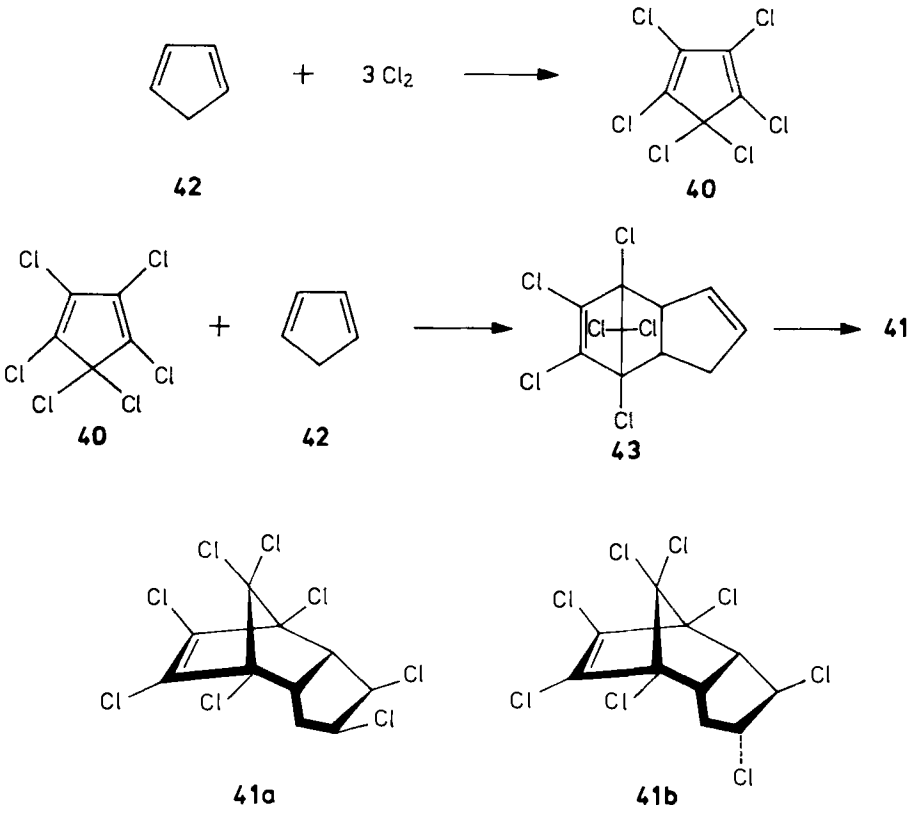


41

Chlordane is prepared by reacting hexachlorocyclopentadiene **(40)** formed as the main product in the chlorination of cyclopentadiene **(42)** with hypochlorite or in the high temperature chlorination (470°C) of pentane, neopentane or cyclopentane with cyclopentadiene (Diels–Alder reaction), and chlorinating the 4,5,6,7,8,8-hexachloro-4,7-methano-3a,4,7,7a-tetrahydroindene (chlordene, **43**) yielded by this reaction until two additional chlorine atoms are absorbed, obtaining 4,7-methano-1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydroindane **(41)** as the final product.

While chlordene **(43)** has only a weak insecticidal effect, the efficiency of chlordane **(41)**, which contains two more chlorine atoms, is 300 times greater, indicating that the efficiency of insecticides of the cyclodiene type is highly structure-specific. Even slight modifications of the molecule greatly affect the efficiency.

The steric structure of the compounds is also of great importance from the activity viewpoint. From the two possible stereoisomers (Büchel *et al.*, 1966), only β-chlordane **(41a)** of 1-*exo*-2-*exo* structure has a strong insecticidal effect while its stereoisomer, α-chlordane of 1-*exo*-2-*endo* structure **(41b)**, is considerably weaker (March, 1952).



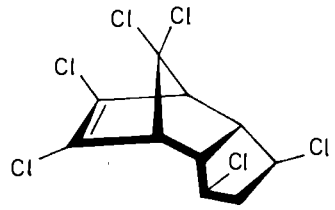
The technical product contains 60% of β-chlordane and 25–40% of other chlorinated cyclopentadiene derivatives, including heptachlor **(44)** (Riemschneider, 1950; March, 1952). It is a yellow or brown viscous liquid smelling slightly of camphene. The technical product is very sensitive to alkali action, and the presence of iron compounds may accelerate decomposition.

Chlordane is moderately phytotoxic, therefore an overdose may damage, and, in particular, scorch young plants.

It exerts its insecticidal action as a contact, respiratory and stomach poison, and is used against both chewing and sucking insects and soil pests. It also has an acaricidal effect.

Several structural isomers of chlordane have been prepared by various reactions. These differ mostly in the position and orientation of the chlorine atoms attached to the cyclopentane ring. Among all the derivatives, including also β-chlordane, δ-chlordane **(45)** is the most efficient and thus is a frequent component of the technical product (Büchel *et al.*, 1966).

In relation to the acute effect of chlordane, it belongs to the group of insecticides moderately toxic to warm-blooded organisms, its acute oral LD_{50} value being



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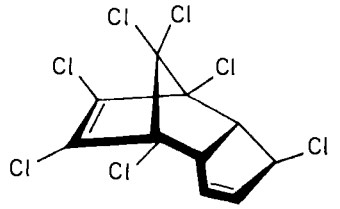
460–590 mg/kg for rats. At the same time it has a considerable chronic toxicity. Therefore, in most countries, the maximal permitted residue in various foodstuffs is very low, generally 0–0.3 mg/kg.

In warm-blooded organisms it is converted to hydrophylic metabolites. During this metabolisation, one or both chlorine atoms of the cyclopentane ring are exchanged for hydroxyl groups (Ludwig, 1966; Poonawalla and Korte, 1971; Barnett and Dorough, 1974). Owing to their water-solubility, these metabolites are excreted with urine from the organism. Similarly, hydrophylic metabolites are also formed in the organisms of insects (Korte, 1966).

Of the various components of technical chlordane, 1,4,5,6,7,8,8-heptachloro-4,7,-methano-3a,4,7,7a-tetrahydroindene of structure **44** (heptachlor) proved to be the most efficient (Kearns *et al.*, 1949; March, 1952). An independent method of preparation was discovered by Hyman (1945), Herzfeld and Ordas (1951) and others. The starting material is chlordene **(43)** which, on chlorination, yields heptachlor either directly or by the intermediate formation of 1-hydroxy-, 1-acetoxy- or 1-bromo-chlordene.



44

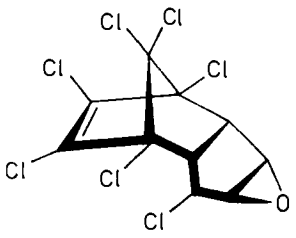
As an insecticide its efficiency is four to five times as great as that of chlordane, and it is also potent against some insect pests, against which chlordane has little effect.

The technical product contains about 67% heptachlor and 33% related compounds, including α-chlordane. It is sensitive to heat, light, moisture, acids, alkalies and oxidative action.

In the insect organisms, it is metabolised to the heptachlor epoxide of structure **46.** Heptachlor epoxide is more active than the parent compound, therefore this

conversion is a typical example of bioactivation (Davidow and Radomski, 1953; Brooks, 1966; Soloway, 1965).

The toxicity of heptachlor to warm-blooded animals is about four to five times that of chlordane, its peroral LD_{50} for rats being 90–135 mg/kg. It is thus a relatively toxic insecticide. As in insects, heptachlor epoxide (**46**) is formed which is more toxic also to warm-blooded organisms, than heptachlor (Davidow and Radomski, 1953; Mitchell, 1963). According to Korte and associates heptachlor epoxide is further converted to hydrophylic metabolites, including the 1-hydroxy derivative **47** (Bunyan *et al.*, 1966; Lichtenstein and Schulz, 1960; Kaul *et al.*, 1970a; 1970b).



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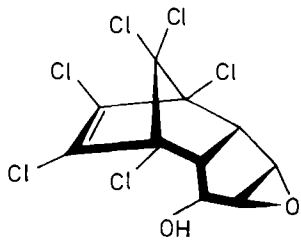

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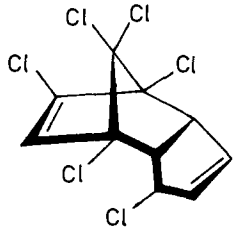
According to the evidence of continuous feeding experiments to rats, maximum accumulation of heptachlor is reached after 2–4 weeks. Heptachlor is not permitted on the feed of lactating animals as it causes heptachlor epoxide to appear in the milk. Because of this a residue value of 0 ppm has been prescribed in most countries.

In spite of the fact that in warm-blooded organisms chlordane and heptachlor are substantially converted to hydrophylic metabolites and are excreted in this form, accumulation in the fatty tissues is considerable. In the USA the presence of these compounds was established in 73% of the milk product investigated and in 77% of the meat and fish samples. At the same time, animal experiments showed that their carcinogenicity is probable. Therefore, the Environmental Protection Agency recommended a complete ban on the use of these insecticides in the USA.

The photochemical decomposition of heptachlor (**44**) yields through the excited singlet state the mono-dechlorination isomer pair **48** and **49**, while triplet-sensitisers (e.g. acetone) give rise through the triplet state to the formation of 2,3,4,4,5,6,10-heptachloropentacyclo-(5.3.0.$0^{2,3}$.$0^{3,4}$.$0^{3,7}$)-decane ("photo-heptachlor", **50**) (Rosen *et al.*, 1969; McGuire *et al.*, 1970; Anderson *et al.*, 1968; Henderson and Crosby, 1967; Rosen, 1967).

An important achievement in the research on insecticides of the diene group was the development of 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-*exo*-1,4-*endo*-5,8-dimethanonaphthalene (aldrin, HHDN, **51**) (Lidov, 1953). The preparation of the compound involves two Diels–Alder reactions. First, bicyclo-(2,2,1)-2,5-heptadiene (**52**) is prepared by the diene synthesis of acetylene and



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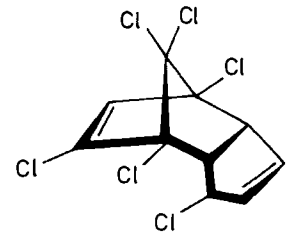

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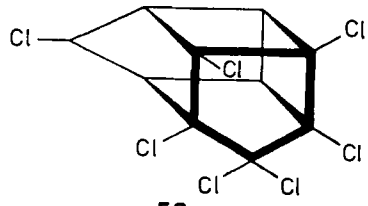

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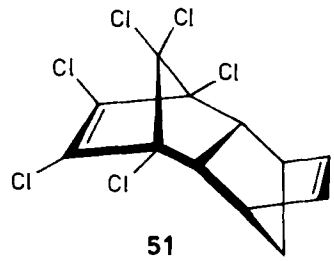

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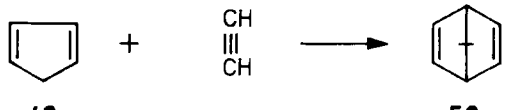
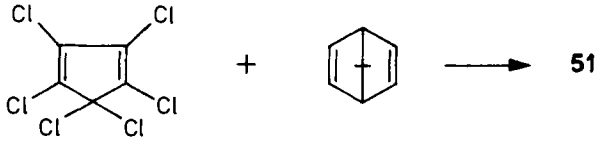
cyclopentadiene (**42**), and secondly it is then reacted as the dienophylic component with hexachlorocyclopentadiene (**40**) as the 1,3-diene component:



42 **52**



40 **52**

Pure aldrin is a white crystalline compound; the technical product is a waxy, brown substance, containing about 78–95% of aldrin in addition to other products, some of which have insecticidal properties. One part of the impurities decomposes during storage by elimination of hydrochloric acid. This decomposition can be inhibited by using acid inhibitors, for example epichlorohydrin, as stabiliser.

Aldrin is very stable to organic and inorganic acids and bases occurring in the soil. Its vapour tension is high, $8 \cdot 10^{-4}$ Pa at 25°C. Owing to its chemical stability and volatility, it can also be used as a soil insecticide. The first property ensures a lasting effect, and the second a gas effect in the air space among the soil particles.

It has a good compatibility with all the other pesticides and with fertilisers, but certain mineral substances used as carriers cause catalytic dehydrochlorination. This can be avoided by the use of inhibitors, for example urea and hexamethylenetetramine.

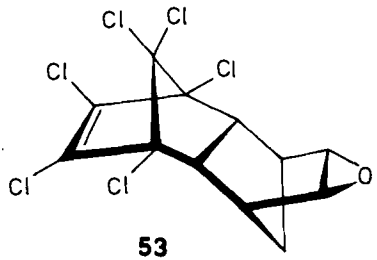
Aldrin is highly poisonous to warm-blooded organisms, its peroral toxic dose for male rats being 67 mg/kg (Steiner and Gruch, 1959). It is easily absorbed through the skin. Therefore, when handling, proper precautions must be taken to avoid contact with exposed surfaces of the body. Symptoms of acute poisoning in humans are indisposition, nausea, vomiting, headache, spasms and fainting. In the case of a lethal dose, death occurs within 24 hours. Chronic toxicity experiments on dogs showed hypertrophy of the liver and a pathological lesion of liver cells. Therefore, a maximum permissible aldrin residue of 0–0.1 ppm is mandatory in most countries, while the prescribed pre-harvest period varies in different countries, but is generally between 20 and 42 days.

Aldrin is converted in the soil, in plant, insect and warm-blooded organisms to its epoxide, dieldrin (**53**) (Winteringham and Barnes, 1955; Gianotti *et al.*, 1956; Bann *et al.*, 1956; Gannon and Decker, 1958; Gannon and Bigger, 1958). Its behaviour in warm-blooded organisms has been studied extensively by Korte, Ludwig and their associates (Korte and Rechmeier, 1962; Korte *et al.*, 1962; Korte and Stiasni, 1962; 1964; Korte, 1966; Ludwig *et al.*, 1964; Ludwig 1966a; 1966b).

On oxidising aldrin with peracetic acid or perbenzoic acid, an epoxide group is formed at the site of the double bond not substituted by chlorine atoms. The 6,7-epoxy-1,2,3,4,10,10-hexachloro-1,4,4a,5,6,7,8,8a-octahydro-*exo*-1,4-*endo*-5,8-dimethanonaphthalene formed is known by the name dieldrin (**53**, HEOD) (Soloway, 1954; 1965).

The technical product has a dieldrin content of 85%. Like aldrin it is not sensitive to alkalies but its vapour tension is lower, being $2.4 \cdot 10^{-5}$ Pa at 25°C. Unlike aldrin, it is not used as a soil insecticide because of its low volatility.

In discussing the mechanism of action of dieldrin and related cyclodiene insecticides, we are confined only to assumptions devoid of adequate experimental



53

support. On the basis of symptoms of poisoning found in insects, the action of dieldrin might be similar to that of γ-BHC and different from that of DDT. The character of the symptoms emerging in vertebrata is indicative of an effect on the central and peripherial nervous system (Gowdey *et al.*, 1952; Natoff and Reiff, 1967; Revzin, 1968; Wang *et al.*, 1971). Shankland and Shroeder (1973) concluded from their experiments on counteracting dieldrin action that it acts on the presynaptic membranes of cholinergic junctions causing the liberation of presynaptic acetylcholine reserves.

Methylenedioxyphenyl derivatives, primarily sesamex, can strongly synergise the action of aldrin, presumably by the inhibition of microsomal enzymes responsible for biodegradation (Brooks and Harrison, 1964; Brooks, 1966; 1968; Sun *et al.*, 1967; Casida, 1970; Khan *et al.*, 1970). From the viewpoint of environmental hygiene this may become important, because the application of synergists may enable the use of analogues acting in the same way as compounds used at present, but which are more rapidly decomposed (Hennessy, 1969).

Dieldrin is toxic to warm-blooded organisms, its peroral LD_{50} value for rats being 50–87 mg/kg. Like aldrin, it can easily be absorbed through the respiratory tracts, the digestive canal and the skin. Symptoms of poisoning are rapid loss of weight, loss of appetite and spastic convulsions which, in acute cases, quickly prove fatal (Hodge *et al.*, 1967).

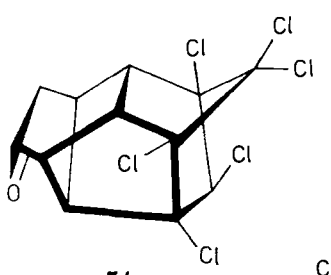
In experiments on mice, aldrin and dieldrin showed a carcinogenic effect. Although no direct conclusion regarding the danger to human beings can be drawn from these experiments, their manufacture for crop protection purposes in the United States was prohibited from October 1974 by the Environmental Protection Agency. Maximum permissible residue values for dieldrin vary, in general, between 0 and 0.1 ppm.

Dieldrin in concentrated solution or in the solid state is converted by the action of light to photo-dieldrin (**54**) of the structure 4,5-*exo*-epoxy-1,9,10,10,11-*exo*-12-hexachloro-8,3,7,6-*endo*-8,9,7,11-*exo*-pentacyclo-(7.3.0.$0^{2,6}$.$0^{3,8}$.$0^{7,11}$)-dodecane (Parzons and Moore, 1966; Robinson *et al.*, 1966; Rosen *et al.*, 1966; Harrison *et al.*, 1967). Its insecticidal action is about twice that of dieldrin. Its acute toxicity to warm-blooded organisms is also higher than that of dieldrin.

Photo-dieldrin (**54**), which is also formed by the action of sunlight on the plant surfaces treated with dieldrin, is converted in the organism of male rats predominantly to the keto derivative of structure **55**, while in the organism of female rats other, more polar, metabolites are formed (Klein *et al.*, 1970; Matthews and Matsumura, 1969).

In the presence of a hydrogen donor (e.g. hexane), in dilute solution, dieldrin is converted to the dechlorination product **56** by the action of light of <260 nm wavelength. Under similar conditions aldrin undergoes an analogous conversion (Henderson and Crosby, 1967).

The behaviour of aldrin and dieldrin — and of other insecticides of the diene group — in warm-blooded organisms has been studied by Korte, Ludwig and their co-workers using ^{14}C-labelled compounds (Korte and Rechmeier, 1962; Korte and



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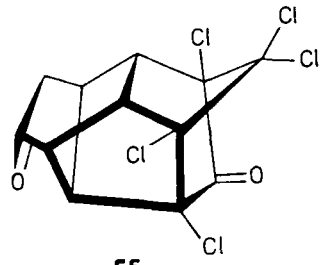

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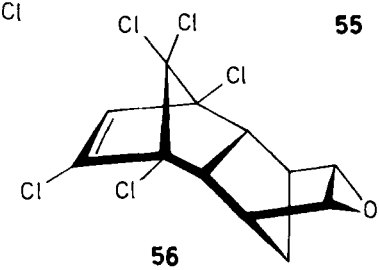
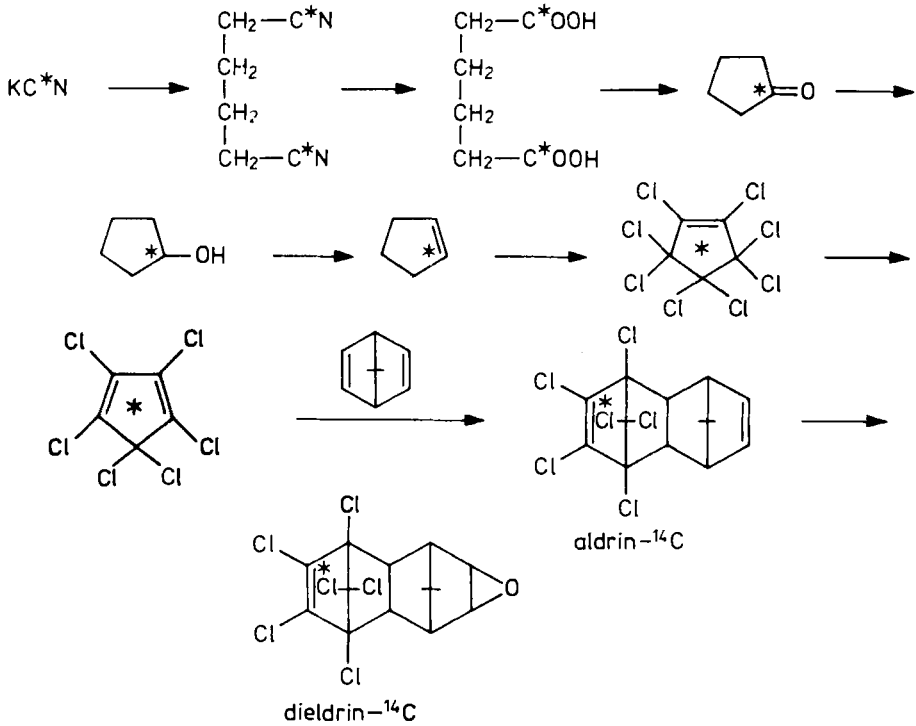


56

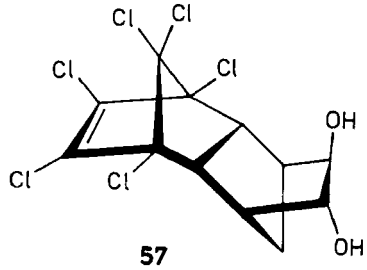
Stiasni, 1962; 1964; Korte *et al.*, 1962; Ludwig *et al.*, 1964; Ludwig, 1966a; 1966b). The synthesis of aldrin-^{14}C and dieldrin-^{14}C required for experiments with animals was carried out as shown in Scheme 1.5.



Scheme 1.5

In experiments in which animals were supplied with food containing 0.2 ppm of labelled aldrin, a saturation equilibrium was established in 50 days. Thereafter a quantity equal to the daily intake was excreted daily.

Contrary to earlier data, according to which aldrin and dieldrin accumulate in an unchanged form in warm-blooded organisms, Korte *et al.* proved that dieldrin and aldrin, after previous oxidation to dieldrin, are converted to hydrophylic metabolites. Of these metabolites, the component occurring in the largest amount was identified as one of the two enantiomorphic isomers of 6,7-(*E*)-dihydroxy-dihydroaldrin (**57**) (Korte *et al.*, 1962; Ludwig *et al.*, 1964; Mörsdorf *et al.*, 1963).



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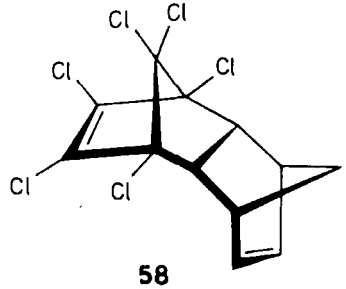
Experiments with rats showed that this metabolite is present in the urine in a quantity corresponding to 95% of the total radioactivity, and in the excrement in a quantity of 70% of the total radioactivity. Other metabolites present in smaller amounts are predominantly the as yet unidentified O-acyl derivatives of dihydroxydihydroaldrin.

The LD_{50} values of dihydroxydihydroaldrin for rats are 1250 mg/kg (oral administration) and 51 mg/kg (intravenous administration) indicating that the living organism can detoxify insecticides belonging to the diene group.

Dieldrin is toxic to fish, and because of its toxicity to warm-blooded organisms, it is also suitable for application against field-mice.

The *endo-endo* isomer of aldrin, 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-*endo*-1,4-*endo*-5,8-dimethanonaphthalene (**58**) is known by the name isodrin.

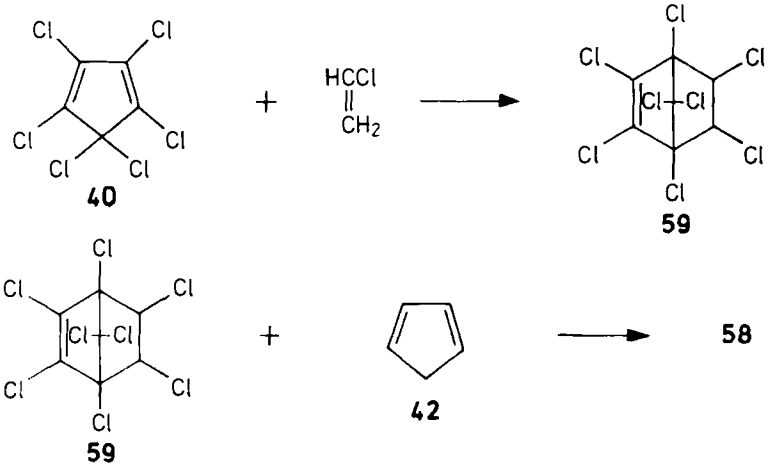
This compound is synthesised by first preparing, using the Diels–Alder reaction of hexachlorocyclopentadiene (**40**) and vinyl chloride, 1,2,3,4,5,7,7-hepta-



58

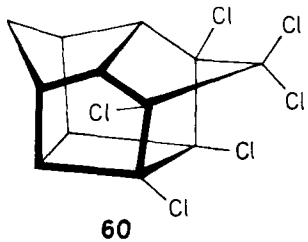
chlorobicyclo-(2,2,2)-2-heptene **(59)** which is then heated with cyclopentadiene **(42)** (Bluestone, 1954).

For steric reasons, isodrin is less stable than the *endo–exo* isomer, aldrin. Its insecticidal action is similar to that of aldrin but more efficient. Also its toxicity to warm-blooded organisms is higher. Its peroral LD_{50} value for female rats is 12 mg/kg. Toxicity is similar to that of endrin discussed below. Isodrin is highly toxic to fish, its toxic concentration ranging from 0.0015 to 0.0025 ppm in various species.



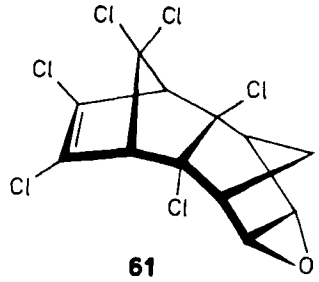
In warm-blooded organisms, as well as under *in vitro* conditions, it is epoxidised to endrin by the liver microsomes in the presence of oxygen and NADPH (Wong and Terrière, 1965). This pattern of epoxidation is characteristic of all cyclodiene insecticides. While the ethylene group of the ring containing the chlorine atom is not chemically reactive, the double bond of the chlorine-free ring undergoes the known addition reaction of unsaturated compounds. Isodrin is excreted from the organism in the form of hydrophylic metabolites. A similar metabolism also takes place in the organism of insects and even of plants (Weisberger *et al.*, 1968).

As in the other cyclodiene insecticides, isodrin is converted to the compound of structure **60** by the action of ultraviolet light (Cookson and Grundwell, 1958; Cookson and Berd, 1961).



60

When isodrin (**58**) is oxidised with peracetic acid, the epoxide of isodrin, i.e. the *endo-endo* isomer of dieldrin, 6,7-epoxy-1,2,3,4,10,10-hexachloro-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-*endo*-5,8-dimethanonaphthalene (endrin, **61**) is formed.



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Like isodrin, endrin is less stable than its *endo–exo* isomer, dieldrin. Therefore, a small amount of hexamethylenetetramine is added as a stabiliser to preparations containing endrin as an active substance. Endrin is moderately volatile, its vapour tension at 25°C being $3 \cdot 10^{-5}$ Pa.

Endrin is one of the most potent insecticides but at the same time, it is very poisonous to warm-blooded organisms. Its peroral LD_{50} value is 7.5 mg/kg in rats and 3 mg/kg for monkeys. In most countries a residue of 0 ppm is prescribed. Its high toxicity to warm-blooded organisms makes it very suitable not only for the control of insects, but also of rodents, for example voles, field-mice, etc.

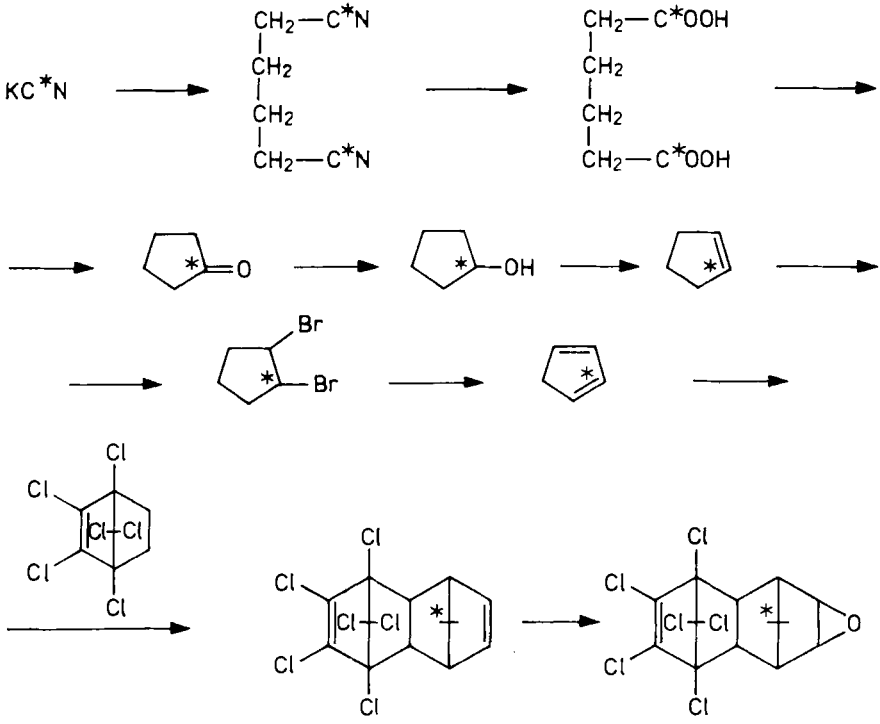
The mode of action of endrin is unknown. The symptoms of poisoning, as for other insecticides of the diene type, are indicative of neurotoxic action. The histopathological pattern of poisoning is the same as that of the other chlorinated hydrocarbon insecticides.

Endrin is highly poisonous to fish. Sensitivity to endrin varies among the different species of fish but, for several species, the LD_{50} value is about 0.0003 ppm. Therefore, in several countries, water protection regulations make its use on land in the proximity of water subject to permission. Because of its high toxicity, the maximum permissible residue in most of the European and oversea countries is 0 ppm, but in Canada it is 0.1 ppm.

The behaviour of isodrin and endrin in warm-blooded organisms has been investigated by Korte, Ludwig and their co-workers using ^{14}C-labelled compounds. Isodrin-^{14}C and endrin-^{14}C have been synthesised according to the route shown in Scheme 1.6 (Ludwig, 1966).

The investigations of the authors show that, in the same way as dieldrin, endrin and — following a previous epoxidation to endrin — isodrin are converted by warm-blooded organisms predominantly to the hydrophylic metabolite dihydroxy-dihydroisodrin and are excreted in this form. The rate of excretion is higher than that of aldrin and dieldrin.

An interesting representative of the diene-type insecticides, 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methylene-2,3,4-benzodioxathiepin-3-



Scheme 1.6

oxide (endosulfan, **62**) was marketed in 1956 under the name Thiodan®. It is prepared by reacting hexachlorocyclopentadiene (**40**) with butenedioldiacetate in a Diels–Alder reaction.

After saponification the diacetate of the bis-hydroxymethyl-hexachlorobicycloheptene **63** obtained is then treated with thionyl chloride arising **62** (Frensch and Goebel, 1958).

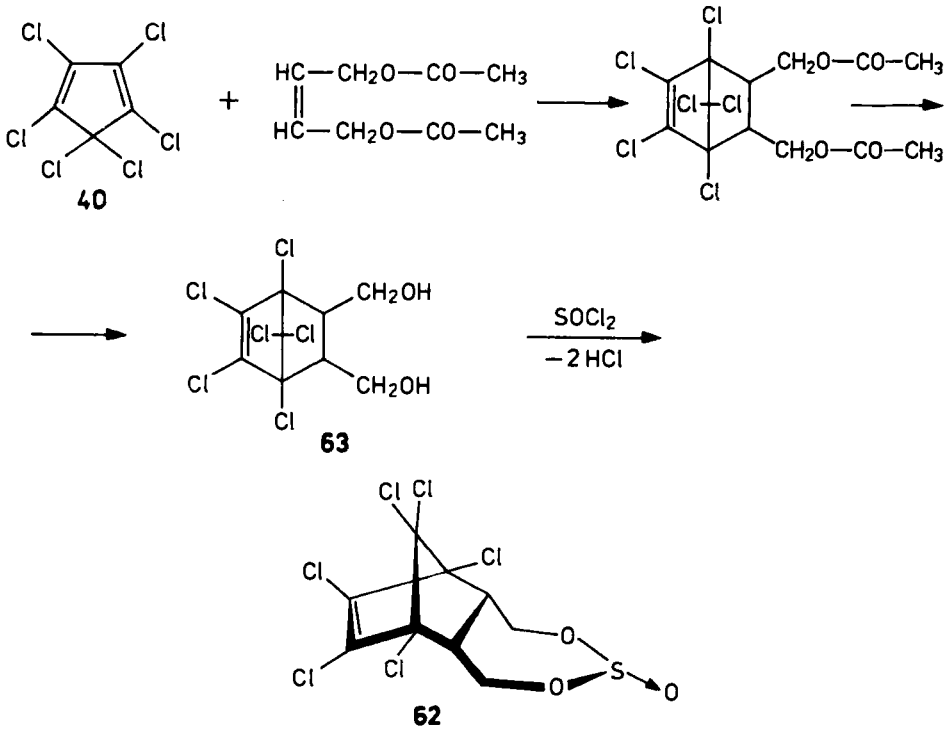
The technical product is a mixture of α-and β-endosulfan, the two isomers differ from each other with respect to the *exo-* and *endo*-positions of the sulfite group.

Endosulfan is very stable in water, but is saponified by alkalies or acids and is reconverted to diol **63.** Its vapour tension is low which ensures a lasting effect.

Endosulfan acts as a stomach or contact poison, depending on the insect species involved. It has a very wide spectrum of action, and it is efficient against a great number of chewing and sucking insects.

Its mode of action and, consequently, the toxic symptoms are different from those of other chlorinated hydrocarbon insecticides. The insects affected do not exhibit the excitation phenomena characteristic of chlorinated hydrocarbons.

The compound is only moderately toxic to bees, which permits—according to some, though not all, publications—its application to flowering cultivated plants.



It is toxic to warm-blooded organisms, its peroral LD_{50} value for rats being 40–50 mg/kg, and to cats 2 mg/kg. Its cumulative properties have not yet been established. It is rapidly resorbed from the digestive tract, but also undergoes fast decomposition and elimination (Dorough *et al.*, 1978).

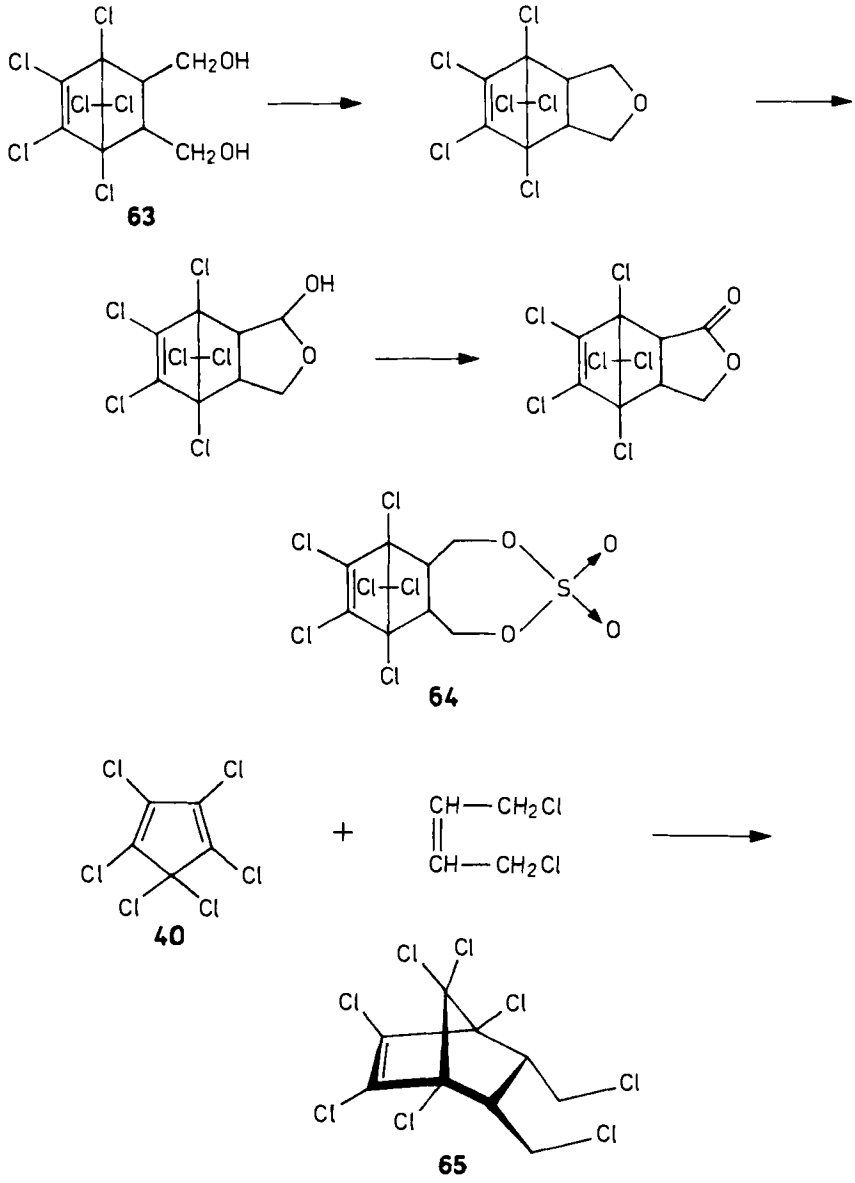
According to the investigations of Gorbach (1966), endosulfan is not persistent in warm-blooded organisms. It is converted partly by hydrolysis to the dialcohol **63**, and partly oxidatively to endosulfan sulfate (**64**). The dialcohol **63** undergoes further conversion yielding products with ether, hydroxyether and lactone groupings in place of the diol moiety.

Tolerance values prescribed for residues in various countries vary from 0.5 to 2.0 ppm.

It is very toxic to fish and in this respect can be grouped with toxaphene, endrin and isodrin. Its LD_{50} value is 0.005–0.010 mg/l.

The compound 5,6-bis(chloromethyl)-1,2,3,4,7,7-hexachlorobicyclo-2,2,1-heptene, formed by the addition of hexachlorocyclopentadiene (**40**) and *cis*-dichlorobutene, was introduced in 1957 under the name alodan (**65**).

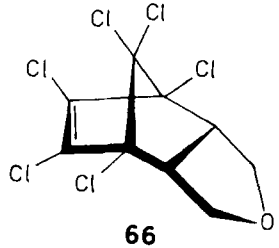
Alodan is an insecticide infrequently used in plant protection, but, owing to its low toxicity to warm-blooded organisms, its prime importance is against the ectoparasites of domestic animals, mites and storehouse pests. Its peroral acute



toxicity (LD_{50}) in rats is about 15000 mg/kg. The exact mechanism of its toxicity could not be established, because even the purely quantitatively still tolerable dose is insufficient to kill 50% of the experimental animals.

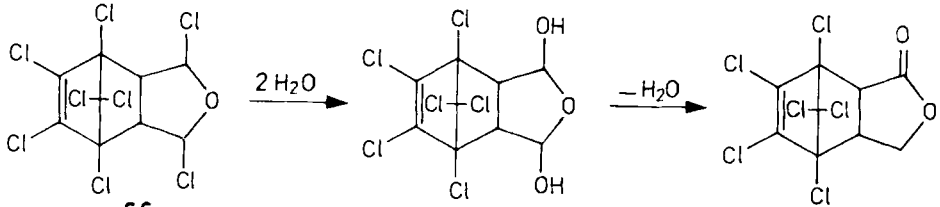
The preparation containing 1,3,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-4,7-methylenephthalan (isobenzan, **66**) as the active substance was marketed in 1959

(Feichtinger *et al.*, 1954). It is a very potent insecticide and, at the same time, it is efficient against mites. It is highly toxic to warm-blooded organisms, its peroral LD_{50} value in rats being 4.8 mg/kg. However, this high toxicity is partly counterbalanced by its low stability, so that accumulation or residual effect is negligible. It is very efficient against soil pests.



66

Following the intravenous administration of ^{14}C-labelled isobenzan Ludwig *et al.* (1964) established the presence of a lactone of the structural formula **67.** The formation of this metabolite proceeds as follows:



66 67

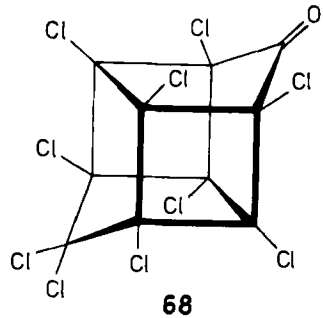
The peroral LD_{50} of the lactone **67** in warm-blooded organisms is 300 mg/kg. This indicates that, as in many other insecticides of the diene type, isobenzan is detoxified by warm-blooded organisms.

1.3.5 Cyclobutapentalene derivatives

On reacting hexachlorocyclopentadiene **(40)** with sulfur trioxide or with chlorosulfonic acid, decachlorooctahydro-1,3,4-metheno-2H-cyclobuta-(c,d)-pentalene-2-on (chlordecone, **68**) is formed.

Although the compound was first synthesised by Gilbert and Giolito (1951), they failed to recognise the actual structure of the compound obtained and described it as decachloro-4,7-methanoindenon **(69)** and patented it as an insecticide. Clarification of the true structure is due to McBee *et al.* (McBee *et al.*, 1956; Ungnade and McBee, 1958).

It was put on the market under the name Kepone®, primarily for the control of chewing insects. It acts as a stomach poison and is moderately toxic to warm-blooded organisms (LD_{50} = 95–140 mg/kg for rats). Its mechanism of action might be based on a direct interaction with muscle lactate dehydrogenase (Anderson *et al.*, 1978).



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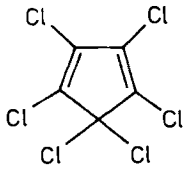

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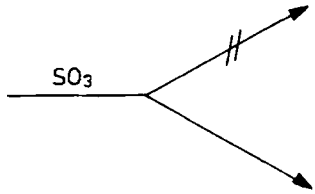
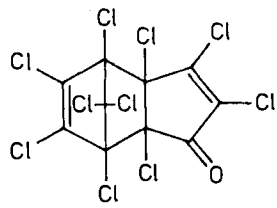
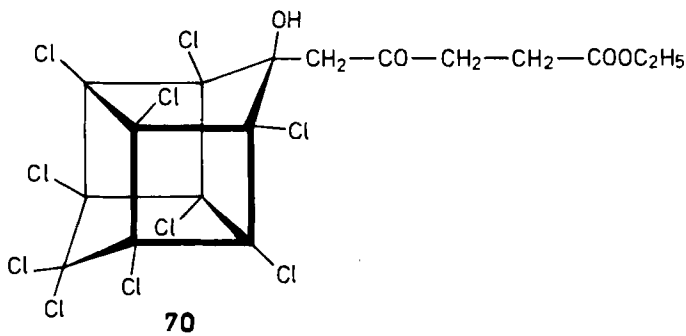




69

68

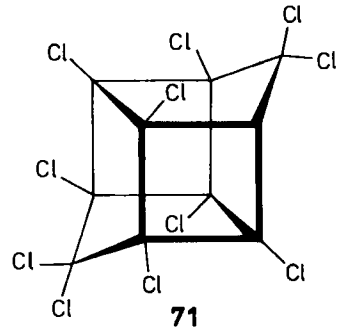
Its condensation product with levulinic acid ethyl ester (**70**) was marketed under the name kelevan (Gilbert *et al.*, 1965; Anderson and Nakakihara, 1968; Strong and Sbur, 1968).



70

When hexachlorocyclopentadiene (**40**) is heated with aluminium chloride, dodecachlorooctahydro-1,3,4-metheno-2H-cyclobuta-(c,d)-pentalene (dechloran) of structure **71** is formed by dimerisation.

The actual structure of dechloran, as in chlordecone, has not been properly recognised and has been described as dodecachlorotetrahydromethanoindene of structure **72** (Prins, 1946; Newcomer and McBee, 1949). Clarification of the actual structure of the compounds is also linked with McBee (1956).

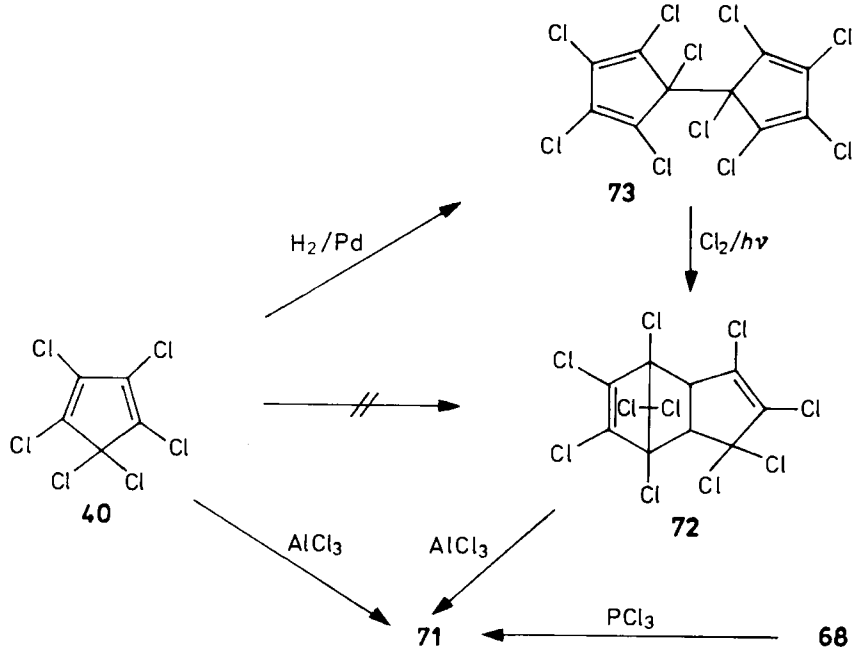


71

At the same time, the product of structure **72** is actually formed when hexachlorocyclopentadiene (**40**) is subjected to reductive dechlorination, and the bis(pentachloro-2,4-cyclopentadiene-1-yl) (pentac, **73**) formed again absorbs two chlorine atoms by chlorination under ultraviolet light.

This latter product is isomerised to dechloran (**71**) by aluminium trichloride or antimony pentachloride (McBee *et al.*, 1955). Dechloran is also formed from chlordecone (**68**) by the action of phosphorus trichloride, as shown in Scheme 1.7.

Dechloran is effective against the fire ant (*Solenopsis* spp.) in a dose not greater than a few grams per hectare. Its acute LD_{50} value for rats is 300–600 mg/kg.



Scheme 1.7

Due to the high degree of molecular symmetry, it is a very stable compound, which is reflected by its extraordinarily high melting point (485°C). It is a potent paralyser of muscle lactate dehydrogenase activity (Hendrickson and Bowden, 1975). Owing to this property, its stability, its high toxicity to aquatic life and high lipophility, its use may constitute great environmental hazard. Characteristic of its high stability is the fact that its presence was detected in the fish of Lake Ontario, although nowhere used in the catchment area of the lake (Kaiser, 1974). At the same time, its photochemical conversion products show an increased biodegradability (Ivie *et al.*, 1974; Alley *et al.*, 1974). In 1978, the Environmental Protection Agency banned its application in the USA as it had caused cancer and birth defects in mice and had been detected in human tissue samples.

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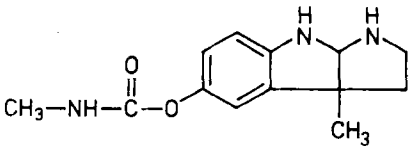
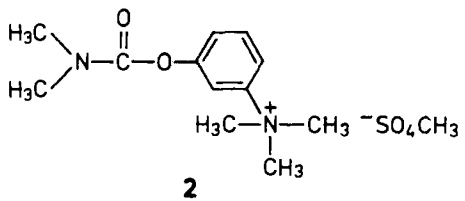
1.4 Carbamates

Several representatives of carbamic acid esters are considered in the literature to be strongly toxic compounds. The main alkaloid of the plant *Physostigma venenosa,* physostigmine **(1),** and also prostigmine **(2),** which is of synthetic origin, are compounds with cholinergic action and are of importance in medicine.



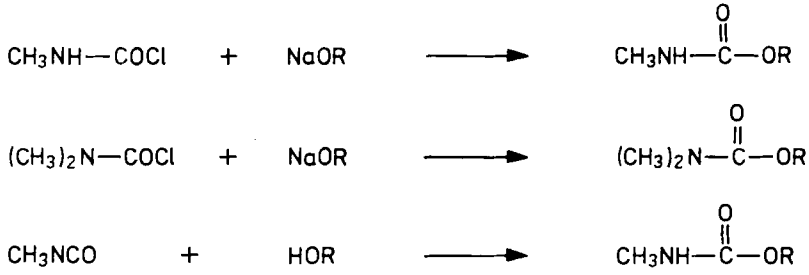
1



2

These compounds themselves do not exhibit insecticidal action, but owing to their potent bioactivity, workers in insecticide research in the mid-1940s directed their attention to N-substituted carbamic acid esters. Pioneer work in this field is linked with the names of Metcalf and Gysin (Metcalf and March, 1950; Kolbezen *et al.*, 1954; Gysin, 1952).

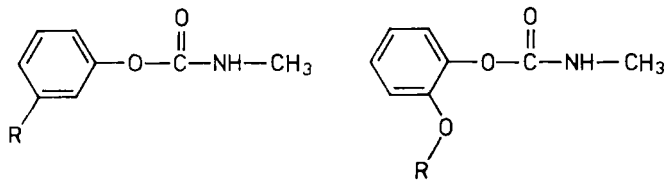
Most carbamates used as insecticides are esters of aromatic and heterocyclic hydroxy derivatives of N-methyl- and N,N-dimethylcarbamic acids. They are usually prepared by the reaction of methyl- or dimethylcarbamoyl chloride with the alkali metal salt of the corresponding hydroxy derivative, or alternatively, the hydroxy derivative is carbamoylated with methyl isocyanate (Gysin, 1952).



Carbamates generally act quickly. They are strongly toxic to a wide range of insect pests, but have a weak effect on the red spider mite. Some of them exhibit systemic characteristics. The duration of their action varies considerably. In a similar manner to the phosporic acid esters discussed later, they exert their action by paralysing the cholinesterase enzyme. During this process, the carbamate part of the molecule is attached to the esteratic site, and the aromatic part to the anionic site of the cholinesterase enzyme. As the distance between the esteratic and anionic sites is 50 nm in the cholinesterase molecule, carbamate insecticides will be most efficient if the distance between the two groups to be bound to the two sites of the enzyme is also 50 nm. (Metcalf and Fukuto, 1965; 1967; Fukuto *et al.*, 1967).

The structural requirements of their action, their mode of action and their metabolism in the living organism have been investigated by Metcalf, Fukuto and other members of the Riverside research group. They found that N-methyl and N,N-dimethyl derivatives are the most efficient. With an increasing number of carbon atoms in the N-alkyl group, the efficiency decreases rapidly. The aromatic groups linked to the carbamoyl group can be varied within wide limits, and the presence of a compact substituent group (methyl, ethyl, isopropyl, *t*-butyl, dimethylamino, etc.) in position 2 or 3 relative to the ester bond is advantageous, as shown by the example of the efficient derivatives **6–13.**

Phenyl N-methylcarbamates with an alkyl substituent on the aromatic ring are most efficient when the alkyl group is in the *meta*-position with respect to the carbamate group, while alkoxy and alkylmercapto groups in the *ortho*-position give the highest efficiency. In both instances, the alkyl group will be located roughly at a distance corresponding to the *meta*-position from the carbamate group (Metcalf and Fukuto, 1965).

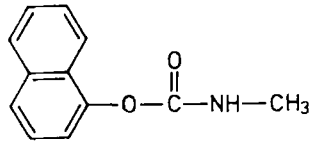


Analysis of the fly-head acetylcholinesterase data by multiple regression showed that the equilibrium constant for the enzyme-inhibitor complex is related to Hansch's π-constant and ring position terms. Reversible binding of these compounds to acetylcholinesterase probably occurs through hydrophobic bonding (Wustner *et al.*, 1978).

Phenyl N-methylcarbamates, which contain a quaternary alkylammonium group in position 3 on the phenyl group, show a remarkably high cholinesterase inhibiting effect. However, like the similar prostigmine **(2),** they have no insecticidal effect because they cannot penetrate the lipoid layers on account of their polar character, and thus do not reach the site of action. If the quaternary ammonium group is replaced with the isosteric but chargeless *t*-butyl group, the cholinesterase-

inhibiting effect will be decreased but, as a result of the translocation ability of the compound, a strong insecticidal effect is exhibited.

Of the N-methylcarbamates of aromatic phenols, 1-naphthyl N-methylcarbamate (carbaryl, **3**), obtained by the reaction of α-naphthol with methyl isocyanate, was the first to find practical application (Lambrech, 1959; 1960). It is the most widely used carbamate insecticide and is marketed under the trade name Sevin®.

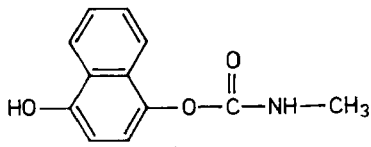


3

Carbaryl is a very potent contact and respiratory poison and its spectrum of action is different from that of most of the carbamic acid derivatives. It is very efficient against chewing insects, and proved particularly successful for the control of insect pests in orchards. It is 70 times more toxic than DDT towards bees, but is inefficient against red spider mite (Georghiou and Metcalf, 1962; Haynes *et al.*, 1957; Johnson and Stansbury, 1965).

A very advantageous property of carbaryl, compared with other carbamic acid esters, is its low toxicity to warm-blooded organisms. Its oral acute LD_{50} value for rats is 400–600 mg/kg. The prescribed pre-harvest interval is in general 7 days and permissible residue values are about 3 ppm.

Owing to its widespread practical application, the metabolism of carbaryl has been investigated extensively. In the human organism it is converted partly hydrolytically to 1-naphthol, and partly oxidatively to 4-hydroxycarbaryl (**4**) and 5,6-dihydro-5,6-dihydroxycarbaryl (**5**) (Knaak *et al.*, 1968; Leeling and Casida, 1966; Camp and Arthur, 1967). These metabolites are eliminated from the organism mainly as glucuronides or sulfates.



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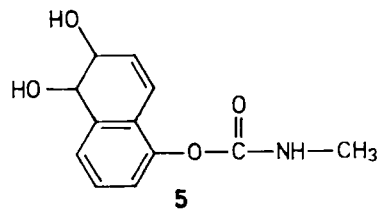
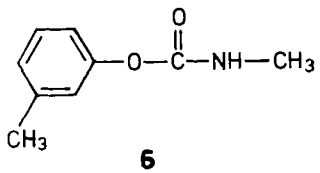


5

The ratio of oxidative and hydrolytic processes differs substantially, depending on the species. Thus, e.g., in the monkey and pig organisms hydrolytic decomposition plays a very minor role.

The success of carbaryl encouraged the synthesis of N-methylcarbamates of other aromatic phenols. The N-methylcarbamates of alkyl- and chloro-substituted

phenols (**6–13**), with largely identical effects, show differences mainly with respect to their spectrum of action and their toxicity to warm-blooded organisms. The most important members of this group are:



6
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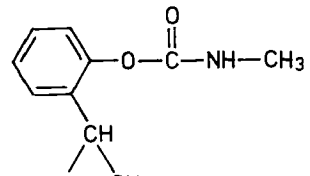
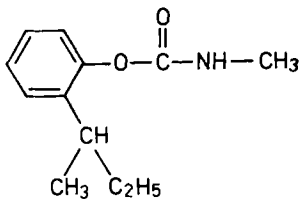


7
MIPC



8
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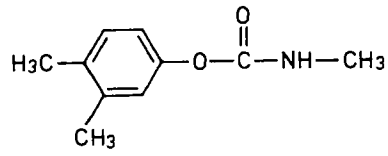

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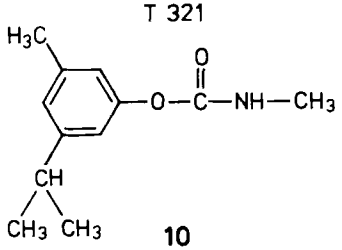

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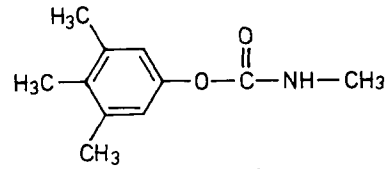

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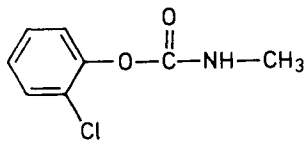

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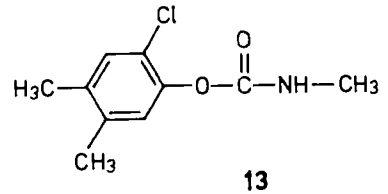


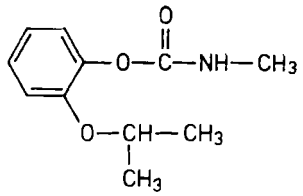
13
chlorxylam

The spectrum of action of 2-chloro-4,5-dimethylphenyl N-methylcarbamate (**13**) is broader than that of carbaryl, and includes also plant lice. Its toxicity to mammals is similar to that of other members of the group, its LD_{50} value for rats being 30–40 mg/kg.

The most important representative of phenyl N-methylcarbamates containing alkoxy substituents is 2-isopropoxyphenyl N-methylcarbamate (**14**), known under the name propoxur. It is an insecticide with a very broad spectrum of action and

acts as a contact and stomach poison. Owing to its moderately acute and low chronic toxicity in mammals, it is also suitable for hygienic use (Unterstenhöfer, 1963; Bracha, 1964).

In the formal sense, 2,3-dihydro-2,2-dimethylbenzofuran-7-yl N-methylcarbamate (carbofuran, **15**), marketed under the trade name Furadan®, can be considered as the bicyclic analogue of 2-alkoxyphenyl N-methylcarbamates (e. g., **14**). (Heiss *et al.*, 1964; Amburst and Gyrisco, 1965; Metcalf *et al.*, 1967.)



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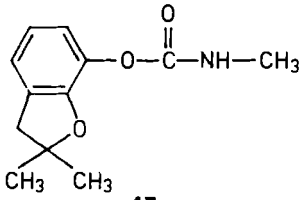
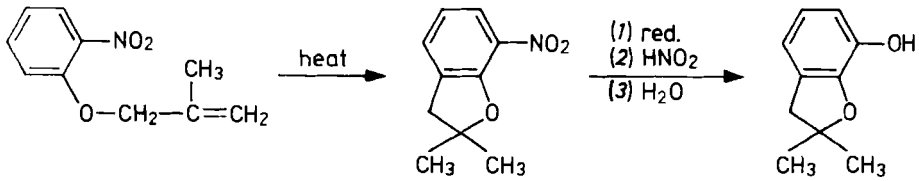


15

The synthesis of 2,3-dihydro-2,2-dimethyl-7-benzofuranol (**16**), required for the preparation of carbofuran, is carried out according to the following route:



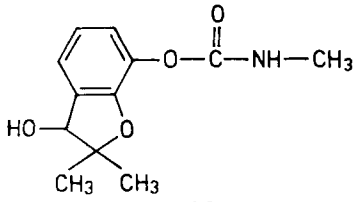
16

Carbofuran is a systemic insecticide, acaricide and nematocide with a very broad spectrum of action. It is toxic to warm-blooded organisms, its LD_{50} value for rats being 11 mg/kg. This disadvantage is somewhat counterbalanced by its rapid decomposition in plant organisms, the half-time of decomposition being less than 5 days.

Owing to its practical importance and its toxicity to warm-blooded organisms, its metabolism has been investigated extensively on various test objects, including a laboratory model ecosystem (Metcalf *et al.*, 1968; Ashworth and Sheets, 1972; Dorough, 1968; Knaak *et al.*, 1970; Yu *et al.*, 1974). The most important metabolites are 3-hydroxycarbofuran (**17**) and its glucoside, and 3-ketocarbofuran

(18). Both 3-hydroxy- and 3-ketocarbofuran are toxic but their hydrolysis products, which contain no carbamoyl group, are not toxic.

The insecticidal action, similar to other insecticides, can be increased to some extent by the simultaneous use of sesamex, piperonyl butoxide and other methylenedioxyphenyl type synergists. It has been established that there is an apparent inverse relationship between the original insecticidal efficiency of various carbamates and the synergisability of their effect. Similarly, an inverse relationship has been found between the sensitivity of various insect strains toward carbamates and the extent of synergisation (Fukuto *et al.*, 1962; Metcalf and Fukuto, 1965; Wilkinson *et al.*, 1966). Therefore, several workers attempted to incorporate a synergistic atom group (synergophore) in the carbamate molecule in order to attain a quasi-intramolecular synergistic effect (Fine and Molloy, 1964; Fishbein and Falk, 1969). While, with most other types of insecticides such structural modifications brought about a decrease in efficiency, the incorporation of the synergophore methylenedioxy and 3-propynyloxy groups into the phenyl N-methylcarbamate molecule (**19** and **20**) resulted in maintenance of activity and in the expected synergism (Fukuto *et al.*, 1962; Metcalf *et al.*, 1960).



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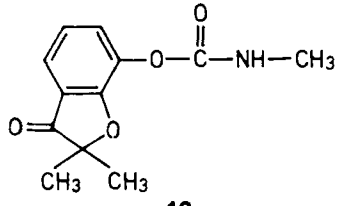

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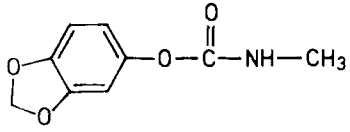

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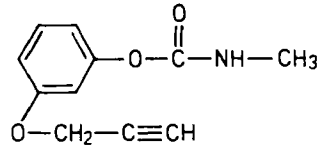
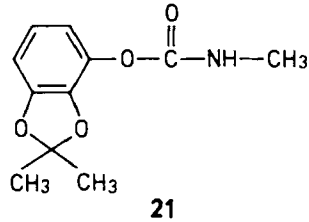


20

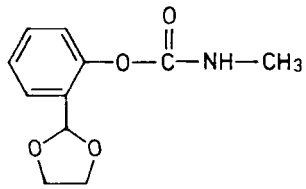
1,3-Benzodioxol-4-yl-carbamates, synthesised by Brooker *et al.* (1972), show a close relationship with derivative **16.** Owing to its advantageous bioactivity and its economical manufacture, of 32 related derivatives, 2,2-dimethyl-1,3-benzodioxol-4-yl N-methylcarbamate (bendiocarb, **21**) has found practical application.



21

Its spectrum of activity is very broad, and its moderate toxicity to warm-blooded organisms, its rapid metabolism and evacuation from the organism and its systemic properties are substantial practical advantages.

Starting from hydroxybenzaldehydes, several workers prepared independently phenylcarbamates the phenyl group of which contains cyclic acetal (1,3-dioxolane) and cyclic mercaptal (1,3-dithiolane) groups (Nikles *et al.*, 1966; Nikles, 1969; Durden and Weiden, 1969; Bachmann and Legge, 1968). Of the former, 2-(1,3-dioxolan-2-yl)-phenyl N-methylcarbamate, dioxocarb **(22)**, and of the latter, 2-(1,3-dithiolan-2-yl)-phenyl N-methylcarbamate, **(23)** attained practical importance.



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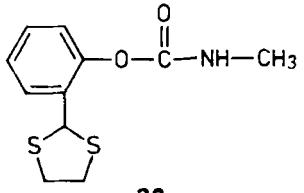


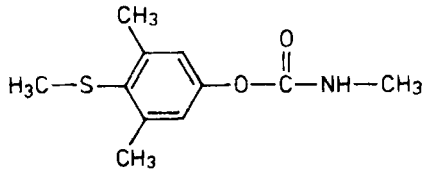
23

A distinctive property of compound **23**, compared to the majority of phenylcarbamates, is its efficiency against plant lice.

Also other phenyl N-methylcarbamates have been developed in which the phenyl group is substituted by a sulfur containing moiety. The most significant compounds within this group are 3,5-dimethyl-4-methylmercaptophenyl N-methylcarbamate (methiocarb, **24**), 2-ethylmercaptomethylphenyl N-methylcarbamate (ethiophencarb, **25**) and 4-benzothienyl N-methylcarbamate (MCA 600, Mobam®, **26**).

These compounds are moderately toxic to warm-blooded organisms, possessing a broad spectrum of insecticidal action (Metcalf *et al.*, 1964; Getzin, 1965).

The role of the sulfur atom in modifying their efficiency has been shown by Durden and Weiden (1969) as well as by Nikles (1969), when demonstrating that the anticholinesterase activity of phenyl methylcarbamates containing a dithiolane



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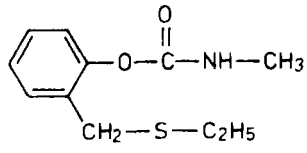

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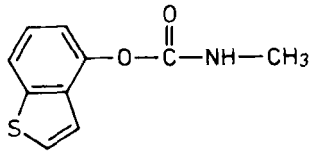
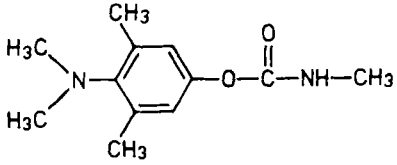


26

substituent (e. g. **23**) is ten times that of the dioxolane analogues lacking sulfur (e. g. **22**). According to their suggestion, the explanation may be found in the strong attachment of the free *d*-orbital of the sulfur atom to the anionic site of the enzyme. Mahfouz and co-workers (1969) came to similar conclusions when investigating the relationship between structure and activity of the sulfur containing phenyl N-methylcarbamates.

Several aryl N-methylcarbamates have been developed in which a nitrogen-containing side chain is attached to the phenyl group. Typical representatives of this class are 3,5-dimethyl-4-dimethylaminophenyl N-methylcarbamate (mexacarbate, **27**) and 3-(N',N'-dimethylaminomethyleneimino)phenyl N-methylcarbamate (**28**) known as formetanat.



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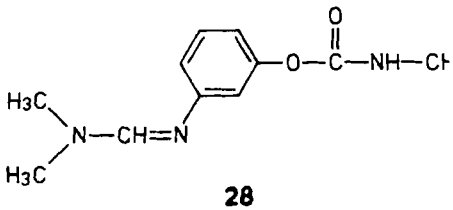


28

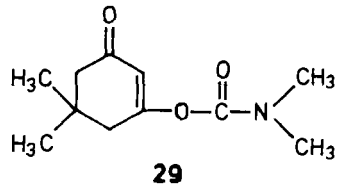
Mexacarbate (**27**) has a very broad spectrum of activity. It is efficient also against plant lice (Shuglin, 1959; Kaeding *et al.*, 1965; Metcalf *et al.*, 1964). Its peroral LD_{50} for mice is 16–63 mg/kg.

Special properties make formetanat (**28**) stand out in several respects from the other carbamate insecticides. It is soluble in water, has also a systemic effect, and is more efficient to red spider mites resistant to phosphoric acid esters than to strains susceptible to phosphoric acid ester insecticides (Peissker *et al.*, 1962; Steinhausen, 1967). The peroral LD_{50} for mice is 20 mg/kg. In both plants and warm-blooded animals the dimethylaminomethyleneimino group is decomposed to an amino group, with concomitant hydrolysis of the carbamate group to yield *m*-aminophenol as end-product (Knowles, 1970; Knowles and Sen Gupta, 1970). Basically the same decomposition products are also formed by the action of light (Su and Zabik, 1972).

O'Brien (1971) pointed out that the majority of insecticidal carbamates are aromatic, suggesting the involvement of π-π interactions in binding them to the enzyme. Thus compound **7** is about 1000 times as active as its cyclohexyl analogue.

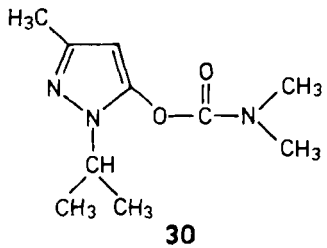
The development of phenyl N-methylcarbamates of relatively simple structure was preceded at the end of the 1940s by the development of those N,N-dimethylcarbamates which contain, with the exception of dimetan (**29**), a heterocyclic group at the site of the phenyl group. Their development is due to the research workers of the Geigy Co., primarily to Gysin.

The active substance of dimetan is 5,5-dimethylcyclo-1,2-hexen-3-one-1-yl N,N-dimethylcarbamate, (**29**) (Gysin, 1952; Wiesmann *et al.*, 1951).



29

Most of the heterocyclic dimethylcarbamates, which have attained practical importance, are prepared from the enol pyrazolones, known as pharmaceutical intermediates, by reaction with dimethylcarbamoyl chloride. 1-Isopropyl-3-methyl-5-pyrazolyl dimethylcarbamate (isolan, **30**) has systemic effects and has proved to be efficient primarily against plant lice and aphids. Its N-phenyl analogue **(31)** is known under the name pyrolan. Dimetilan® **(32)**, 2-dimethylcarbamoyl-3-methyl-5-pyrazolyl dimethylcarbamate containing two dimethylcarbamoyl groups is used to a lesser extent in plant protection, but primarily in the hygiene sector as a fly poison (Anonym, 1949a; 1949b; 1949c). Pirimicarb **(33)**, a pyrimidinyl carbamate, has similar biological properties.



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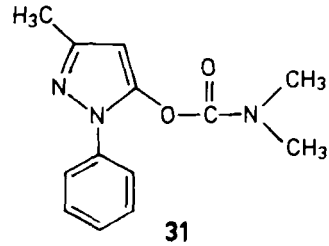

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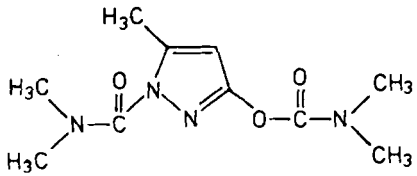

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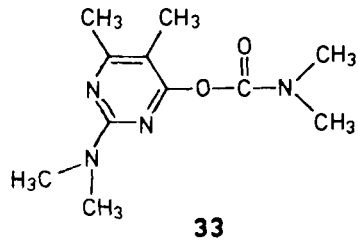
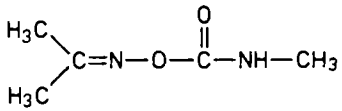


33

All four compounds **(30–33)** are toxic to warm-blooded organisms; their LD_{50} values vary from 50 to 65 mg/kg for rats.

Carbamoyl oximes, formed by the reaction of aldehyde and ketone oximes with isocyanates, have been known since the end of the last century (Goldschmidt, 1889). The pioneer work in the field of their use as insecticides is due to the research group of the Union Carbide Corp., Payne and co-workers (Payne and Weiden, 1962; Weiden *et. al.*, 1965; Payne *et al.*, 1966).

The starting point of their work was an earlier finding that N-methylcarbamoyl-acetone oxime (**34**) and its 2-butanone analogue (**35**) show moderate insecticide action.



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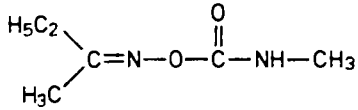
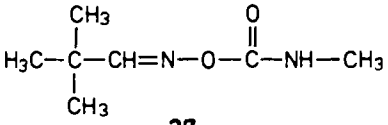


35

The objective of their later work was the preparation of methylcarbamoyl oximes which have a structure similar to that of acetylcholine (**36**). Trimethylacetaldehyde-O-methylcarbamoyl oxime (**37**), prepared in the series of these compounds, actually showed a higher efficiency than derivatives **34** and **35**. According to their assumption this is due to the fact that tne *t*-butyl group is isosteric with the trimethylammonium group of acetylcholine, and thus complements well the anionic surface of acetylcholinesterase.



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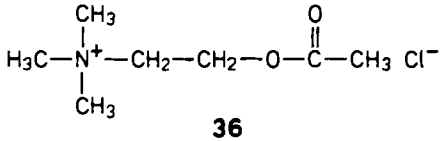
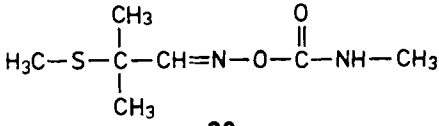


36

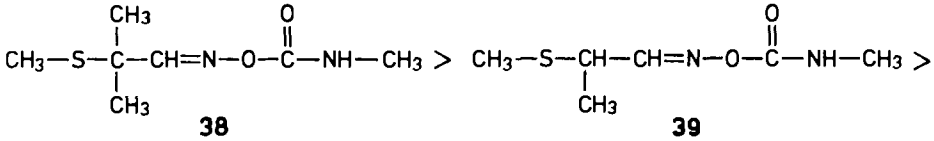
To increase further the effect they prepared analogues of compound **37**, in which one of the three methyl groups of the trimethyl moiety was substituted by an electronegative group such as an alkoxy, methylmercapto, methylsulfinyl, methylsulfonyl, cyano, nitro or azo group. Among these, 2-methyl-2-methylmercaptopropionaldehyde-O-methylcarbamoyl oxime, (**38**), known under the common name aldicarb, proved to be the most efficient.



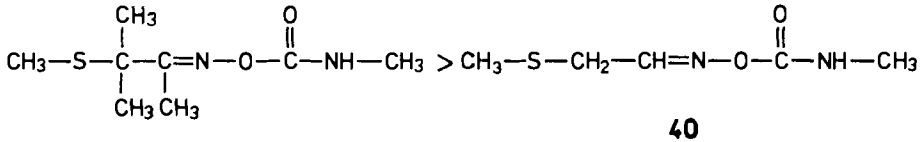
38

Further structural modifications of compound **38** did not yield more efficient products. Substitution of the methyl group linked to the sulfur atom for an alkyl group with longer carbon chain decreased the efficiency, which ceased completely on substituting a heterosubstituted group of higher molecular weight. Similarly, elimination of one of the methyl groups on carbon atom 2 (**39**) brought about a moderate decrease, while the absence of both methyl groups (**40**) caused a strong

decrease in efficiency. The bioactivity of these derivatives decreases in the following order:

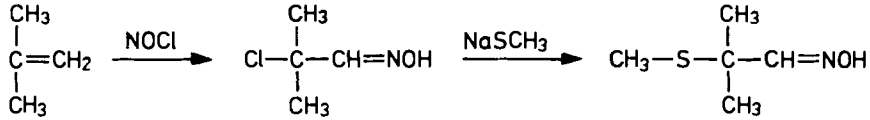


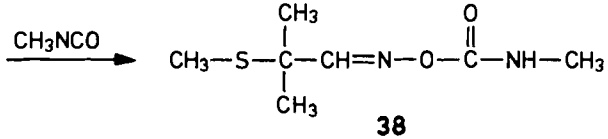
38 **39**



40

The preparation of aldicarb is illustrated by the following reaction scheme:

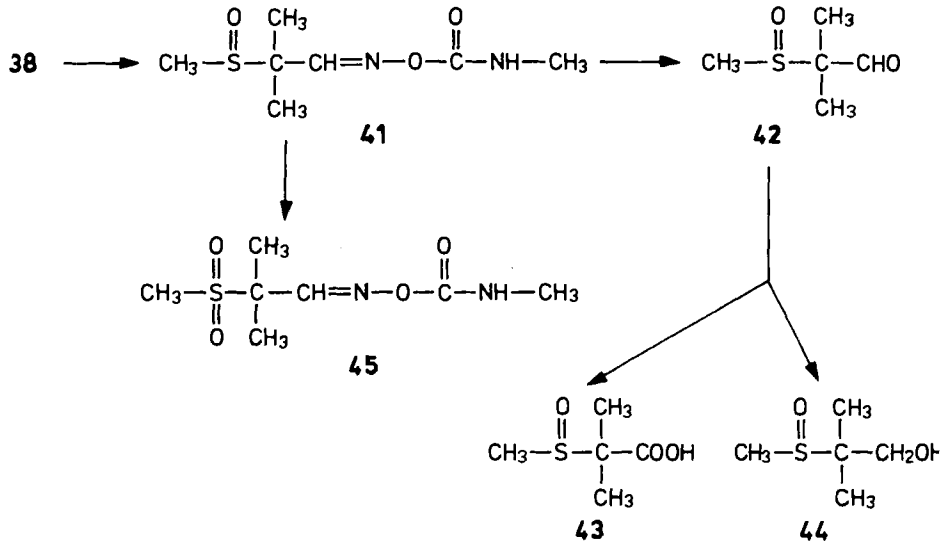




38

Aldicarb is an insecticide, acaricide and nematocide with a very broad spectrum of action. At the same time, it shows the highest toxicity of all the known carbamate insecticides to warm-blooded animals. Its LD_{50} for rats is 0.93 mg/kg.

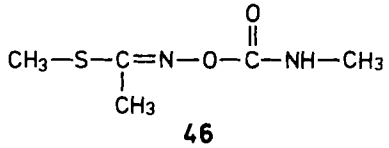
Its systemic effect is related to its metabolism. In plants it is converted to its sulfoxide **(41)**, which is water soluble and therefore easily translocated in the transport system. The sulfoxide is a 10–20 times stronger cholinesterase inhibitor than aldicarb. However, when applied directly to insects it is less toxic because, due to its hydrophilic nature, it can hardly penetrate the insect cuticle. Presumably, a similar bioactivation takes place also in the insect organism. As metabolism proceeds, the sulfoxide derivative **41** is hydrolysed to 2-methyl-2-methylsulfinyl-propionaldehyde **(42)**, which is partly converted by oxidation to 2-methyl-2-methysulfinylpropionic acid **(43)**, and partly by reduction to the corresponding alcohol **(44)**, as shown in Scheme 1.8. Part of the sulfoxide is converted to sulfon **(45)**, which is the carrier of the persistent systemic effect (Bartley *et. al.*, 1966; Metcalf *et. al.*, 1966; Dorough, 1970).



Scheme 1.8

The advantageous biological properties of aldicarb stimulated a search for further oxime carbamates which contain a sulfide-sulfur atom as an electronegative part of the molecule.

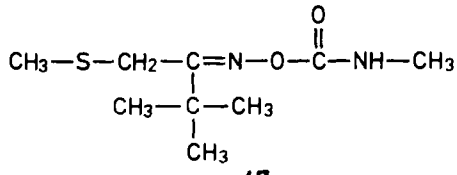
A few years after the synthesis of aldicarb, several research groups prepared, independent of each other, analogues of aldicarb which have only one carbon atom instead of two between the sulfur atom and the oxime-nitrogen (Anonym, 1966a; 1966b; Anders, 1967). Finally, 1-methylmercaptoacetaldehyde-O-methylcarbamoyl oxime (methomyl, **46**) was put onto the market as the result of work by the research group of the Du Pont Co.



46

The spectrum of action of methomyl is similar to that of aldicarb (**37**), but its toxicity to warm-blooded organisms is lower; the LD_{50} for rats being 26 mg/kg.

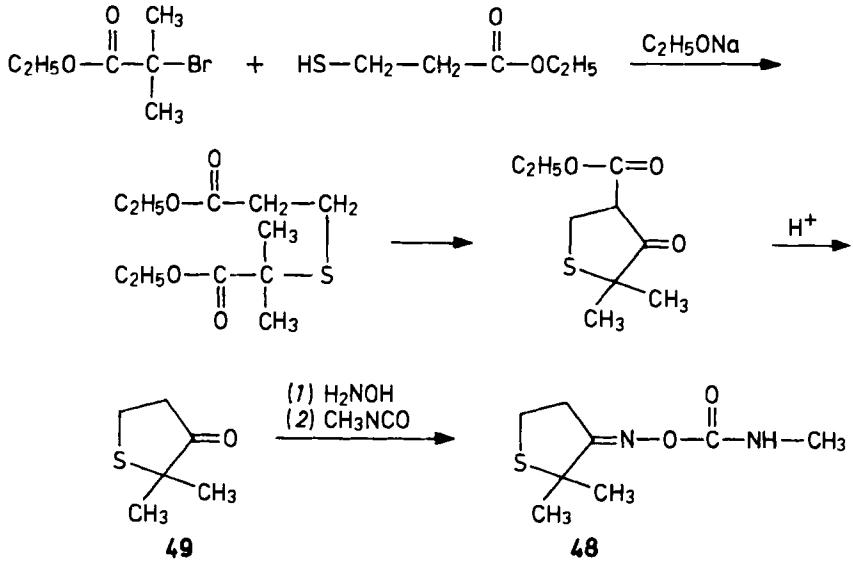
3,3-Dimethyl-1-methylmercapto-2-butanone-O-methylcarbamoyl oxime (DS-15 647, **47**), developed in recent years by the research group of the Diamond Shamrock Corp., represents a return to the basic skeleton of aldicarb (**37**). The metabolism of this compound is similar to that of aldicarb (Whitten and Bull, 1974).



47

The aldicarb molecule was also the starting point of research work aimed at the preparation of its cyclic analogues. This work was carried out independently by the research groups of the Union Carbide Corp. and the Diamond Shamrock Corp. (Anonym, 1971; Durden and Weiden, 1974).

In the investigations of Durden and Weiden, of the 21 derivatives prepared 2,2-dimethylthiophan-3-one-O-methylcarbamoyl oxime (**48**) proved to be the most efficient. 2,2-Dimethylthiophan-3-one (**49**), necessary for its preparation, was obtained according to the known synthesis scheme for thiophan-3-one derivatives (Berezovski *et al.*, 1963; Acheson *et al.*, 1961). Then, after reacting with hydroxylamine, it was carbamoylated with methyl isocyanate, as shown in Scheme 1.9

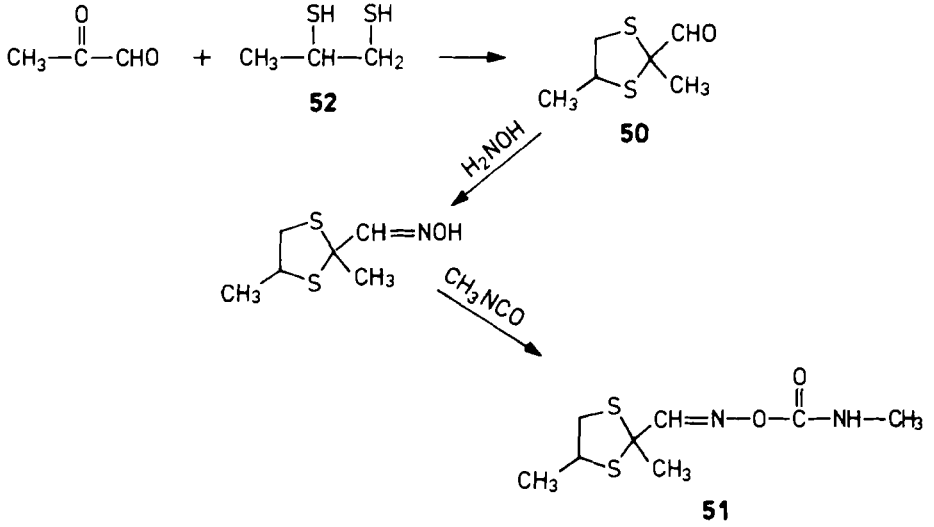


Scheme 1.9

Compound **47** is similar to aldicarb (**38**), but it has a somewhat weaker systemic insecticidal action and, contrary to aldicarb, it has no nematocidal effect.

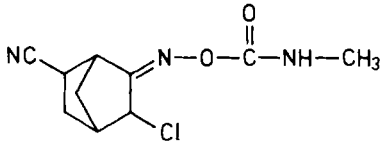
Fridinger and co-workers (1971) found that, with 1,2-dithiols, pyruvic aldehyde yields, instead of the expected mercaptal ketones, mercaptol aldehydes (e.g. **50**). Using this reaction, the oximes of the mercaptol aldehydes prepared by these

workers yielded on carbamoylation with methyl isocyanate carbamate insecticides of high efficiency. From a practical point of view, the most significant compound of this type is 2,4-dimethyl-1,3-dithiolanecarboxaldehyde-O-methylcarbamoyl oxime (MBR 6168, Tirpate®) **51**. For its synthesis, 1,2-propanedithiol **(52)** is used as 1,2-dithiol which gives with pyruvic aldehyde the mercaptol aldehyde **(50)** as intermediate.



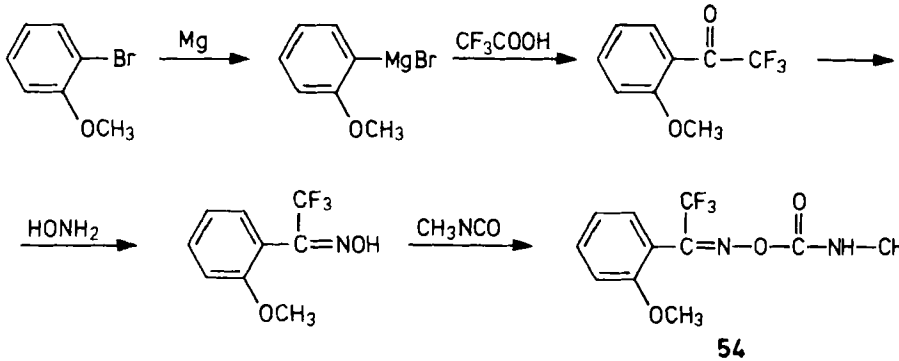
Compound **51** is one of the most toxic carbamate insecticides to warm-blooded animals. Its acute oral LD_{50} for female rats is 1.13 mg/kg.

A special example of the oxime carbamates is *exo*-3-chloro-*endo*-6-cyano-2-norbornanone-O-methylcarbamoyl oxime (UC 20047 A, Tranid®, **53**) (Kilsheimer and Manning, 1961; Payne *et al.*, 1965). It has a contact insecticidal and acaricidal action. It is also a strong poison for warm-blooded animals.



Rosenfeld and Kilsheimer (1974) prepared several 2,2,2-trifluoroacetophenone oxime methylcarbamates substituted on the ring. Among these, *o*-methoxy-2,2,2-trifluoroacetophenone oxime N-methylcarbamate **(54)** and *o*-fluoro-2,2,2-trifluoroacetophenone oxime N-methylcarbamate **(55)** are the most efficient. Their insecticidal action is nearly identical to that of carbaryl **(3)**, while their cholinesterase-inhibiting effect surpasses substantially that of carbaryl.

For the preparation of this type of compounds, the corresponding substituted bromobenzene is reacted with magnesium to convert it to the substituted phenylmagnesium bromide. The Grignard reagent obtained is then treated with trifluoroacetic acid:



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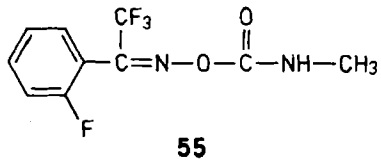
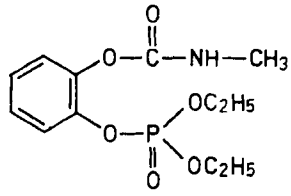


55

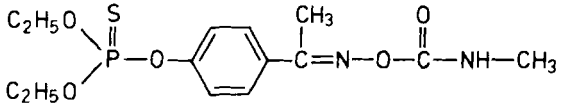
The derivatives prepared by Hetnarski and O'Brien (1972), which contain a phosphate ester group in addition to the carbamoyl group, lead to the other large family of insecticides, the phosphoric acid esters. The theoretical basis of their work was the assumption, that the simultaneous presence of two bioactive groups results in a linkage of two functional groups at the active surface of the cholinesterase enzyme. This increases the possibility of carbamoylation or phosphorylation of the enzyme. However, even the compound **56**, the most efficient member of this group, did not surpass the efficiency of those carbamates containing no phosphate ester group. This conforms with the pharmacological experience that the presence of two biologically active groups within a molecule mutually weakens the efficiency, presumably because the attractions, acting in the direction of the various functional groups of the site of action, mutually compensate each other.



56

The anticholinesterase effect decreased in the order *ortho* > *meta* > *para* position of the carbamate with respect to the phosphate groups. Hetnarski and O'Brien (1972) established a linear correlation between the infrared P→O stretching frequency of the single derivatives and their anticholinesterase activity. Similarly, efficiency was decreased by substituting the hydrogen atom at the carbamoyl group of some known carbamate insecticides by a dialkyl phosphoryl or a dialkyl thiophosphoryl group (Fahmy *et al.*, 1970).

A further compound containing both carbamate and phosphate ester groups is 4-[O-(O,O-diethylphosphorothioyl)]acetophenone oxime N'-methylcarbamate (R-14805, **57**).



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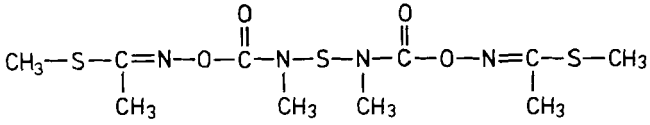

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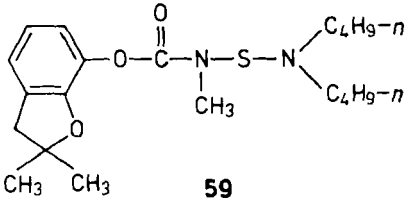

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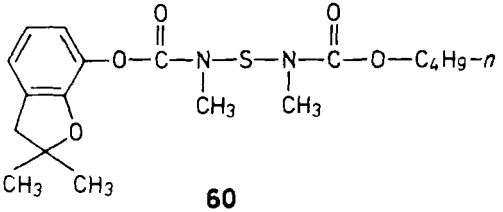

60

Its metabolism in rats was investigated by Menn and co-workers (1976), demonstrating that the activation is initiated by P=S→P=O conversion (oxon formation), while detoxification resulted from hydrolysis of the alkyl and aryl phosphate ester group, as well as from cleavage of the C=N and O—C bond of the oxime carbamate moiety.

Fukuto and associates (Black *et al.*, 1973a; 1973b; Fahmy *et al.*, 1974; 1983; Fukuto *et al.*, 1962; Fukuto, 1983) and independently Drabek and Boegner (1978a; 1978b; 1981; 1982); Drabek and Bachmann (1983) have substituted the proton on

the nitrogenatom of known methylcarbamate insecticides by a variety of functional groups, to obtain N-sulfenylated, sulfinylated, sulfonylated and phosphinothiolated carbamates. The rationale for the design of these derivatives was based on the premise of introducing a "delay factor" into the methylcarbamates, resulting in improved mammalian toxicity along with retention of insecticidal activity. These proinsecticidal methylcarbamates have shown the expected level of selective activity, as the delay factor is capable of cleavage in insects, yielding the parent compounds, while cleavage proceeds less readily in mammals, giving time for the detoxifying hydrolysis to occur.

The most promising representatives of this class are sulfenylated derivatives of methomyl **(46)** and of carbofuran **(15)**, such as larvin **(58)**, carbosulfan **(59)** and CGA-73 120 **(60)**.

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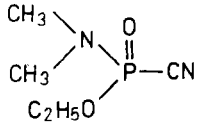
1.5 Organophosphorus compounds

Research in organic compounds containing phosphorus spans the last one and a half century. The beginning is marked by the work of Lassaigne (1820), who investigated the interaction of alcohol and phosphoric acid. Thénard (1847) prepared several phosphines, describing therewith organophosphorus compounds for the first time. Hofmann (1872) was the first to prepare alkanephosphonic acids. The true pioneers of classical, but still modern, phosphorus ester chemistry were the German Michaelis (1897) and the Russian Arbuzov.

Lange and Krueger were the first to report on the strong bioactivity of organophosphorus compounds. In their paper published in 1932, they described the toxic properties of the fluorophosphates they had prepared. At the end of the 1930s and the beginning of the 1940s, Saunders *et al.* (McCombie and Saunders, 1946) and, independent of them, Schrader, prepared several phosphonofluorides which proved to be strongly toxic. In the course of his investigations, Schrader prepared the compounds which became known under the names tabun **(1)**, sarin **(2)** and soman **(3)**. Owing to their possible use in chemical warfare, the results of this research were kept secret during the World War II.



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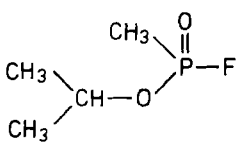

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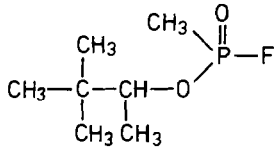


3

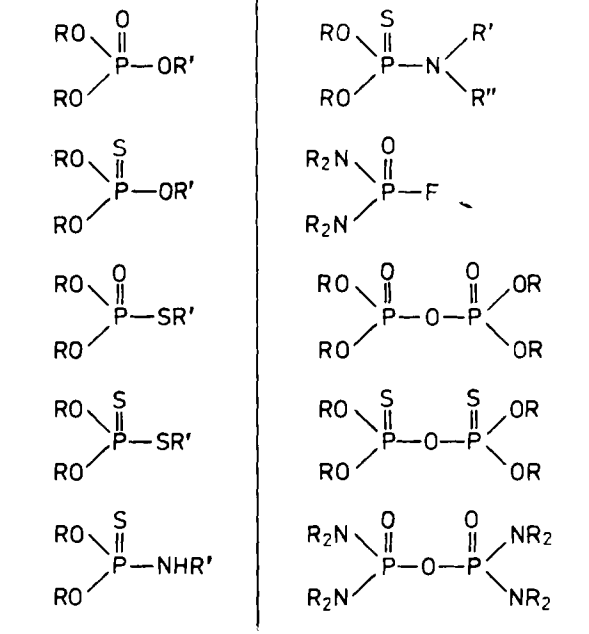
Extensive investigations of the biological effect of these compounds elucidated the fact that, in addition to their toxicity to warm-blooded animals, some of the organophosphorus compounds are also strongly toxic to insects. Partly for this reason, and partly because of the anticipated peaceful intentions after the end of the World War II, research on phosphorus compounds was purposefully directed to the development of pesticides active against agricultural insect pests. The development of the first insecticides on phosphorus ester basis to be used in agriculture — bladan, parathion, potasan, systox and others — is linked with the name of Schrader. In view of the excellent initial results, other research groups soon wanted their share in the work on phosphorus ester insecticides.

As a result of this extensive research, the selection of phosphorus ester insecticides with respect to efficiency, duration of action, toxicity, range of activity, and behaviour in the plant is very broad. Indeed, modern plant protection would be inconceivable today without their use. Their importance has been further augmented in the early sixties when the detrimental properties of the chlorinated hydrocarbon insecticides, thus their accumulation in the environment and their persistence in human organisms, became apparent. These drawbacks brought about a change in the attitude of toxicologists with regard to optimal toxicological

characteristics. Finding a method for their rapid decomposition became more and more desirable even at the price of an increased acute toxicity, meaning an increased hazard during application. Organophosphorus insecticides, together with carbamates, represented the only practical alternative at that time.

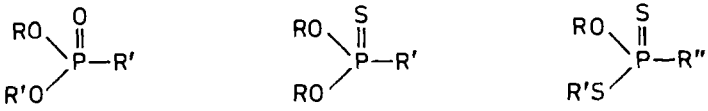
Organophosphorus compounds used as insecticides contain the pentavalent phosphorus atom. In the fundamental state the phosphorus atom has a $3s^2 3p^3$ external configuration; however, $3d$ orbitals also contribute to the formation of its compounds. Transition to the $3s^2 3p^2 3d$ state, corresponding to the trigonal bipyramide, requires a high activation energy of about 800 KJ/mole (Hudson, 1965).

Table 1.2
Types of organophosphorus compounds

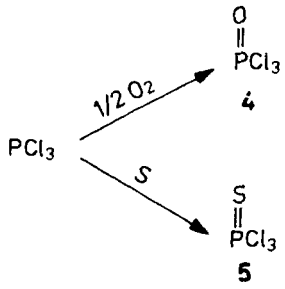


The major part of the phosphorus-containing insecticides cannot be considered as organophosphorus compounds in the strict sense because they do not contain a P—C bond. These compounds are esters, amides, anhydrides and fluorides of phosphoric, phosphorothioic and phosphorodithioic acids. Most of them can be classified in one of the types shown in Table 1.2.

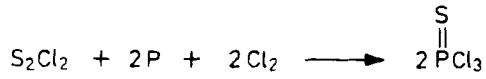
The number of insecticides containing a P—C bond and thus considered as organophosphorus compounds in the strict sense is considerably lower. They are predominantly esters of alkane- and benzenephosphonic acids and their sulfur analogues:



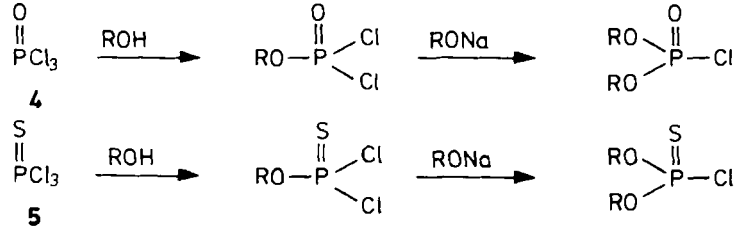
Phosphorus trichloride is the starting material used most frequently for the preparation of the esters, amides and anhydrides of phosphoric and phosphorothioic acids. It can be oxidised to phosphoryl chloride (**4**) and, heated with sulfur in the presence of a catalyst, to thiophosphoryl chloride (**5**) (Perot, 1962).



Thiophosphoryl chloride (**5**) can also be prepared by the introduction of chlorine into a mixture of disulfur dichloride and yellow phosphorus (Kovács *et al.*, 1972).

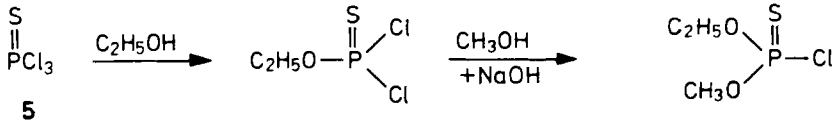


On reaction with alcohols, these compounds give alkyl phosphorodichloridates and alkyl thiophosphorodichloridates, respectively, which can be converted with a second mole of alcohol in the presence of an acid-binding base to dialkyl phosphorochloridate and its thio analogues (Fletcher *et al.*, 1948; Melnikov *et al.*, 1959).



On the basis of the stepwise exchangeability of the chlorine atoms, Melnikov *et al.* (1958) developed a process for the preparation of mixed dialkyl phosphorochloridothioates, feasible also on an industrial scale. This involves the reaction

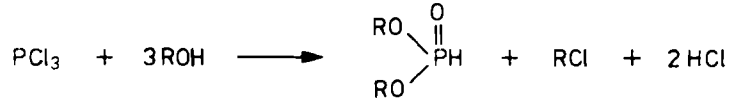
of thiophosphoryl chloride with a molar amount of one of the alcohols, generally one of higher carbon atom number, and then reaction with a second alcohol, whereby a molar quantity of alkali is simultaneously added to the reaction mixture:



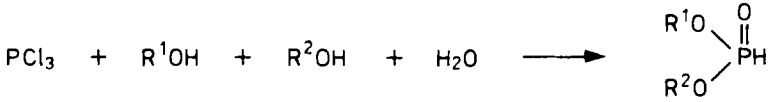
5

Dialkyl phosphorochloridothioates are intermediate products in the preparation of most compounds of a phosphorothioate ester base.

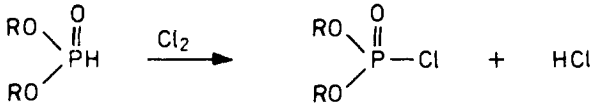
In the reaction of phosphorus trichloride with three moles of alcohol, dialkyl phosphonate ("dialkyl phosphite") is formed, together with hydrochloric acid and alkyl chloride.



Mixed dialkyl phosphonates can also be prepared by the reaction of phosphorus trichloride with a mixture of two different alcohols and water (Mandelbaum *et al.*, 1965).

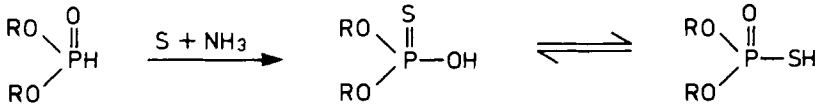


The dialkyl phosphorochloridates discussed earlier can also be prepared by chlorination of dialkyl phosphonates (Hardy *et al.*, 1944; Jenkins, 1944; McCombie *et al.*, 1945):



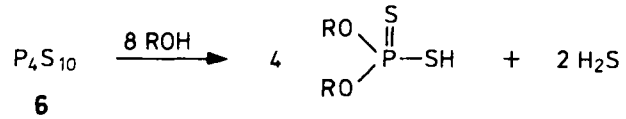
Instead of elemental chlorine, sulfuryl chloride or carbon tetrachloride can also be used as chlorinating agent (Steinberg, 1950; Fiszer and Michalski, 1952; Schrader, 1964).

Dialkyl phosphonates form with sulfur, in the presence of ammonia, dialkyl phosphorothionates, which are in equilibrium with their thiolo isomers (Jonas, 1949).



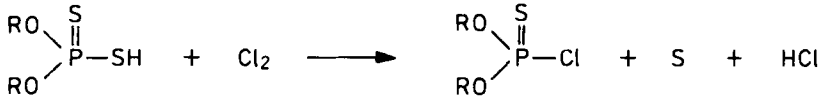
With alkylating agents, the salts of dialkyl phosphorothionates form O,O,S-trialkyl phosphorothioates. Dialkyl phosphonate can also be used as an alkylating agent (Melnikov *et al.*, 1965).

An important starting material in the preparation of phosphorus esters containing two sulfur atoms is phosphorus pentasulfide (**6**), formed by the reaction of phosphorus and sulfur at high temperature. Reaction in an anhydrous medium with alcohols gives O,O-dialkyl phosphorodithioates with evolution of hydrogen sulfide (Christmann, 1928; Malatesta and Pizzotti, 1945).

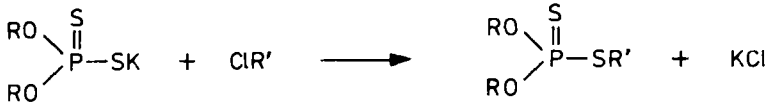


6

Dialkyl phosphorothiochloridates, mentioned earlier, can be prepared by chlorination of O,O-dialkyl phosphorodithioates (Hechenbleikner, 1947; 1949).



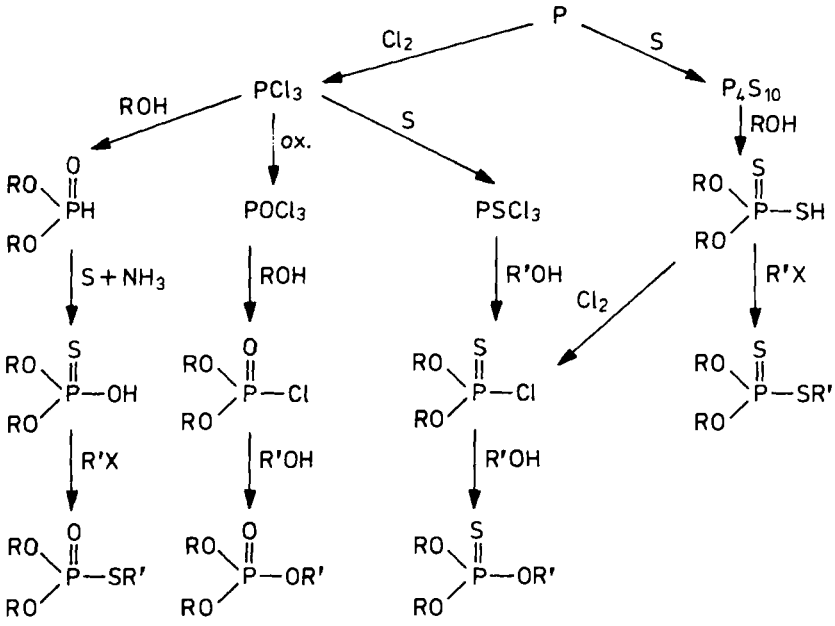
The salts of O,O-dialkyl phosphorodithioates can also be alkylated to form O,O,S-trialkyl phosphorodithioates. This reaction is used in the preparation of several important insecticides.



The preparation of the most important types of phosphorus ester insecticides and of their intermediates is summarised in Scheme 1.10

The action of phosphorus esters in the living organisms has been investigated extensively. While conclusions on the mechanisms of their action on warm-blooded animals are in agreement and can be considered as proved, opinions differ with respect to the mechanism of their insecticidal action. Excellent monographs cover this theme, such as the reviews of Heath (1961), O'Brien (1967), Triggle (1965), Fest and Schmidt (1973).

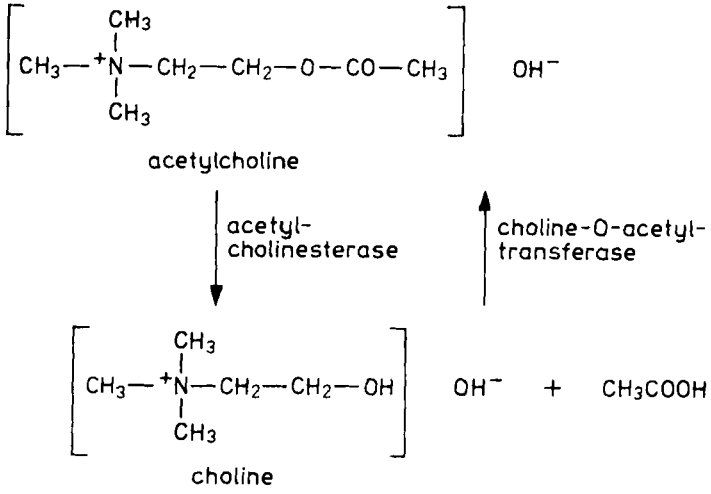
A decisive factor in their effect on warm-blooded animals is their ability to inhibit the function of the enzyme acetylcholinesterase. Synapses, myoneural junctions and ganglia of the nervous system transmit neural impulses by the mediation of acetylcholine. The function of acetylcholinesterase is to hydrolyse acetylcholine when muscle function ceases, and thereby to restore the state of rest. Hydrolysis of



Scheme 1.10

acetylcholine results in inactive choline and acetic acid from which, upon new neural impulses, acetylcholine is reformed by the enzyme choline-O-acetyltransferase with participation of ATP and CoA (Scheme 1.11).

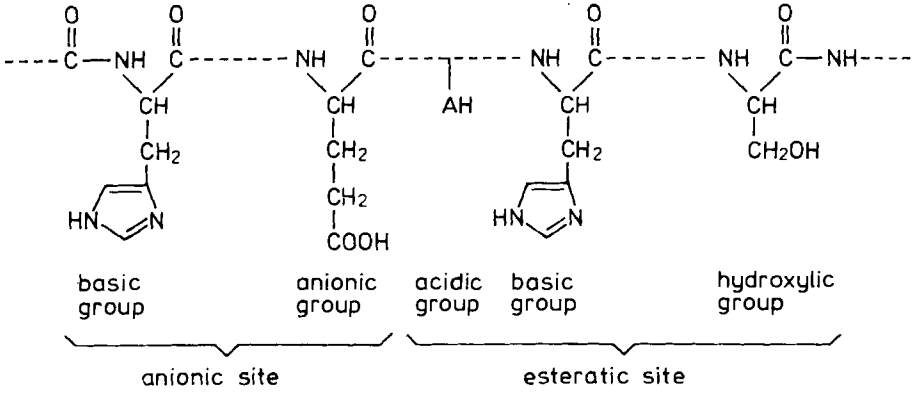
Following the research work of Wilson *et al.* in the 1950s, a pattern of the active zones of acetylcholinesterase emerged, according to which the active zone consists



Scheme 1.11

of two active sites. One of these is the anionic site, containing the imidazole ring of histidine in the polypeptide chain, which binds the cationic part of acetylcholine by Coulomb forces. The second active site is the esteratic site containing the hydroxyl group of serine which, on acylation, causes the hydrolysis of acetylcholine (Wilson and Bergmann, 1950a; 1950b; Bergmann *et al.*, 1950; Wilson *et al.*, 1950).

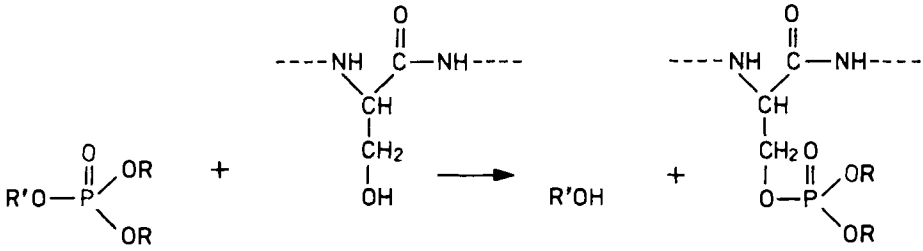
The original Wilson model had to be modified when on the basis of investigations in connection with the kinetics of enzyme action and with the pH optima of the substrate, it had to be assumed, that the sites of action of the active zone contain more functional groups, i.e. several subsites (Krupka and Laidler, 1961; Krupka, 1962; 1963; 1964; 1965; 1966). According to this concept, which is in good agreement with experimental results, the anionic active site of the active zone of acetylcholinesterase contains a basic and an anionic group, and its esteratic active site an acidic, a basic and a primary alcoholic group. The imidazole ring of histidine represents the basic group; the anionic group is one of the carboxylic groups of an aminodicarboxylic acid, presumably glutamic acid, and the primary alcoholic group is furnished by the hydroxymethyl group of serine. The nature of the acidic group has not yet been elucidated in detail. The schematic structure of the active zone of acetylcholinesterase is shown in Scheme 1.12.



Scheme 1.12

The complex of the enzyme with acetylcholine (Michaelis complex) is produced by the formation of an ionic bond between the quaternary nitrogen cation of acetylcholine and the anionic group of the enzyme, while the acidic group of the esteratic part protonates the ester-oxygen of acetylcholine. At the same time, the imidazole ring of the anionic part forms a hydrogen bond with a water molecule, and the imidazole ring of the esteratic part forms a hydrogen bond with the alcoholic group of serine, thereby activating the hydrolysis of acetylcholine, i.e. the acetylation of serine. The formation of the enzyme–substrate complex produces a conformational change in the enzyme, which is another precondition of enzyme activity (Stein and Koshland, 1953; Sanger, 1963; Engelhard *et al.*, 1967).

The phosphorus ester molecule, blocking the activity of acetylcholinesterase, first takes up a steric orientation determined by the anionic and acidic groups of the enzyme, and this is then followed by hydrolysis of the phosphorus ester and by phosphorylation of the hydroxyl group of serine at the esteratic site of the enzyme:

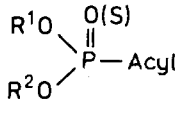


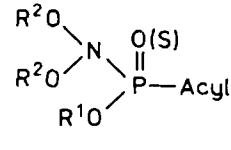
The phosphorylation of acetylcholinesterase is rapid while the hydrolysis of the phosphorylated enzyme is a slow process. Therefore, the enzyme is unable to function on prolonged blocking of the esteratic site. Acetylcholine accumulates which finally results in endogenic acetylcholine poisoning.

In humans, the symptoms of acetylcholine poisoning resemble on the one hand the syndrome of nicotine poisoning (muscle twitch, excitability, followed by muscular paralysis) and, on the other hand, the syndrome of muscarine poisoning (nausea, pain, exudation, increased diuresis, dyspnoea, pulmonary oedema). Owing to the effect on the central nervous system, the loss of sense of orientation, ataxy, tremor, derangement of consciousness and fainting occur simultaneously.

Investigation of the action of phosphorus esters in insects is impeded by the fact that, although the presence of acetylcholinesterase has been established in insects, it is not yet clear whether the enzyme plays a role in their neural activity. This is difficult to establish since acetylcholinesterase is not homogenous. Tripathi and O'Brien (1973) established the presence of seven acetylcholinesterase isoenzymes in the housefly, which varied markedly in their sensitivity to phosphorus esters. It seems probable that in the insecticidal action other mechanisms also play an important role besides the blocking of acetylcholinesterase. Thus, for example, organic phosphorus esters may bring about the liberation of endogenous substances which induce increased acetylcholine production by stimulating the electrical activity of the insect nerve (Brady and Sternburg, 1967).

On the basis of the relatively few compounds investigated at that time, Schrader (1952b) had already formulated in 1937 an empirical rule, *viz.* in order to be effective against insects, phosphorus esters must contain an acyl group. This rule initially involved only the esters and ester amides of phosphoric acid and phosphorothioic acid and was expressed by the formulae:





where R^1 and R^2 may be alkyl, alkoxy, or substituted amino groups alike (Schrader, 1950e).

According to this concept the acyl group may be represented by one of the following organic or inorganic anions: fluoride, cyanate, thiocyanate, enolate, mercaptide and different acid groups (Schrader, 1963). The concept of the acyl group may embrace in the wider sense a second phosphoryloxy group, an aryloxy or a heteroaryloxy group.

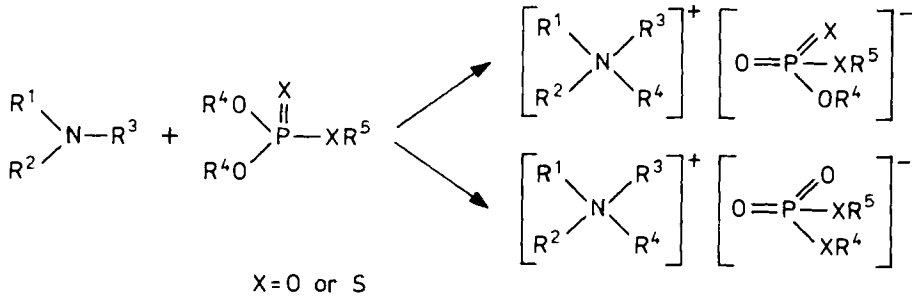
Although some of the phosphorus esters which are effective insecticides seem to refute the general validity of the structural conditions published by Schrader, most of the compounds so far correspond to this empirical rule. This has been a useful guide in the development of several active derivatives.

Phosphorothiolates are weaker cholinesterase inhibitors than the corresponding phosphates. At the same time, phosphorothiolates often show an efficiency higher by several orders of magnitude than that of phosphates. The main factor in producing this "thiolo effect" is that the 100° valence angle of the P—S—C bond provides better steric conditions for linkage to the enzyme than the 109° angle of the P—O—C bond (Niculescu-Duvas *et al.*, 1968; Cambanis *et al.*, 1969). Also methyl esters are less toxic than ethyl esters (Schrader, 1965; 1967).

Study of the structure–activity relationship is limited to empirical findings if the overall biological action and not its individual components are investigated as a function of chemical structure. Biological action is composed of several steps such as uptake, translocation, binding to the enzyme, inhibition of enzyme function, hydrolysis of the phosphorylated enzyme, etc. These steps assert themselves to a different degree in the development of the biological action, which makes the establishment of exact relationships very difficult. The investigations, therefore, which give really valuable information on the structure–activity relationship are those which relate chemical structure to single components of the total biological action. An important contributor to the total bioactivity of phosphorus esters is cholinesterase inhibition. This can be considered as a characteristic parameter in the investigation of the structure–activity relationship. In spite of this, the toxic effect seldom shows good correlation with the cholinesterase-blocking effect; measurement of the enzyme-inhibition does not give adequate information on the toxic effect to be expected.

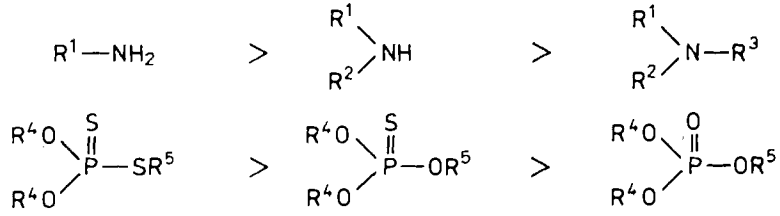
Another important feature in the biological action of phosphorus esters is their alkylating property. It is probable that the alkylating ability also plays a direct role in the exertion of the biological action, but it is primarily of importance in the detoxication of the phosphorus ester molecule and in the duration of action. On the basis of theoretical considerations, Melnikov stated in 1961 and it has been widely accepted since then that phosphorus esters alkylate esterases, nitrogen and sulfur compounds of minor importance for the organism, and dealkylate themselves thereby losing their activity (Melnikov, 1972). Several authors studied the dealkylation reaction of phosphorus esters in the presence of amines, amino ketones, amino alcohols, amino acids and other compounds (Shvetsova-Shilovskaya and Lebedeva, 1964; Melnikov *et al.*, 1965; 1967; 1968).

The reaction of phosphoric, phosphorothioic and phosphorodithioic acid esters with tertiary amines proceeds according to the following general scheme:



X = O or S

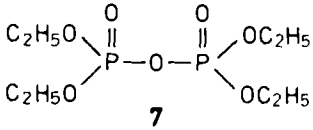
The rate of the alkylation or dealkylation reaction depends on the nature of both the amine and the phosphorus ester, and decreases in the order



Trimethyl phosphate alkylates trimethylamine in acetone solution 200 times more rapidly than triethyl phosphate (Thuong *et al.*, 1964). This may explain the earlier findings that the methylesters of phosphoric acid are less toxic than their ethyl homologues. The decreased toxicity can presumably be traced back to their more rapid dealkylation (Melnikov, 1972).

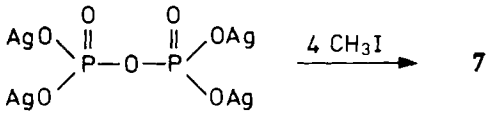
1.5.1 Phosphoric acid derivatives

One of the first known examples of phosphorus ester insecticides was tetraethyl pyrophosphate (TEPP, 7).

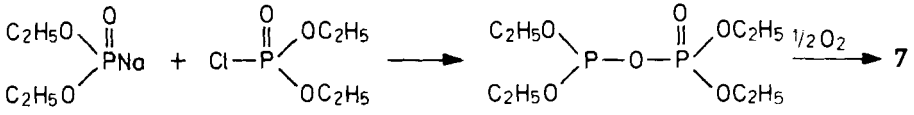


7

The insecticidal effect of TEPP was discovered by Schrader and Kükenthal in 1938 (Schrader, 1963), but its preparation had been reported more than a century earlier by De Clermont (1854), who methylated the silver salt of pyrophosphoric acid with methyl iodide:

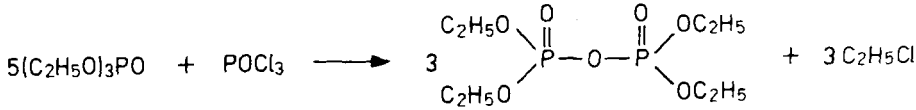


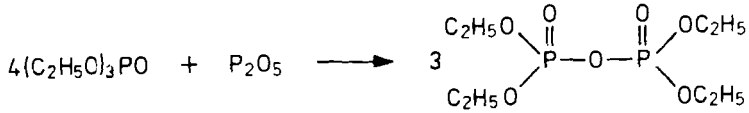
Nylén (1930) converted the sodium salt of diethyl phosphonate with diethyl phosphorochloridate (**8**) and oxidised the mixed phosphorus acid–phosphoric acid anhydride obtained:



8

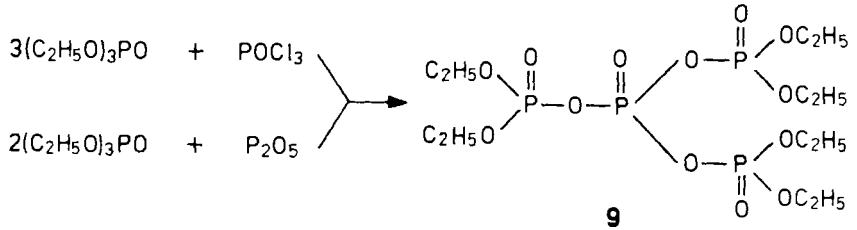
According to "Schrader's process", phosphoryl chloride reacts in the ratio 1 : 5 with triethyl phosphate, to give TEPP as the main product (Schrader, 1939; Willis, 1948). In the process developed by Woodstock (1942) phosphorus pentoxide is used instead of phosphoryl chloride:





7

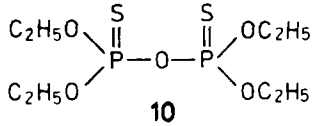
When phosphoryl chloride and triethyl phosphate are used in a ratio of 1 : 3 in Schrader's process, or phosphorus pentoxide and triethyl phosphate in a ratio 1 : 2 in Woodstock's process, the product formed consists mainly of hexaethyl tetraphosphate (HETP, **9**) (Schrader, 1939; Woodstock, 1942)



9

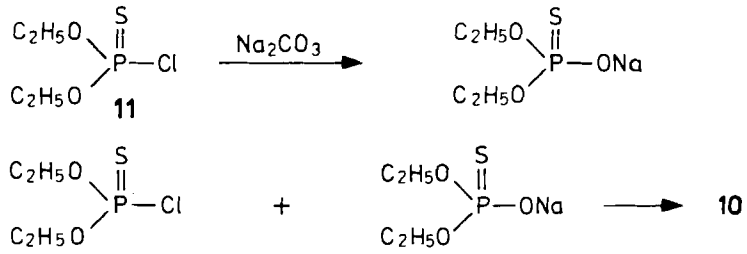
HETP was put onto the market in 1943 under the name Bladan® as the first insecticide of the phosphorus ester type. In spite of their strong insecticidal properties, TEPP and HETP were not widely used because of several disadvantages. They are among the most toxic phosphorus esters, their oral LD_{50} for rats being about 1.1 mg/kg. They are rapidly hydrolysed at room temperature by water to decompose to the inactive diethyl phosphate. The halftime of decomposition is 7 hours at 25°C.

The thiono analogue of TEPP, O,O,O',O'-tetraethyl dithiopyrophosphate (sulfotep, **10**), is more stable to hydrolysis.



10

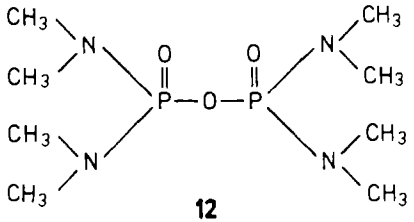
Several methods of preparing sulfotep are known. The process developed by Schrader, which is also used industrially, based on the partial hydrolysis of diethyl phosphorothionochloridate (**11**) is the most important. In this reaction, sodium diethyl thionophosphate is formed, which reacts with the unreacted diethyl phosphorothionochloridate to give **10** (Schrader and Mühlmann, 1950; Schrader, 1958):



Sulfotep is very toxic to man, but less so than its oxo-analogue; its LD_{50} for rats is 5 mg/kg. Owing to its high vapour tension, it is used mainly as a fumigant in greenhouses under the name Bladafum®.

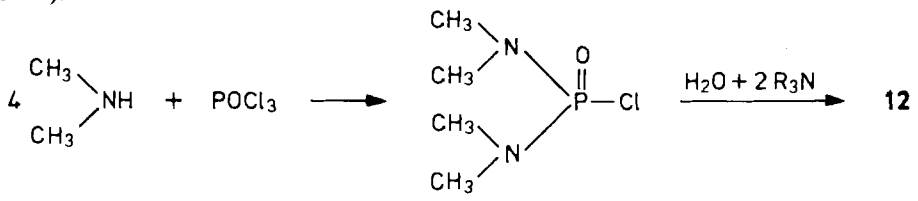
The fact that sulfotep (**10**) is more stable to hydrolysis than its oxo-analogue (**7**) is consistent with the general observation that the esters of phosphorothioic acids show a higher stability to hydrolysis than the respective esters of phosphoric acid. This can be ascribed to the fact that thion-sulfur is less electronegative than oxygen attached to the phosphorus atom by a double bond; thus because of its reduced charge, the phosphorus atom is less exposed to the attack of the hydroxyl ion.

A further improvement in chemical stability was achieved in octamethyl pyrophosphoroamidate (OMPA, **12**), which became known under the name schradan.



12

OMPA is prepared by partial hydrolysis of tetramethyl chlorophosphonoamidate, obtained by the reaction of dimethylamine and phosphoryl chloride, in a way analogous to the preparation of sulfotep **(10)** (Schrader and Kükenthal, 1941):



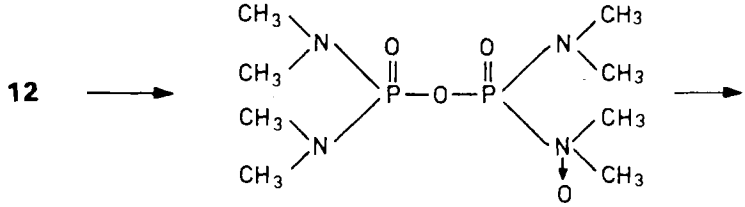
Schradan obtained its name after its discoverer Schrader. As distinct from other phosphorus esters, schradan is readily soluble in water as well as in organic solvents, but it is very stable in aqueous media. In alkaline media it is slowly hydrolysed.

OMPA is strongly toxic to warm-blooded animals: its LD_{50} for rats being 8 mg/kg, and is a relatively weak contact insecticide.

At the same time, extensive investigations of its mode of action revealed a novel property of the compound. It is translocated from the surface of the sprayed leaves or from the roots, into the tissues and from there, *via* the circulation of tissue fluids, into more distant parts of the plant. This "systemic effect" has several practical advantages: *(1)* the chemical in the tissues is not exposed to the same climatic factors (rain, sunshine, atmospheric oxygen, etc.) as on the surface of the leaves; *(2)* insects hidden at sites difficult to reach by spraying (abaxial surface, recesses of leaves) may also be killed; *(3)* the pesticide often penetrates the new shoots which develop after spraying, and protects them against insect pests; *(4)* when the chemical is absorbed by the leaf surface it poisons only the pests feeding by suction from the leaf tissues (plant lice, mites), while useful insects with other modes of feeding are spared.

After the discovery of the systemic effect of schradan, purposeful research for the preparation of systemic insecticides began. As a result of this work, compounds with improved practical properties were placed on the market and the use of schradan virtually ceased.

The fact that schradan has scarcely any contact effect is probably due to the fact that the carrier of the cholinesterase-inhibiting action is not the compound itself but its N-oxide **(13)** formed by enzymatic oxidation in the plant organism (Casida and Stahmann, 1953). This compound is unstable and, soon after its formation, the anhydride linkage is hydrolysed whereby inactive acid products are formed:



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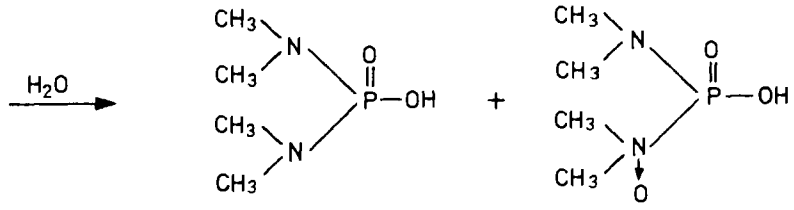
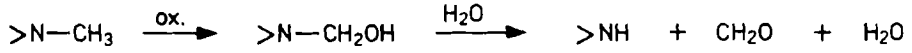


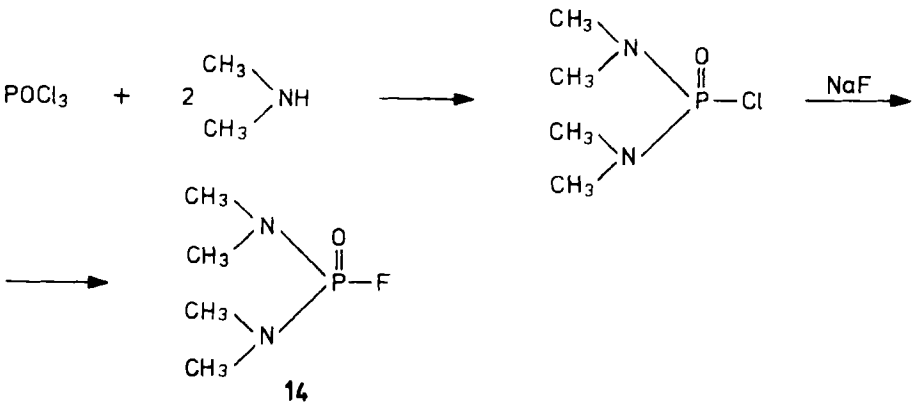
Fenwick (1958) found that the oxidative activation of schradan in the insect organism occurs *via* hydroxylation of the N-methyl groups. The N-hydroxymethyl derivative formed as intermediate product is subsequently hydrolytically demethylated to biologically inactive products:



Oxidative processes play an important role in the degradation of organic phosphorus ester insecticides. However, one of the degradation product is often biologically more active than the parent compound. The oxidative activation of schradan is a typical example, and may serve as a guide of more general validity to the biochemical transformation of other N-alkyl phosphoroamidates.

1.5.2 Phosphorofluoridates

The ester fluorides of phosphoric acid and phosphonic acids were the earliest known examples of biologically active phosphorus compounds. Sarin **(2)** and soman **(3)**, previously mentioned, did not attain practical importance because of their high toxicity, but they were the starting point for the development of other derivatives more suitable for agricultural purposes. Within this framework Schrader developed N,N,N′,N′-tetramethyl phosphorodiamidofluoridate **(14)**, which is used under the name dimefox. It is produced by the reaction of phosphoryl chloride with dimethylamine and the subsequent interaction of the phosphorochloridate formed with sodium fluoride (Schrader, 1947).

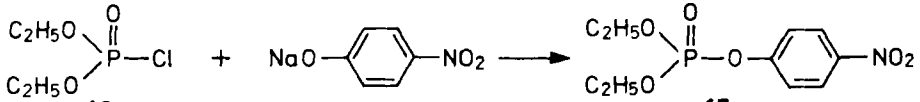


14

Dimefox is very toxic: its LD_{50} for rats being 3–5 mg/kg. It has a weak contact-insecticidal effect but at the same time excellent systemic properties. It is mainly used in hop cultures against plant lice and mites. The concentration of the insecticide in the hop plant attains its maximum one week after treatment of the soil and from this time on degradation causes a continuous decrease in concentration (Dejonckheere, 1974).

1.5.3 Substituted dialkyl-phenyl phosphates and phosphorothioates

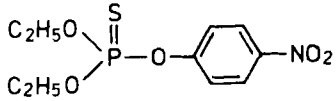
The first example of this most important group of phosphorus esters, diethyl-*p*-nitrophenyl phosphate (paraoxon, **15**), was prepared by Schrader (1948a) by the reaction of diethyl phosphorochloridate (**16**) with sodium *p*-nitrophenolate:



16 **15**

The strong insecticidal and acaricidal effect of this compound is linked with a high toxicity to warm-blooded animals (LD_{50} for rats is 3 mg/kg), so that it has not been used in agriculture. In ophthalmology it is used as a miotic agent under the name Mintacol®.

The thio analogue of paraoxon, diethyl-*p*-nitrophenyl phosphorothioate (parathion, **17**), is practically more adequate because of its lower toxicity to warm-blooded animals and higher stability against hydrolysis. It was prepared by Schrader in 1944, and the elucidation of its biological properties was due to Kükenthal and Unterstenhöfer (Schrader and Kükenthal, 1948; Unterstenhöfer, 1948; Schrader, 1952b).



17

Parathion is prepared by a method analogous to that of paraoxon (**15**), the reaction of diethyl phosphorothionochloridate (**11**) with sodium *p*-nitrophenolate.

Its industrial manufacture began in 1947 in the USA, and in 1948 in FRG. Because of its excellent practical properties, it soon became an indispensable tool in modern plant protection. Since then, several new phosphorus ester insecticides have been developed, but parathion has maintained its leading role and is still the first among insecticides of a similar type with respect to world production capacity.

Parathion is a yellow liquid with a boiling point of 116°C at 133 Pa. It is stable in neutral and acid media but is rapidly saponified by alkalies.

In the first hydrolysis step *p*-nitrophenol and inactive diethyl phosphorothioate (**18**) are formed. Owing to its rapid hydrolysis in the alkaline pH range, parathion cannot be used together with substances with an alkaline reaction.

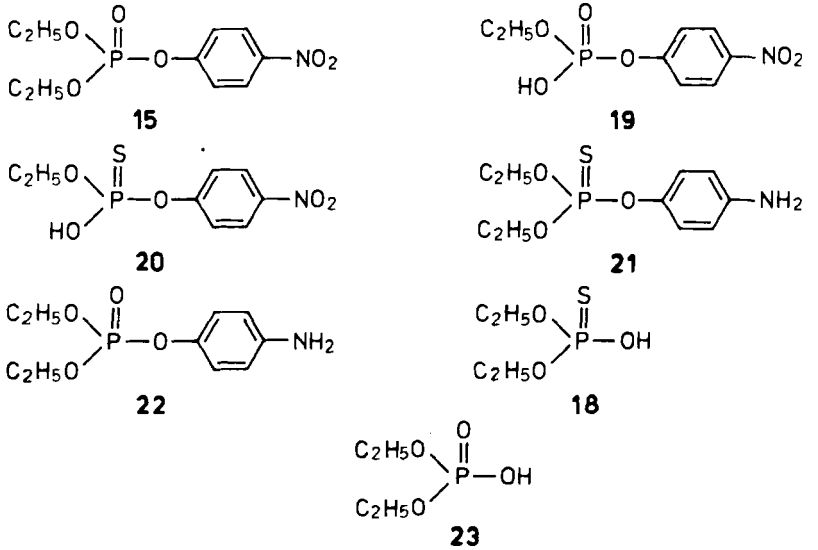
Parathion acts as a contact and stomach insecticide. It has no systemic effect, but it penetrates a certain distance from the sprayed surface into the leaf tissues (Frohberger, 1949; O'Brien and Smith, 1961). The range of action of parathion is very broad; in this respect it is foremost among the phosphorus ester insecticides. About four-hundred pests are known which can be controlled effectively with parathion. In addition to its insecticidal action, it is also an effective ovicide.

Formulations of parathion with mineral oils have proved to be very effective as winter sprays against various hibernating forms of orchard pests. It is particulary potent against plant lice, flies and caterpillars, killing these pests in concentrations as low as 0.0001–0.0008%. It is hazardous to bees. Spraying with parathion at blossom time is therefore not permitted.

The biological action of parathion is presumably based on the mode of action characteristic of phosphorus esters, i.e. phosphorylation of acetylcholinesterase. In all probability, however, *p*-nitrophenol liberated in the process also contributes to its effectiveness.

Although parathion is less toxic than its oxo analogue, paraoxon **(15)**, it can nevertheless be classed among the strongly active phosphorus ester insecticides; its oral LD_{50} for rats being 6.4 mg/kg.

The most important metabolic processes in warm-blooded animals are oxidation of the thiol group, O-dealkylation, and reduction and hydrolysis of the nitro group. Accordingly, the most important metabolites are paraoxon **(15)**, deethyl paraoxon **(19)**, deethyl parathion **(20)**, "aminoparathion" **(21)**, "aminoparaoxon" **(22)**, diethyl phosphorothioate **(18)** and diethyl phosphate **(23)** (Ahmed *et al.*, 1958; Plapp and Casida, 1958; Seume and O'Brien, 1960; Hollingworth, 1969; Appleton and Nakatsugawa, 1972) (Scheme 1.13).

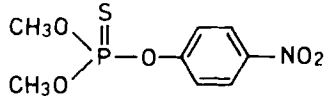


Scheme 1.13

The amino analogue of parathion (**21**) is biologically less active than the unchanged parathion, but it is more stable to hydrolysis. It is excreted mainly as a glucuronide.

Preparations containing parathion are turned brown by the action of strong sunshine and are decomposed. This may explain why parathion is rather rapidly deactivated on green plant surfaces. Its action on living plants lasts 1–8 days, which is a fraction of the duration of action measured on lifeless surfaces, an obvious indication that the rapid decomposition is caused for a great part by the enzyme system of the plant.

The methyl analogue of parathion, O,O-dimethyl-O-*p*-nitrophenyl phosphorothioate (parathion-methyl, **24**), has insecticidal properties similar to those of parathion.



24

Based on the process developed by Schrader (1948c), its production began in 1949. It is 2–3 times more sensitive to hydrolysis than parathion. In a manner similar to parathion, it undergoes thion–thiol isomerisation at high temperatures. However, isomerisation results in different products. While O,O-diethyl-S-*p*-nitrophenyl phosphorothioate (**25**) is formed from parathion, the isomerisation of parathion-methyl under identical conditions yields O,S-dimethyl-O-(*p*-nitrophenyl) phosphorothioate (**26**) (McPherson and Johnson, 1956).

17 **25**

24 **26**

The thiol isomer (**26**) is very unstable. Once decomposition has started, it proceeds like a chain reaction and results in the rapid breakdown of the molecule.

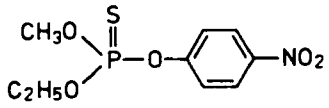
Parathion-methyl, like parathion, is a rapidly acting contact and stomach poison. It also has some fumigant action. Its range of action is similar to that of parathion. In insects it is metabolised to the respective oxo analogue.

Parathion-methyl is less toxic to humans than the ethyl homologue. This is in agreement with the general experience that dimethyl phosphoric acid and dimethyl thiophosphoric acid derivatives are less toxic to warm-blooded animals than the

diethyl homologues. The LD_{50} for rats is 15–20 mg/kg. Among other factors, the higher hydrolysis rate contributes to this lower toxicity.

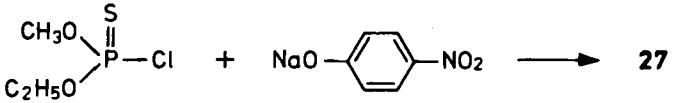
Parathion-methyl has the disadvantage that its action is not reliable at temperatures below 12°C.

Melnikov *et al.*(1958) synthesised O-methyl-O-ethyl-O-*p*-nitrophenyl phosphorothioate (methyl-ethyl-thiophos, **27**).



27

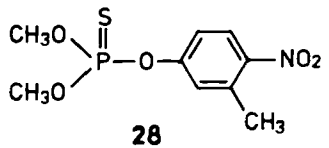
It was prepared according to the general scheme of preparation for derivatives of the parathion type, starting from methyl ethyl thionophosphorochloridate and *p*-nitrophenol:



As regards its chemical and physical properties, the compound occupies an intermediate position between parathion (**17**) and parathion-methyl (**24**), but its insecticidal efficiency somewhat exceeds that of both compounds (Melnikov, 1963).

The outstanding insecticidal properties of parathion induced several research groups to prepare related derivatives in which the aromatic ring contains other substituents besides the nitro group in *para*-position. From a practical point of view, an important finding was that the introduction of a methyl group into the aromatic ring considerably decreases toxicity, while it does not alter substantially the insecticidal effect.

On the basis of this finding, Czechoslovakian, German and Japanese workers independently developed fenitrothion, which has the chemical composition O,O-dimethyl-O-(3-methyl-4-nitrophenyl) phosphorothioate (fenitrothion, **28**) (Drábek and Pelikan, 1956; Lorenz, 1960; Suzuki *et al.*, 1960).

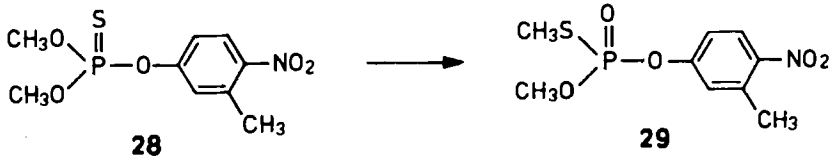


28

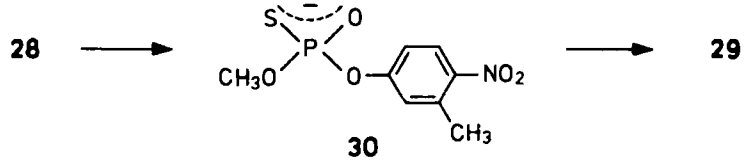
Fenitrothion is about one and half times more stable to hydrolysis than parathion-methyl.

Its isomerisation proceeds in a way similar to that of parathion-methyl (**24**), resulting in the O,S-dimethyl isomer (S-methyl fenitrothion, **29**).

Technical fenitrothion always contains the S-methyl isomer in varying quantities. The toxicity of the thiol isomer is higher and its stability to hydrolysis



lower than that of fenitrothion (Kovačičova *et al.*, 1973). Štasny and Truchlik (1974) found that the polarity of the solvents used for the manufacture of fenitrothion and for the preparation of the formulation strongly affects the degree of isomerisation, which is highest when dipolar, aprotic solvents are used. Tertiary amines used as catalists in the manufacturing process also promote this undesirable isomerisation. The isomerising agent is alkylated with the formation of onium salt, this is then followed by dealkylation and formation of an ambident anion **(30)**, which is realkylated on the sulfur atom:



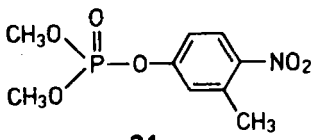
The oral LD_{50} of fenitrothion for rats is 500 mg/kg. The methyl group in the *meta*-position reduces its toxicity thirty-fold compared to that of parathion-methyl **(24)**. Miyamoto (1969) presumes, on the basis of experiments, that this reduced toxicity is due to the fact that the toxic oxo-analogue **(31)**, formed during metabolism, penetrates the brain to a lesser degree than the oxo analogue of parathion-methyl which lacks the methyl group on the aromatic ring.

Contrary to this, Hollingworth *et al.* (1967) traced back the toxicity-reducing effect of the 3-methyl group to a difference in the structure of acetylcholinesterase of insects and those of vertebrates. They found that the substituent on the phenyl ring in position 3 forms in the order H < methyl < isopropyl a bond of increasing strength between the enzyme from fly heads and the toxic compound, while the reverse order was found in the case of bovine erythrocyte acetylcholinesterase. From this they concluded that the distance between the anionic and esteratic centres is 0.1 nm larger in the insect enzyme than in the mammalian enzyme.

In green plants the half-life of fenitrothion decomposition is the same as that of parathion or parathion-methyl, i.e. 1–2 days, whereas the half-life of the oxo-analogue is only a few hours.

Miyamoto and Ohkawa (1978) have shown that the rat liver mixed function catalyses oxidative desulfuration of fenitrothion to fenitrooxon **(31)** and also the hydroxylation of the 3-methyl group, yielding 3-hydroxymethyl-fenitrooxon **(32)**, which is more potent than fenitrooxon.

Toxicity is reduced also by the substitution of the nitrophenyl group with a chlorine atom. O,O-Dimethyl-O-(3-chloro-4-nitrophenyl) phosphorothioate



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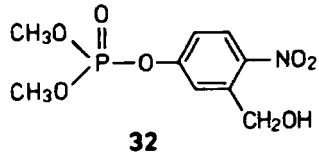
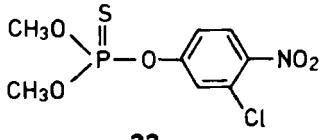


32

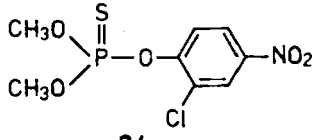
(chlorthion, 33), developed by Schrader (1952a, 1954), has an LD_{50} value of 880 mg/kg for rats.



33

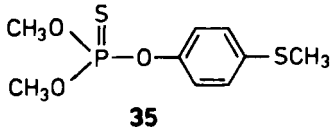
Chlorthion is slightly more sensitive to hydrolysis than its analogue, parathion-methyl (**24**), lacking the chlorine substituent. A methyl group in the *ortho*-position with respect to the nitro group thus increases and a chlorine atom decreases the stability to hydrolysis.

The 2-chlorine analogue of chlorthion is known under the name dicapthon (**34**). The transfer of the chlorine substituent from position 3 to position 2 results in a slight decrease in insecticidal and toxic effects (Davich and Apple, 1951; Fletcher, 1950; Gaines *et al.*, 1951).



34

O,O-Dimethyl-O-(*p*-methylthiophenyl) phosphorothioate (**35**) was the first example of the group of compounds which contain a phenyl group with a methylthio group as substituent. It is strongly toxic: its oral LD_{50} for rats being 10 mg/kg. As in the case of several other phosphorus esters, a methyl substituent in the *meta*-position with respect to the phenolic hydroxide strongly decreases toxicity to warm-blooded animals. O,O-Dimethyl-O-(3-methyl-4-methylthiophenyl) phosphorothioate (fenitrothion) of formula **36** was introduced under the name Lebaycid®. Its oral LD_{50} for rats is 313 mg/kg. A second methyl group in the *meta*-position further decreases toxicity (Schrader, 1960; Unterstenhöfer. 1960; Gilbert and Otto, 1962).



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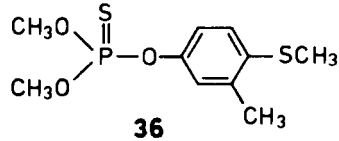
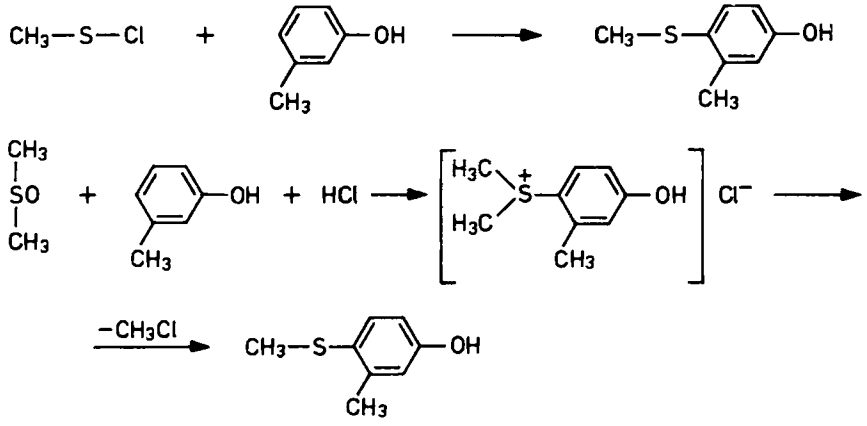


36

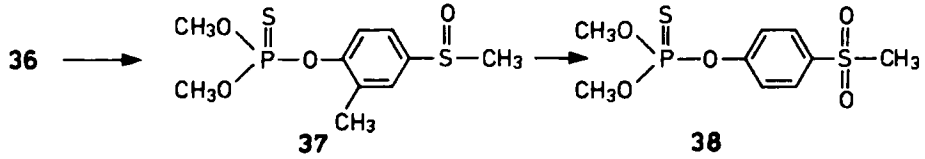
The synthesis of 3-methyl-4-methylthiophenol, required for the preparation of fenthion, has been worked out by Delfs and Wedemeyer. According to their method, *m*-cresol is reacted with methyl sulfene chloride or with dimethyl sulfoxide and hydrochloric acid (Delfs and Wedemeyer, 1957; Wedemeyer and Delfs, 1957), as shown in Scheme 1.14.



Scheme 1.14

Technical fenthion is a yellowish-brown oily liquid, very resistant to climatic factors and sunshine. It is also considerably more stable to hydrolysis than parathion-methyl. 50% hydrolysis of the latter compound proceeds at 80°C in acidic medium in 12.7 hours and in alkaline medium in 5 minutes, and of fenthion in 36 hours and 95 minutes respectively.

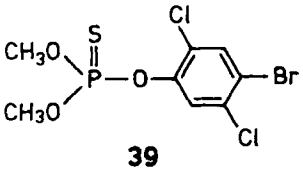
Fenthion is oxidised in the organism to its more effective sulfoxide derivative (**37**). Oxidation results in an increase in the insecticidal effect and simultaneously, toxicity to warm-blooded animals also increases by about three fold. Further metabolism leads to the formation of sulfone **38**, the toxicity of which to warm-blooded animals is similar to that of the sulfoxide, but its insecticidal efficiency is lower.



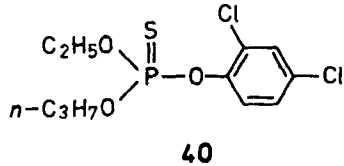
A similar oxidation is effected also by oxidising agents. The oxidation products were also put into use, compound **37** under the name sulfoxide fensulfothion, and compound **38** under the name sulfone oxythioate.

Fenthion is a rapidly acting contact and stomach insecticide with a very low phytotoxicity, and can therefore be used in cultures sensitive to other insecticides.

Derivatives which contain only halogen substituents on the phenyl group are mostly used as nematocides. Of the insecticides to be classified in this group, O,O-dimethyl-O-(4-bromo-2,5-dichlorophenyl) phosphorothioate (bromophos, **39**), its 4-iodine analogue (iodophenvos) and the asymmetrical organophosphoric ester prothiophos (**40**) are the most important (Sehring and Zeile, 1961; Beriger, 1965; Kudamatsu, 1976).



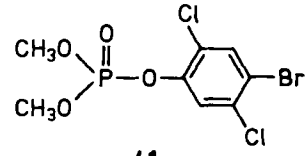
39



40

An advantageous property, characteristic of both compounds, is their very low toxicity to warm-blooded animals. The oral LD_{50} of bromophos for rats is 3750–6100 mg/kg. This, together with the fact that it injures neither the skin nor the mucous membranes, has made possible its use also against the ectoparasites of domestic animals.

The bromophos content of treated products rapidly decreases, after 10 days being less than 1 ppm, and after 20 days it can no longer be detected. Its most important metabolites in plant tissues are 4-bromo-2,5-dichlorophenol, bromoxon (**41**), formed by the exchange of thion-sulfur for oxygen, and mono-demethyl-bromophos (**42**), formed by partial demethylation (Stiasni *et al.*, 1969).



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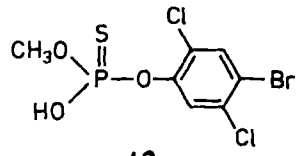
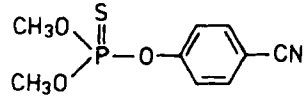


42

O,O-Dimethyl-O-(4-cyanophenyl) phosphorothioate (cyanophos, **43**), developed by Japanese workers, has also an outstandingly low toxicity for warm-blooded animals (Kuramoto *et al.*, 1961). Its oral toxicity for rats being 920 mg/kg.

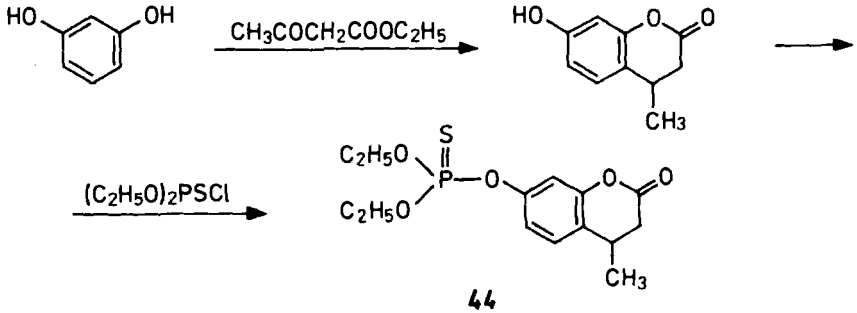


43

1.5.4 Dialkyl-heteroaryl phosphorothioates

The first representative of this type was E 838 (Potasan®), O,O-diethyl-O-(4-methyl-2-oxo-2H-1-benzopyranyl-7) phosphorothioate (**44**), which was developed by Schrader (1948b). 4-Methyl-7-oxycoumarine, required for its preparation, was

obtained according to the method of Pechman and Duisberg (1883) by the reaction of resorcinol with ethyl acetoacetate.

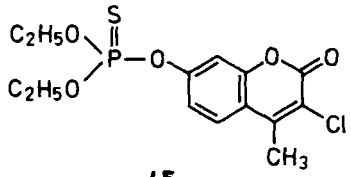


44

Contrary to most phosphorus ester insecticides, this compound has a weak effect on sucking insects, but is toxic to chewing insects, e.g. to the Colorado beetle.

In the pure state it has only a slight cholinesterase-inhibiting effect, but is nevertheless toxic to warm-blooded animals; its oral LD_{50} for male rats being 19 mg/kg. Following the metabolic pattern of most phosphorothioic esters, it is metabolised in animal tissues to its oxo analogue, which is a considerably more effective insecticide than the thio analogue.

Using ethyl α-chloroacetoacetate instead of ethyl acetoacetate as starting material, the chlorine analogue of E 838, O,O-diethyl-O-(3-chloro-4-methyl-2-oxo-2H-1-benzopyranyl-7) phosphorothioate (coumaphos, **45**), is formed (Schrader, 1951).



45

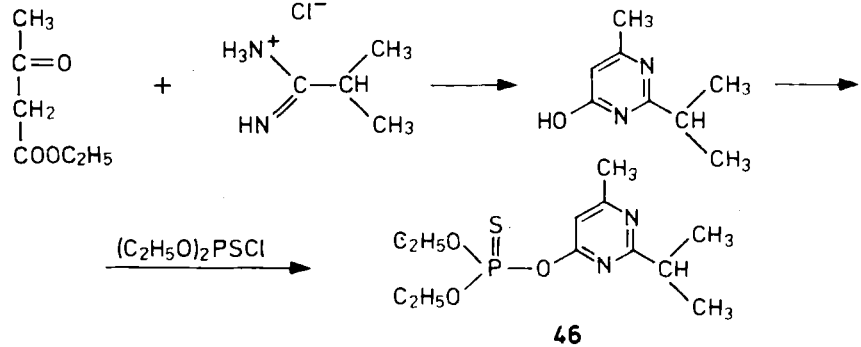
The efficiency against mosquito larvae increased a thousand-fold by the introduction of a chlorine atom, while toxicity to warm-blooded animals decreased to a fifth. This change in structure, seemingly negligible, changes the chemical properties of the compound significantly. Coumaphos is the most stable phosphorus ester insecticide known. When boiled for 2 hours with aqueous sodium carbonate solution, it hydrolyses only to a slight extent, while in neutral aqueous media even boiling for 12 hours does not cause hydrolysis.

Coumaphos is a contact insecticide with a narrow range of action. It has a specific action against various *Dipterae*. Owing to this action and its high stability, it is widely used in the area of hygiene for exterminating flies and the control of ectoparasites of domestic animals.

In the series of heteroaryl derivatives, compounds containing nitrogen as the heteroatom form a considerably larger group. Pioneering work on this group of

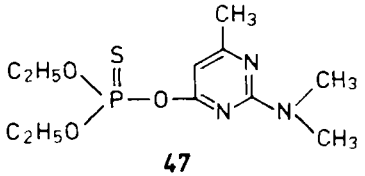
compounds was carried out by Gysin and Margot, who prepared heterocyclic enol derivatives by the reaction of β-ketocarbamic acid esters with hydrazine and amidine derivatives. Initially, these were converted into dimethyl carbamic acid esters, and these syntheses led to the development of carbamate insecticides, discussed already. Later, a series of interesting compounds of a novel type were prepared by phosphorylating these heterocyclic enols.

The first of these was O,O-diethyl-O-(2-isopropyl-6-methyl-4-pyrimidyl) phosphorothioate, **(46)** introduced under the name diazion. It is prepared by condensation of isobutyramide and ethyl acetoacetate, yielding 2-isopropyl-4-methyl-6-oxy-pyrimidine, which is then reacted with O,O-diethyl phosphorothiochloridate in the usual way (Gysin and Margot, 1952).



46

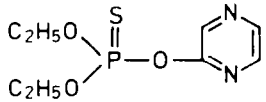
O,O-Diethyl-O-(2-dimethylamino-4-methyl-pyrimidyl-6) phosphorothioate, (pirimiphos-ethyl, **47**) differs from diazinon only with respect to its side-chain (McHattie, 1966).



47

The insecticidal range of action of the two compounds and their toxicity to warm-blooded animals are similar; their LD_{50} for male rats being 108 and 125 mg/kg, respectively.

Of the pyrazine and benzpyrazine derivatives, O,O-diethyl-O-(pyrazinyl-2) phosphorothioate (thionazin, **48**) (Dixon *et al.*, 1958) and its benzene homologue, diethquinalphion **(49)**, which were developed almost simultaneously and independently by the research workers of the Bayer Co. (Schmidt and Hammann, 1966) and the Sandoz Co. (Helfenberger and Lutz, 1966), have attained importance.



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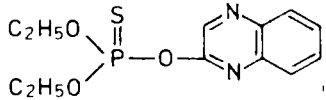
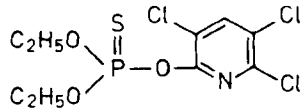


49

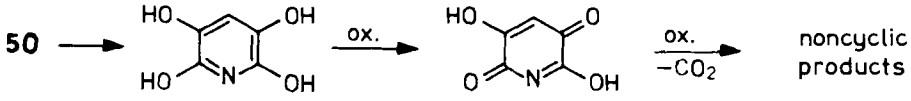
The two compounds differ with respect to their insecticidal and toxicological properties; the LD_{50} of thionazin for male rats being 5 mg/kg and that of diethquinalphion 70 mg/kg.

In the series of derivatives containing one hetero-nitrogen, O,O-diethyl-O-(3,4,6-trichloro-pyridyl-2) phosphorothioate, introduced under the trade name Dursban® **(50)**, attained importance because of its high larvicidal action (Rigterink, 1963; Rigterink and Kenaga, 1966).

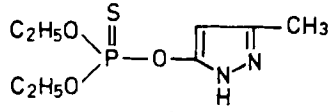


50

It is effective against both sucking and chewing insects; its LD_{50} for rats is 150, for guinea pigs 500 mg/kg. Its action persists for 6–11 weeks on various surfaces but, on plant surfaces, it is enzymatically decomposed in a shorter time. During its photochemical decomposition 2,3,5,6-tetrahydroxypyridine is formed. This compound is oxidatively converted to quinoidal derivatives, which are finally oxidised, with loss of carbon dioxide, to noncyclic decomposition products:



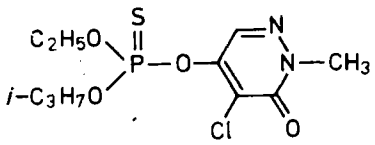
Of the five-membered heterocyclic ring derivatives, O,O-diethyl-O-(3-methylpyrazolyl-5) phosphorothioate **(51)**, introduced under the name Pyrazothion®, is an insecticide with strong systemic action. The development of this compound was a further important result of the research program carried out by the research workers of the Geigy Co. on the phosphorus esters of enolisable heterocyclic compounds obtained from β-ketocarboxylic acid esters (Gysin and Margot, 1952).



51

Konečný *et al.* (1979) described the synthesis of a series of O,O-dialkyl-, O-alkyl-O-(2-chloroethyl)- and O-alkyl-O-(2-ethoxyethyl)-O-(1,5-disubstituted-6-oxo-1H-pyridazin-4-yl) phosphorothioates. The most promising insecticidal, ovicidal and acaricidal activities were given for compounds **52**, **53** and **54**.

However, the mammalian toxicity of these compounds is relatively high: the oral LD_{50} for rats of compound **53** being 9 mg/kg, that of compound **54** 14 mg/kg. Compound **54** is regarded by the authors as a perspective soil insecticide.



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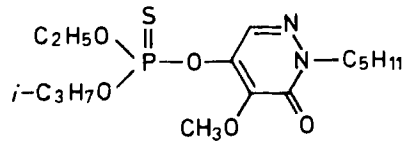

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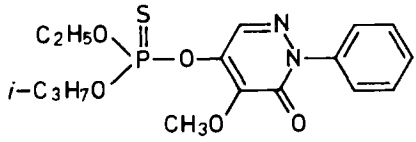
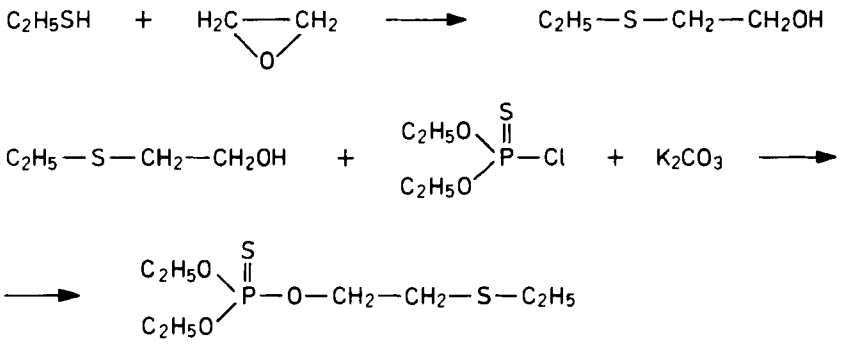


54

1.5.5 Phosphorothioates and phosphorodithioates containing alkylthioalkyl or arylthioalkyl groups

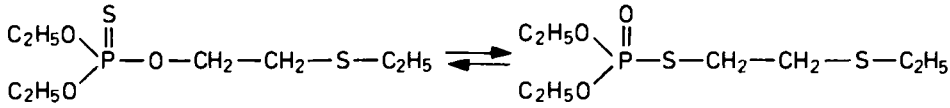
In the chemical sense, the members of this type belong to the larger group of aliphatic phosphorothioates, but their special insecticidal properties, their historical importance and their wide application justifies their discussion as a separate group.

The development of the first and still most important members of the group is linked with the name of Schrader. O,O-Diethyl-O-(2-ethylthioethyl) phosphorothioate (demeton-O, **55**), introduced under the name Systox®, was prepared by the reaction of ethylmercaptane with ethylene oxide, and the reaction of the resulting 2-ethylthio-ethanol with diethyl phosphorothionochloridate in the presence of an acid binder (Schrader, 1950a, 1950b).



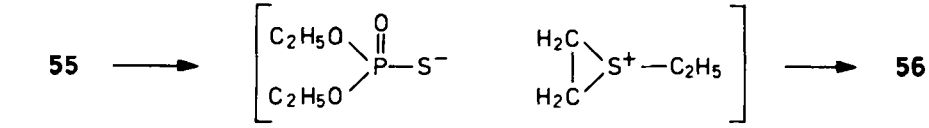
55

However, the compound is unstable in this form. It undergoes partial thion–thiol isomerisation, and the commercial product (demeton, Systox®) contains in equilibrium 30% of the thiol isomer (demeton-O, **55**) and 70% of the thion isomer (demeton-S, **56**) (Schrader, 1950c).

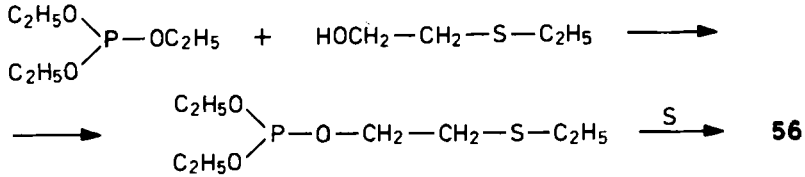


55 **56**

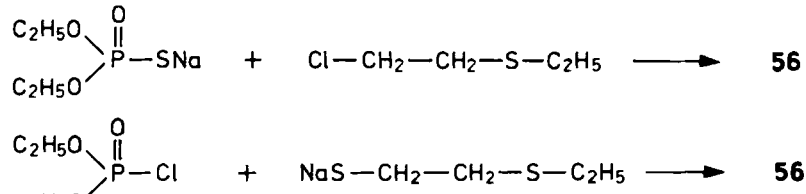
Isomerisation is rapid at high temperatures, proceeding in 3 hours at 130 °C. Polar solvents also accelerate isomerisation, probably due to the fact that isomerisation takes place *via* ionic intermediate products (Fukuto and Metcalf, 1954; Henglein and Schrader, 1955):



Although the most important industrial production of demeton-O is based even today on the original synthesis of Schrader, several other methods of synthesis are known. Thus, for example, according to a process developed similarly by Schrader (1953a), triethyl phosphite is transesterified with 2-ethylthio-ethanol, and the diethyl-2-ethylthioethyl phosphite obtained is reacted with sulfur:



Demeton-S (**56**) can also be prepared directly by the reaction of sodium O,O-diethyl phosphorothioate with ethyl-2-chloroethyl sulfide or by the reaction of diethyl phosphorochloridate with sodium 2-ethylthioethyl mercaptide (Schrader, 1950a; 1950b).

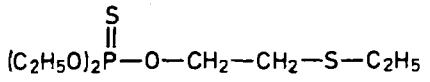
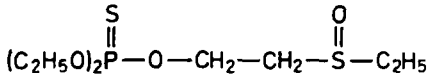
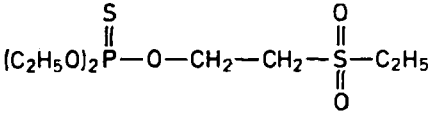
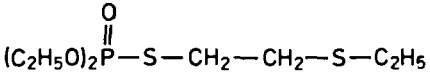
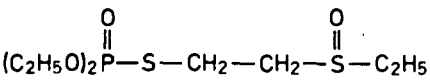
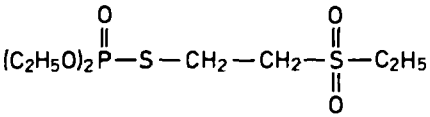
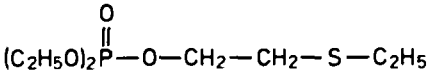
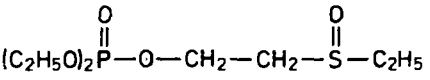
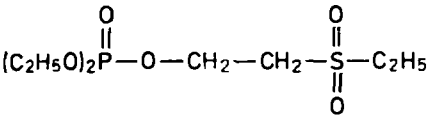


There are considerable differences between the two isomers with respect to their physical, chemical and biological properties. The 50% saponification of the thion isomer requires 75 minutes at 25°C and pH 13, while that of the thiol isomer takes place in 51 seconds. The solubility of the thion isomer in water at 20°C is 60 mg/l, while that of the thiol isomer is 2000 mg/l. This increased water solubility of the thiol isomer brings about its excellent translocation ability in the transport system of the plant. In the technical isomer mixture, therefore, the thiol isomer is actually responsible for the systemic effect.

The thioether sulfur atom of both isomers is oxidised by oxidising agents to a sulfoxide group and on further oxidation to a sulfon group. The investigations of Metcalf *et al.* (1955) showed that the same oxidation also occurs in plants, insects and mammals. Following this, and partly simultaneously, the thion sulfur atom of the thiono isomer **55** is exchanged for oxygen and finally, during hydrolysis, diethyl phosphate and then phosphoric acid are formed.

The biological efficiency of demeton-O (**55**), demeton-S (**56**) and their metabolites is shown by the data of Table 1.3.

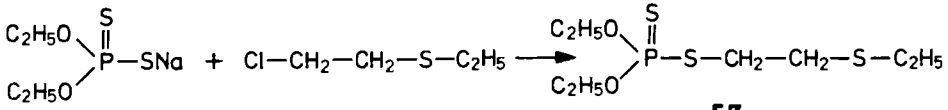
Table 1.3
Biological efficiency

Demeton-O (**55**), demeton-S (**56**) and their metabolites		50% cholinesterase inhibition (molar conc.)	Oral LD_{50} in rats mg/kg
	**55**	2.2×10^{-4}	30.0
		3.6×10^{-6}	100.0
		8.3×10^{-7}	90.0
	**56**	3.5×10^{-6}	1.5
		1.5×10^{-6}	2.0
		6.0×10^{-7}	2.0
		2.4×10^{-8}	175.0
		1.1×10^{-6}	10.0
		1.2×10^{-7}	75.0

As can be seen from the data, the thiol isomer (**56**) is a very strong poison for warm-blooded animals. However, it is rapidly excreted mostly in the form of its nontoxic metabolites. Following oral administration, the feces contain scarcely any metabolites, indicating that it is almost completely resorbed from the gastrointestinal tract.

Demeton is very effective against plant lice and mites, and has been used successfully against San José scale, which is difficult to control. Demeton rapidly penetrates from the sprayed plant surface into the plant tissues, and 1 hour after spraying 30–40% has been absorbed.

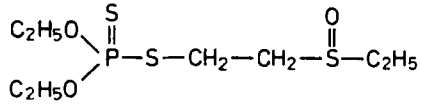
The dithio analogue of demeton, O,O-diethyl-S-(2-ethylthioethyl) phosphorodithioate, is known under the name disulfoton (**57**). It has been prepared by Lorenz and Schrader (1952) by the reaction of O,O-diethyl phosphorodithioate with ethyl-2-chloroethyl sulfide:



57

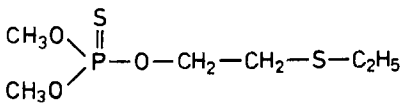
Consistent with the general finding that phosphorodithioates are considerably more stable to hydrolysis than phosphorothioates, disulfoton is very resistant to hydrolysis. Owing to this property and its excellent systemic action, it also protects the plants against sap-sucking insects when used for the treatment of seeds. A disadvantage of disulfoton is its high toxicity to warm-blooded animals, its LD_{50} for rats being 2–12 mg/kg.

Similar to demeton, the sulfide sulfur atom of disulfoton is oxidised to the sulfoxide and the sulfone. The sulfoxide (**58**) of disulfoton is marketed under the name oxydisulfoton. Its biological properties are similar to those of disulfoton.

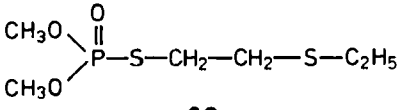


58

The O,O-dimethyl homologues of the derivatives discussed above, such as demeton-O-methyl (**59**) and demeton-S-methyl (**60**), attained importance because of their lower toxicity (Schrader, 1950d; Lorenz *et al.*, 1955; Mühlmann *et al.*, 1954; Lorenz *et al.*, 1955). Demeton-methyl, like its diethyl homologue discussed above, contains 70% of the thiono isomer (**59**) and 30% of the thiol isomer (**60**).



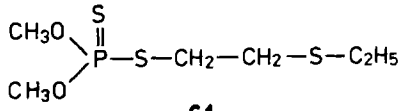
59



60

The oral LD_{50} of demeton-O-methyl for rats is 180 mg/kg.

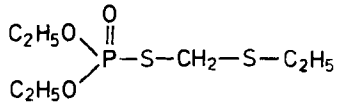
The methyl analogue of disulfoton, O,O-dimethyl-S-(2-ethylthioethyl) phosphorodithioate, is known under the name thiomethon (**61**).



61

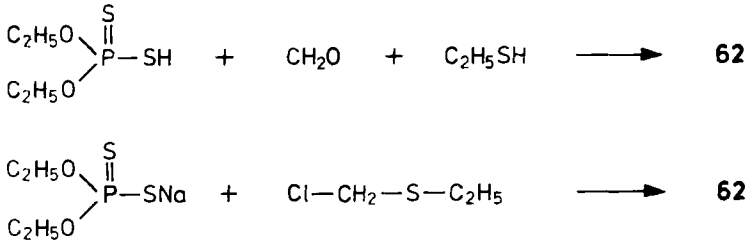
Thiomethon was developed simultaneously but independently by research groups of the Bayer Co. (Lorenz and Schrader, 1952) and the Sandoz Co. (Lutz *et al.*, 1953). Its oral LD_{50} for rats is 85 mg/kg.

Phosphorodithioates containing only one methyl group instead of two between the two sulfur atoms have somewhat different chemical and biological properties compared to thiomethon. A characteristic representative of this type of compound is O,O-diethyl-S-(2-ethylthiomethyl) phosphorodithioate (phorate, **62**).



62

Phorate can be prepared by the reaction of diethyl phosphorodithioic acid, ethyl mercaptan and formaldehyde (Hook and Moss, 1948), or by the reaction of sodium O,O-diethyl phosphorodithioate with ethylthiomethyl chloride (Lorenz and Schrader, 1952).

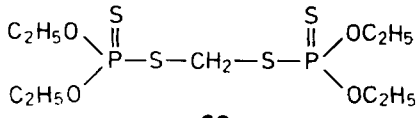


Phorate is a contact and systemic insecticide. It belongs to the most toxic insecticides known; its LD_{50} for rats being 2 mg/kg. Phorate is distinguished by its volatility. Owing to this property, it also exerts its insecticidal action as fumigant.

It is considerably more sensitive to hydrolysis than disulfoton, as a result of the mercaptal structure. Its metabolism in plants is identical with that of disulfoton and, sulfoxide and sulfone derivatives, more readily soluble in water, are formed.

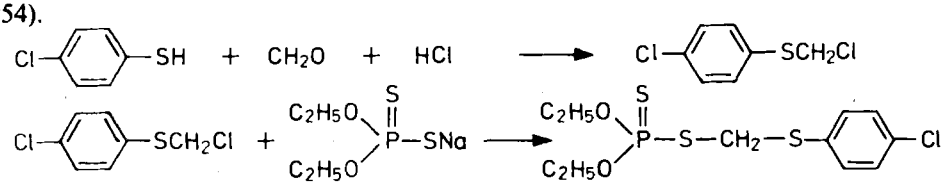
O,O,O′,O′-Tetraethyl-S,S′-methylene bis(phosphorodithioate) (ethion, **63**) can be considered as a double phorate molecule, and its action is similar to that of phorate. It is prepared by the interaction of diethyl phosphorodithioic acid with methylene

bromide or with formaldehyde (Lorenz and Schrader, 1958; Willard and Henahan, 1956).



63

When using 4-chlorophenylthiomethyl chloride instead of ethylthiomethyl chloride in the synthesis of phorate, O,O-diethyl-S-(*p*-chlorophenylthiomethyl) phosphorodithioate, known by the name carbophenthion **(64)** is formed (Fancher, 1954).

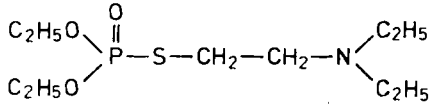


64

Its LD_{50} for rats is 30–120 mg/kg, and its oral single dose LD_{50}, tested on various birds, is 29–35 mg/kg (Jennings *et al.*, 1975). Carbophenthion is an effective contact insecticide and acaricide with hardly any systemic effect. On the surface of foliage it is converted by atmospheric oxygen into its oxo derivative (P=O analogue), which has a considerably higher cholinesterase-inhibiting effect.

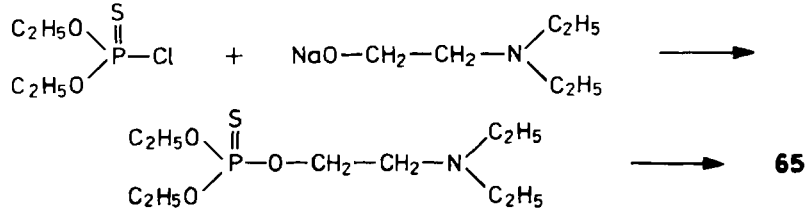
1.5.6 Dialkyl-dialkylaminoethyl phosphorothioates

Amiton, O,O-diethyl-S-(2-diethylaminoethyl) phosphorothioate **(65)** is the sole representative of practical importance of this type of insecticide (Ghosh and Newman, 1955). It has a basic character because of its tertiary nitrogen atom, and forms water-soluble salts with acids. Its oxalic acid salt was introduced under the trade name Tetram®.



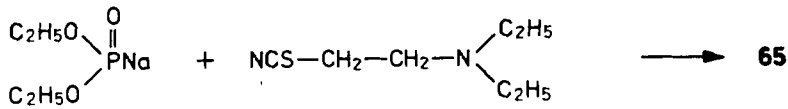
65

According to one method of preparation, O,O-diethyl phosphorothiochloridate is reacted with the sodium salt of 2-diethylamino-ethanol, and the thiono isomer formed is isomerised by heating:



According to Schrader (1953b), the reaction of sodium diethyl phosphite with 2-diethylaminoethyl rhodanide gives the required product directly.

Amiton is a very potent insecticide and acaricide with a strong ovicidal action.

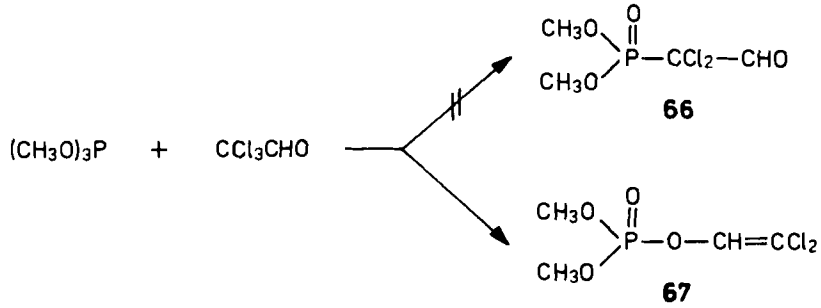


65

However, its use is limited owing to its high toxicity: its LD_{50} for rats being 3 mg/kg, and for mice 0.5 mg/kg. It is easily absorbed by the skin and, due to its volatility, it can exert its action also in the vapour phase.

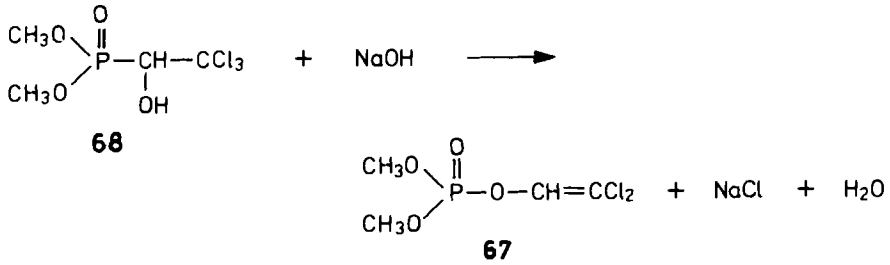
1.5.7 Dialkyl-vinyl phosphates

Between 1948 and 1952 Morris and Van Winkle (1952), Arbuzov and Alimov (1951), and Perkow *et al.* (1952) investigated independently the reaction of polyhalogen aldehydes, primarily of chloral, with trialkyl phosphites. The conversion was assumed by some workers to be a true Michaelis–Arbuzov reaction and, accordingly, it was thought erroneously that the product formed in the reaction of chloral and trimethyl phosphite is the phosphonate of formula **66**. Perkow *et al.* (1952) established that α-halogen carbonyl compounds give with trialkyl phosphites an anomalous Michaelis–Arbuzov reaction, so that the actual reaction product is 2,2-dichlorovinyl phosphate, **67**. This reaction is known in the literature as Perkow's reaction.



Independent of these workers, Lorenz *et al.* (1955) found that O,O-dimethyl-(1-hydroxy-2,2,2-trichloro)ethane phosphonate (trichlorfon, **68**), to be discussed later, on interaction with alkali loses one mole of hydrogen chloride, and that subsequent rearrangement also yields product **67** (dichlorvos, DDVP).

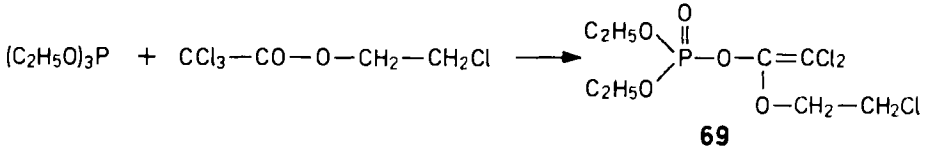
Dichlorvos is a very effective insecticide, used in plant protection against sucking and chewing insects and leaf miners, and in the hygiene sector against flies. It is highly volatile and therefore also has a fumigant action. It is rapidly hydrolysed in plants to dimethyl phosphate and dichloroacetaldehyde, so that it can also be used shortly before harvest. The oral LD_{50} for rats is 62 mg/kg.



68 **67**

In animals demethylation is mainly responsible for the detoxication of dichlorvos. The methyl group acceptor is presumably the mercapto group of glutathione. In warm-blooded animals detoxication is very rapid. In insects, however, it is slow, because insects do not have a detoxication mechanism resulting in demethylation. Löfroth (1970), Wennerberg and Löfroth (1974) and Löfroth and Wennerberg (1974), interpreting erroneously their experimental findings, came to the conclusion that dichlorvos and other phosphorus esters with alkylating properties have in addition to their cholinesterase-inhibiting effect also a mutagenic or carcinogenic effect, because they are able to convert the guanine of DNS into 7-methyl-guanine. However, their assumptions concerning both the mechanism of the alkylation reaction and the mutagenic and carcinogenic effect of dichlorvos, have been disproved by others (Buselmaier *et al.*, 1972; Dean and Thorpe, 1972; Epstein *et al.*, 1972; 1975).

The Perkow reaction of triethyl phosphite with 2-chloroethyl trichloroacetate gives O,O-diethyl-O-[1-(chloroethoxy)-2,2-dichlorovinyl] phosphate **(69)**, introduced under the trade name Forstenon® (Sallmann, 1952).

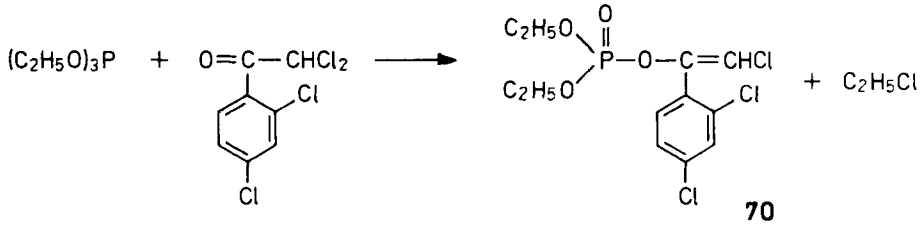


69

It is about ten times more toxic than dichlorvos, and due mainly to its high toxicity to warm-blooded animals its use was banned.

Not only the α-polyhalogen aldehydes, but also the α-polyhalogen ketones give the Perkow reaction with trialkyl phosphites, whereby vinyl phosphates are formed containing one chlorine atom less. In the reaction of triethyl phosphite with dichloromethyl-2,4-dichlorophenylketone, O,O-diethyl-O-[1-(2,4-dichlorophenyl)-2-chlorovinyl] phosphate (chlorfenvinphos, **70**) is formed (Wheatstone and Harman, 1960; Wheatstone *et al.*, 1966). The technical product serving as the active ingredient of Birlane® contains 84.8% *Z*- and 9.6% *E*-isomer.

Chlorfenvinphos can be grouped among the moderately toxic insecticides. Its action is lasting, but after a few months it is decomposed to harmless compounds. When environmental conditions are known, the decomposition time can be predicted. When used for soil treatment, its half-life in peat soil is 22 weeks, in clay

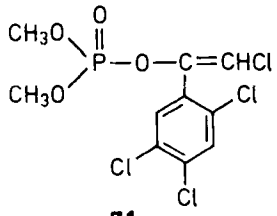


70

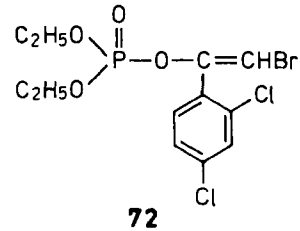
soil 15 weeks and in sandy soil 7 weeks. Its vapour tension is low. Owing to these properties, it is very suitable for soil disinfection.

O,O-dimethyl-O-[1-(2,4,5-trichlorophenyl)-2-chlorovinyl] phosphate (tetrachlorvinphos, **71**) can be prepared in an analogous way (Phillips and Ward, 1962).

Polish research workers prepared several analogues of chlorfenvinphos in order to develop a derivative with similar action but less toxic. The result of this work was O,O-diethyl-O-[2-bromo-1-(2,4-dichlorophenyl)vinyl] phosphate (bromfenvinphos, **72**). It is prepared by the Perkow reaction with triethyl phosphite and dibromoethyl-2,4-dichlorophenyl ketone (Fulde *et al.*, 1974; Zwierzak, 1974).



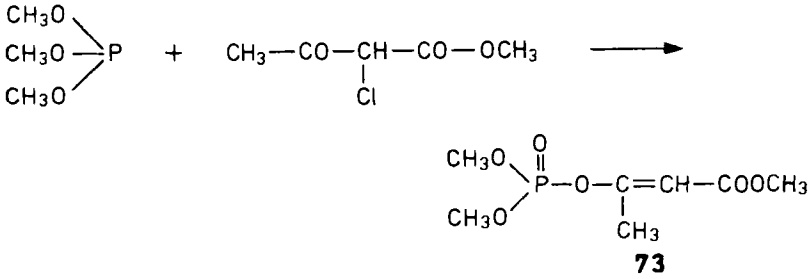
71



72

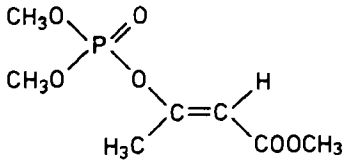
Bromfenvinphos has mainly a contact insecticidal effect identical to that of chlorfenvinphos (**71**), but its oral and dermal toxicity measured in rats is only one third or one fourth that of the latter (Majda and Chruscielska, 1974).

Based on the research work of Stiles (1952), one of the most important phosphorus ester insecticides, O,O-dimethyl-O-[(1-methyl-2-carbomethoxy)vinyl] phosphate (mevinphos, **73**) was introduced in 1957 under the trade name Phosdrin®. It is prepared by the Perkow reaction from trimethyl phosphite and methyl α-chloroacetoacetate.

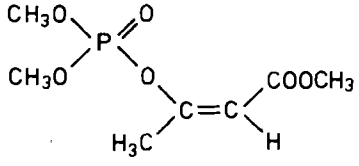


73

The compound is a quick-acting contact and systemic insecticide and, being volatile, it has also a fumigant action. Both leaves and roots of the plant absorb the compound rapidly. Of its stereoisomers, the *Z*-isomer (*Z*-mevinphos, **73a**) is a hundred times more active than the *E*-isomer (*E*-mevinphos, **73b**), so that the *Z*-isomer is virtually the sole carrier of the insecticidal effect.

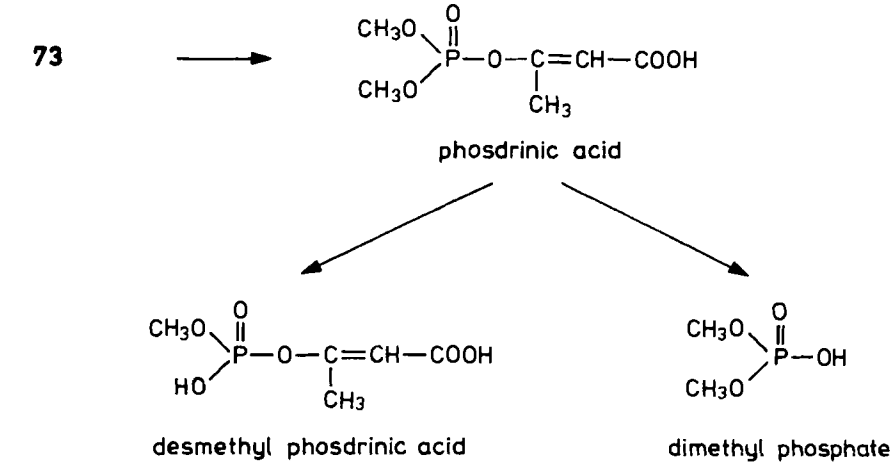


73a



73b

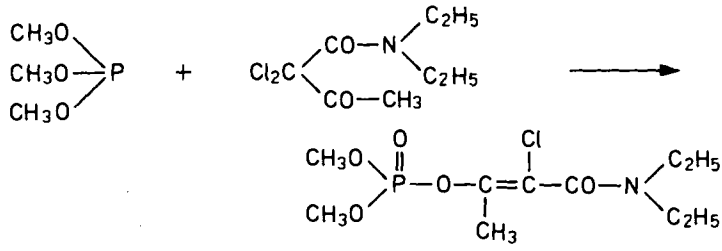
From the point of view of application, mevinphos has the important distinctive property of being rapidly hydrolysed by enzymes in the plant. Hydrolysis products are phosdrinic acid, demethyl phosdrinic acid and dimethyl phosphate:



The decomposition products are biologically inactive. Decomposition is very rapid, so that mevinphos can be used shortly before harvest in spite of its high toxicity to warm-blooded animals (LD_{50} for male rats is 3.7 mg/kg). The prescribed preharvest time varies in many countries between 1 and 7 days.

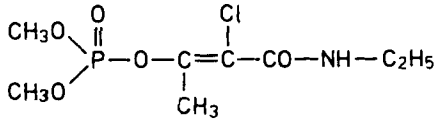
O,O-Dimethyl-O-[1-methyl-2-chloro-2-(N,N-diethylcarbamoyl)vinyl] phosphate (phosphamidon, **74**) prepared by the reaction of trimethyl phosphite with α,α-dichloro-acetoacetic acid diethylamide, is an insecticide with a very broad range of actions (Beriger and Sallmann, 1955; Anliker, 1961). It penetrates the plant tissues a few hours after spraying.

The metabolism of phosphamidon in the plant increases the insecticidal action transitorily because the monoethyl amide (**75**), formed by dealkylation, is more effective than the original compound. However, further metabolism results in inactive hydrolysis products.

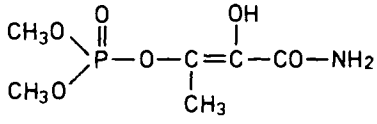


74

The presence of seven phosphorus-containing metabolites could be detected in the urine of rats. The most important of these is the product formed by dealkylation of the nitrogen atom and hydrolysis of the chlorine atom **(76)** (Menzer and Dauterman, 1970; Bull *et al.*, 1967).



75

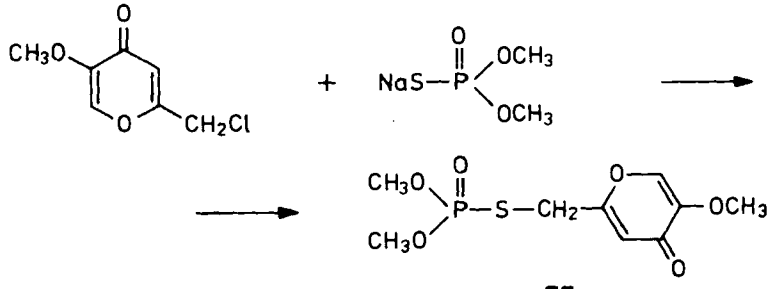


76

1.5.8 Heteroarylmethyl phosphorothiolates and phosphorodithioates

An important group of insecticides of the phosphorus ester type are those compounds in which the sulfur atom of the phosphorothiolic acid or of the phosphorodithioic acid is linked through a methylene bridge to a heteroaromatic ring. They are mostly prepared by the reaction of the sodium salt of the desired phosphorothiolic acid or phosphorodithioic acid with the chloromethyl derivative of the respective heterocyclic compound.

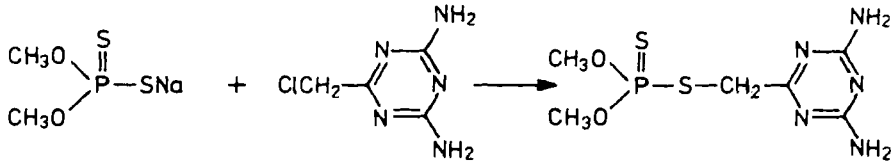
The most important of the phosphorothiolic acid derivatives within this group is O,O-dimethyl-S-[(5-methoxy-4-oxo-4H-pyran-2-yl)methyl] phosphorothioate (endothion, **77**) prepared by Métivier (1955a; 1955b) by the reaction of 2-chloromethyl-5-methoxy-4-oxo-4H-pyran with the sodium salt of O,O-dimethyl phosphorothioate:



77

Endothion is a systemic insecticide with an action lasting for 8–14 days. Its LD_{50} for rats is 30–50 mg/kg.

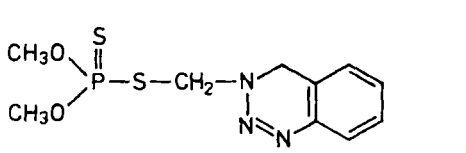
The other members of this family of compounds are phosphorodithioic acid derivatives. Of these, menazon, O,O-dimethyl-S-(4,6-diamino-1,3,5-triazin-2-yl)-methyl phosphorodithioate (**78**), distinguishes itself by its low toxicity to warm-blooded animals. It is prepared by cyclisation of biguanide and ethyl chloroacetate, upon which the 2-chloromethyl-4,6-diaminotriazine formed is reacted with sodium O,O-dimethyl phosphorodithioate (Anonym, 1958).



78

It has a long residual action. Spraying with its aqueous solution protects plants for 18–26 days against sucking insects.

Several derivatives are known of this type, in which the methylene group linking the sulfur atom of phosphorodithioic acid with the heterocyclic ring is attached to one of the ring nitrogen atoms. The [4-oxo-1,2,3-benzotriazin-3-(4H)-yl]methyl ester of O,O-dimethyl phosphorodithioic acid has been introduced under the name azinphos-methyl (**79**), its N-phthalimidomethyl ester under the name phosmet (**80**) and its (2-methoxy-5-oxo-Δ^2-1,3,4-thiadiazolin-4-yl)methyl ester under the name methidathion (**81**). The (6-chloro-2-oxo-2H-benzoxazolin-3-yl)methyl ester of O,O-diethyl phosphorodithioic acid was introduced under the name phosalone (**82**) (Lorenz, 1953b; 1953c; Fancher, 1955; Brähler *et al.*, 1958; Anonym, 1962).



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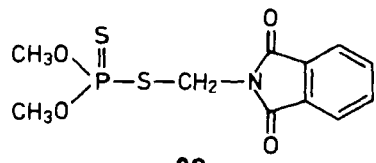

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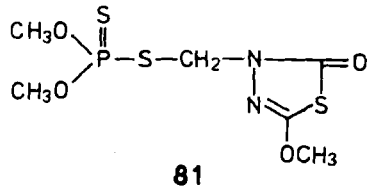
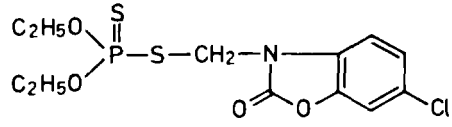


81

Azinphos-methyl and phosmet are typical contact insecticides with high stability and thus with a long residual action, whereas methidathion, readily absorbed by the leaf tissues, is an insecticide possessing systemic properties. The oral LD_{50} of

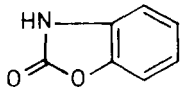
azinphos-methyl for rats is 13 mg/kg while its dermal toxicity is 220 mg/kg. The oral LD_{50} of phosmet is 147–216, that of methidathion 25–48 mg/kg.

Considerations connected with biodegradability served as a theoretical basis in designing the molecule of phosalone **(82)**, the (6-chloro-2-oxo-2H-benzoxazolin-3-yl)methyl ester of O,O-diethyl phosphorodithioic acid (Métivier, 1966).



82

Benzoxazolone **(83)** and its 6-methoxy derivative **(84)** are present in plants and are said to act as fungicides, bactericides and insecticides. Plants also possess the enzyme system which is responsible for the degradation of benzoxazolones. It was to be expected therefore that also synthetic insecticides containing a benzoxazolone moiety will prove to be biodegradable, thus decreasing toxicological hazards.



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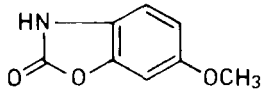
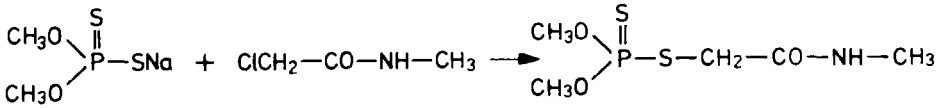


84

Metabolism studies have verified this hypothesis and proved the degradation of phosalon both in animal and plant organisms within a short period. Its oral LD_{50} for rats is 135 mg/kg, and for mice 180 mg/kg. The values of tolerance proposed by WHO/FAO are 2–5 ppm for fruits and 0.1–1 ppm for vegetables (Métivier and Petrinko, 1978).

1.5.9 Phosphorodithioates containing carboxylic acid ester and amide groups

Cassaday *et al.* (1948) prepared several S-carbamoylmethyl phosphorodithioates by the reaction of the salts of O,O-dialkyl phosphorodithioic acids with various N-substituted chloroacetamides, and investigated their biological properties. Of these, practical importance has been attained by O,O-dimethyl-S-(N-methylcarbamoyl)-methyl phosphorodithioate, known by the name dimethoate **(85)**.

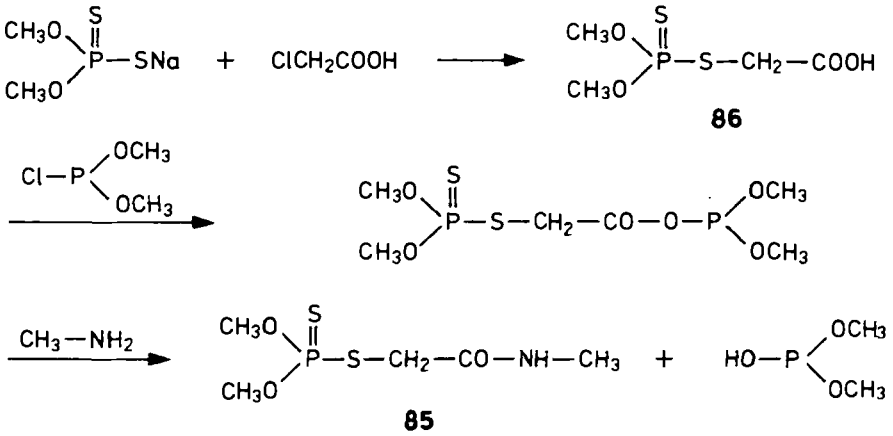


85

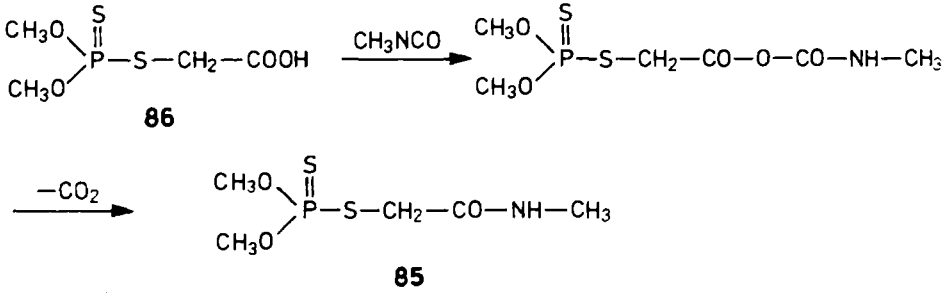
Due to its great practical importance, several other methods have been developed for the preparation of dimethoate. According to the process of Kochmann *et al.*

(1965), the above reaction is carried out in a two-phase system in an acidic medium. Perini and Speroni (1955) used ethyl chloroacetate in their process, Sehring and Zeile (1958) used phenyl chloroacetate instead of chloroacetamide, and treated the carbethoxymethyl or carbophenoxymethyl phosphorodithioate with methylamine to convert it to the desired amide, while in the method of Oertel and Maltz (1962) the corresponding methylammonium-dithiophosphate was used.

The process of Young and Berkelhammer (1959) is also based on the formation of the amide group as the last step. According to this process, O,O-dimethyl-S-carboxymethyl phosphorodithioate (**86**) is reacted with dimethyl phosphorochloridate, and the mixed anhydride formed is treated with methylamine:



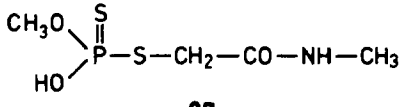
Anhydride formation is also the intermediate step in the process developed by Japanese workers, according to which O,O-dimethyl-S-carboxymethyl phosphorodithioate reacts with methylisocyanate, and the mixed anhydride formed is converted, with the elimination of carbon dioxide, to dimethoate (Anonym, 1961).



At room temperature, the solubility of dimethoate in water is 39 g/l, thus it belongs to the phosphorus ester insecticides of high water solubility. It is stable to hydrolysis in neutral and acidic media, but saponifies rapidly in alkaline media.

Dimethoate is a potent contact and systemic insecticide, effective against a broad range of sucking and chewing insects. Its oral LD_{50} for rats is 250–265 mg/kg.

In insects as well as in warm-blooded animals, demethylation, the cleavage of the C—N and C—S bonds, and the conversion of the P=S bond to a P=O bond are the main reactions. Accordingly, demethyl dimethoate **(87)**, O,O-dimethyl-S-carboxymethyl phosphorodithioate **(86)** and O,O-dimethyl-S-(N-methyl-carbamoyl)methyl phosphorothioate (omethoate, **88**) are formed as metabolites (Santi and Giacomelli, 1962; Bull *et al.*, 1963; Uchida *et al.*, 1964; Miyamoto, 1972).



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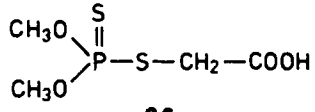

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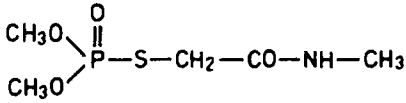
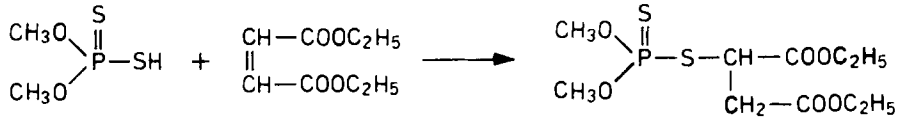


88

Omethoate **(88)** is also on the market. Its insecticidal action and its toxicity to warm-blooded animals are both higher than those of dimethoate, but it is metabolised more rapidly into nontoxic metabolites.

The N-methoxyethyl analogue of dimethoate, medithionate, is a less toxic derivative with similar insecticidal properties (Beriger, 1961). Its LD_{50} for rats is 420–650 mg/kg.

Cassaday (1950), Shostakovski *et al.* (1951) and Melnikov *et al.* (1952) investigated extensively the addition reactions of dialkyl phosphorodithioic acids to unsaturated dicarbonic acid esters, and found that the dialkyl phosphorodithioic acids are added at the double bond in the same way as are mercaptans. This reaction was used by Cassaday (1950) who prepared O,O-dimethyl-S-(1,2-dicarbethoxy)-ethyl phosphorodithioate by the addition reaction of dimethyl phosphorodithioic acid and maleic acid diethyl ester. This compound, known by the name malathion **(89)**, became one of the most important phosphorus ester insecticides because of its low toxicity to warm-blooded animals.

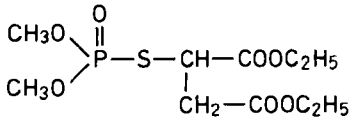


89

The technical production of malathion can be carried out in a single-step process without the intermediate preparation of dimethyl phosphorodithioic acid, starting from phosphorus pentasulfide, methanol and maleic acid diethyl ester (Matolcsy and Oswald, 1955; 1957).

Malathion has a broad range of action, and is effective against both sucking and chewing insects. Its great practical importance is due mainly to the fact that, of all the phosphorus ester insecticides, it is the least toxic to warm-blooded animals: its LD_{50} for male rats being 1200 mg/kg.

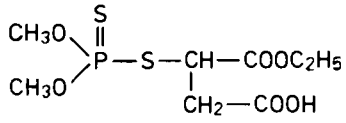
Krueger and O'Brien (1959) found that malathion is metabolised in insects by enzymatic oxidation to its oxo analogue, malaoxon **(90)**.



90

This oxidative conversion increases the insecticidal and toxic effect to many times the original values.

The metabolism of malathion in warm-blooded animals proceeds *via* another route. As the first metabolic step, α-malathion monocarbonic acid **(91)** is formed by hydrolysis of one of the ester bonds. This metabolite is virtually nontoxic to warm-blooded animals (Krueger and O'Brien, 1959; Chen *et al.*, 1969).



91

Malathion is hydrolysed by the enzyme malathionase. Cook and Yip (1958) established the presence of this enzyme in the liver of rats. It has also been found generally present in the liver, kidney, lungs and serum (Seume and O'Brien, 1960), but it is missing from insects sensitive to malathion. This explains, at least partly, the selective action of malathion towards insects.

Menzer and Dauterman (1970) studied extensively the substrate specificity of malathionase and established that carboxy esters with longer carbon chains can be hydrolysed more easily by the enzyme than those with short carbon chains. The stereospecific character of the enzymatic action is shown by the fact that *d*-isomers are hydrolysed more easily than *l*-isomers, and fumaric acid derivatives more easily than maleic acid derivatives.

In fish the conversion of malathion to malaoxon is the dominant metabolic process, increasing the brain acetylcholinesterase-inhibiting potency a thousand-fold (Murphy *et al.*, 1968). Coppage *et al.* (1975) found inhibition of fish brain acetylcholinesterase suitable for the detection of environmental poisoning by malathion.

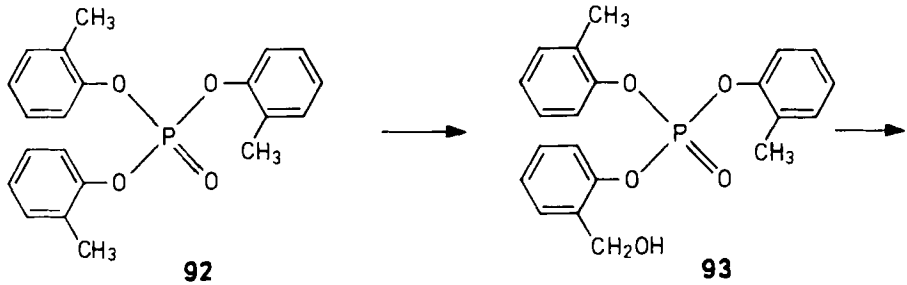
According to O'Brien (1967) malaoxon is able to phosphorylate acetylcholinesterase efficiently because oxygen, due to its higher electronegativity compared to

sulfur, removes more electrons from the phosphorus atom. The decreased electron density of the phosphorus atom allows bonding to the electron dense area in the active site of the enzyme.

O,O-Dimethyl-S-[N-2-chlorophenyl-butyramido]methyl phosphorodithioate (NE-79168) has been developed primarily against a wide range of phytophagous insect (Sági *et al.*, 1983). It is relatively safe to honey bees when used in the evening on crops in flower.

1.5.10 Cyclic phosphates and phosphorothioates

One of the methyl groups of tri-*o*-cresyl phosphate **(92)**, long known for its neurotoxic effect, is hydroxylated in the tissues, and the hydroxymethyl derivative **93** formed is intramolecularly transesterified into the biologically very active metabolite, 2-*o*-cresyloxy-4H-1,3,2-benzodioxaphosphoran-2-one **(94)** (Casida *et al.*, 1961; Eto *et al.*, 1962).



92 93

94

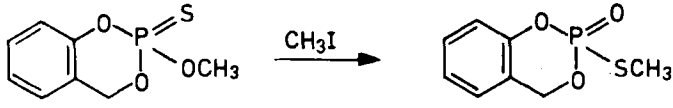
On the basis of this finding, Eto and Oshima (Eto and Oshima, 1962; Oshima and Eto, 1963; Eto, 1969) synthesised several related compounds of this cyclic metabolite. Of these, 2-methoxy-4H-1,3,2-benzodioxaphosphoran-2-one (salioxon, **95**) and its thio analogue, salithion **(96)**, attained practical importance.

95 96

Data in the literature on the toxicity of salioxon and salithion to warm-blooded animals differ considerably. Salioxon used together with malathion exhibits a

synergistic effect. However, the structural requirements for the synergistic and the insecticidal action are not identical: when the methoxy group is exchanged for an aryloxy group, the insecticidal action is reduced while the synergistic action increases.

Eto *et al.* (Eto *et al.*, 1971; Sasaki *et al.*, 1973) found that salithion is converted by methyl iodide into its thiolo isomer of structure **97**. This rearrangement can be considered as a special case of the Pistschimuka reaction.

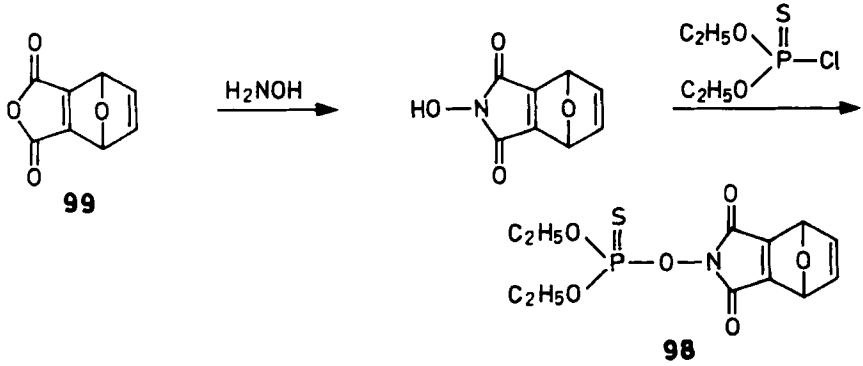


96 **97**

The thiolo isomer (**97**) is an efficient alkylating and phosphorylating agent, converting ribonucleosides to ribonucleoside 3′,5′-cyclic phosphate in the presence of cyclohexylamine (Eto *et al.*, 1968; 1971; 1974).

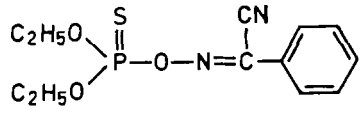
1.5.11 Phosphorylated hydroxylamine derivatives

Characteristic of these compounds is the P—O—N atom group. A typical example is O,O-diethyl-O-[oxabicyclo-(2,2,1)-hept-5-ene-2,3-dicarboximido] phosphorothioate (**98**) known as "DOW 50". The dicarbonic acid anhydride **99** required for its preparation is made by the Diels–Alder reaction, starting from maleic acid anhydride and furan. On treatment with hydroxylamine, this is converted to the oximino derivative, from which the end-product is obtained in the usual way (Rigterink, 1962).



99 **98**

Because of its very low toxicity to warm-blooded animals, its broad range of insecticidal action and its strong initial effect, O-(O,O-diethyl-thiophosphoryl)-α-phenyl-α-hydroximinoacetonitrile (phoxim, **100**) gained importance in recent years. Its oral LD_{50} for rats is 2500 mg/kg. It is prepared by phosphorylation of α-cyanobenzaldoxime (Lorenz *et al.*, 1965; Wybou and Hammann, 1968).



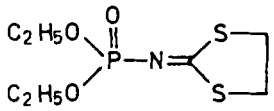
100

1.5.12 Esteramides of phosphoric and phosphorothioic acid

Following the development of schradan (**12**) in 1941, discussed earlier under pyrophosphoric acid derivatives, it was only after an interval of more than two decades that other insecticides were developed with a phosphorus–nitrogen bond in the molecule.

The revival of this type of compound was opened by the development of triamphos in 1960. Although it has a considerable insecticidal effect, it is used mainly as a fungicide, and is therefore discussed in the fungicides section.

O,O-Diethyl-N-(1,3-dithiolan-2-ylidene) phosphoroamidate (phospholan, **101**) has been developed by Addor (1962; 1970). Phospholan is an insecticide and acaricide with a broad range of action, but it has the disadvantage of being highly toxic to warm-blooded animals; its LD_{50} for rats being 8.9 mg/kg. Its methyl homologue (mephospholan, **102**) possesses similar properties.



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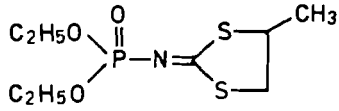
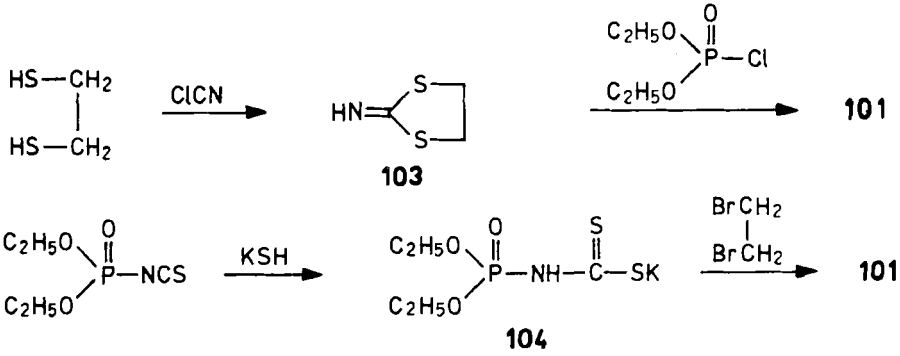


102

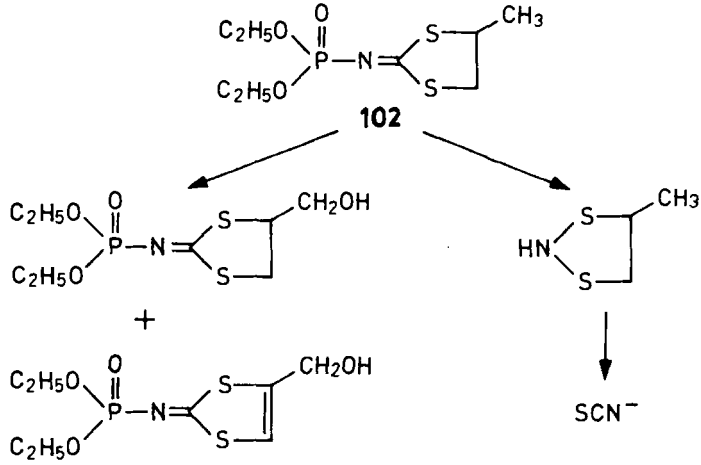
According to the original process of Addor (1962), phospholan is prepared by the reaction of ethylene-1,2-dithiol with cyanogen chloride, followed by the reaction of 2-imino-1,3-dithiolane (**103**) with diethyl phosphorochloridate. According to his later process (1970), N-(O,O-diethylphosphoryl) dithiocarbamate (**104**), obtained by the addition reaction of diethyl phosphoryl isothiocyanate and potassium hydrosulfide, is cyclised with ethylene bromide.



103

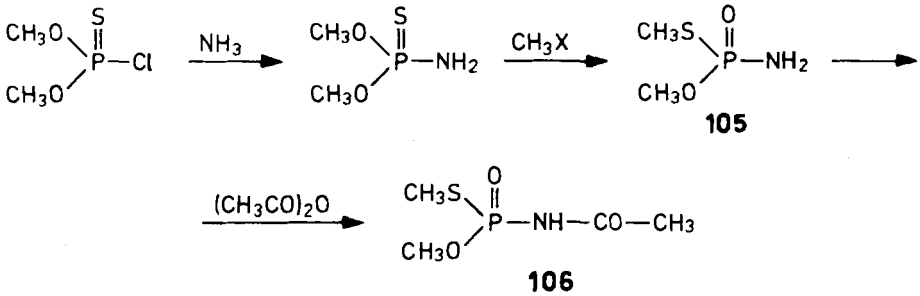
104

In rats the metabolism of mephospholan (**102**) is characterised by hydroxylation of the methyl group of the dithiolan ring, as well as by cleavage of the P—N bond (Zulalian and Blinn, 1977) as shown is Scheme 1.15.



Scheme 1.15

Dimethyl phosphorothiochloridate can easily be converted with ammonia to O,O-dimethyl phosphorothioamidate which, in the presence of a methylating agent undergoes thion→ thiol isomerisation, and is converted to the O,S-dimethyl

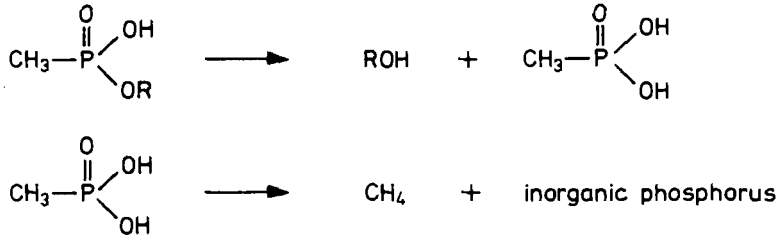


analogue (metamidophos, **105**). Also its N-acetyl derivative (acephate, **106**) is known. Its LD_{50} for rats is 945 mg/kg (Schrader *et al.*, 1964; Hammann, 1970; Magee, 1974).

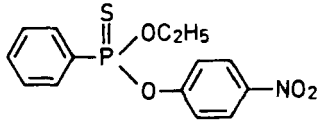
1.5.13 Phosphonic acid derivatives

Among the insecticides containing a phosphorus atom, there are relatively few derivatives of phosphonic acid which can be considered in the strict sense as organophosphorus compounds because of their P—C bond. The P—C bond is thermodynamically very stable. Generally it does not participate in chemical

reactions and the final degradation products of phosphonic acid esters are phosphonic acids of the general formula RPO_3H_2, which are nontoxic. Alkane phosphonates have been assumed to be resistant also to biological transformations. Yet, Cook and co-workers (1978) showed that they can be degraded microbiologically by removal of the alkoxy group followed by cleavage of the C—P bond to yield methane and orthophosphate or phosphonic acid, as a result of hydrolytic or reductive mechanisms, respectively.

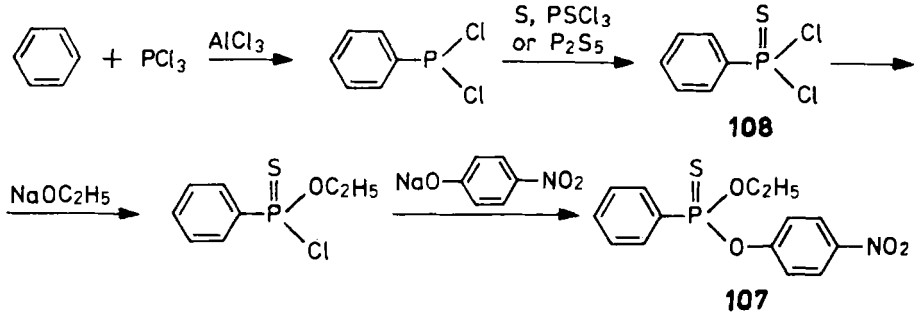


The first phosphonate insecticide, O-ethyl-O-*p*-nitrophenyl-benzenephosphonothioate (EPN, **107**) was developed by Jelinek (1948).



107

The preparation of EPN illustrates at the same time the general mode of preparation of arene- and partly of alkane phosphonic and phosphonothioic acid esters (Bilroth, 1932; Gottlieb, 1932; Kinnear and Perren, 1948; 1952; Buchner and Lockhart, 1951; Jensen, 1951; Kabachnik and Godovikov, 1956; Karavanov and Ivin, 1965). Benzene is reacted with phosphorus trichloride in the presence of aluminium trichloride to give benzene phosphonodichloridite. This is reacted with $PSCl_3$, P_2S_5 or elementary sulfur to yield benzenephosphonodichlorothioate (**108**), which is then treated in the same way as for the preparation of phosphoric and phosphorothioic acid esters.

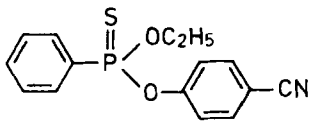


108

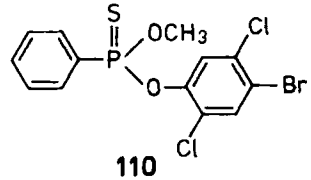
107

The LD_{50} of EPN for rats is 36 mg/kg. Its insecticidal action is weaker than that of the structurally related parathion **(17)** and, owing to these disadvantageous properties, its application was terminated at the beginning of the 1950s. Following this, new phosphonate esters were introduced only after ten years, when phosphonate analogues of several phosphate esters had been developed.

One of these is the phosphonate analogue of cyanophos **(43)**, cyanofenphos **(109)**, O-ethyl-O-*p*-cyanophenyl-benzenephosphonothioate, developed by Kuramoto *et al.* (1961). Its LD_{50} for mice is 46 mg/kg, i.e. it is about twenty times more toxic than cyanophos. The phosphonate analogue of bromophos **(39)** is known under the trade name Phosvel® **(110)**.

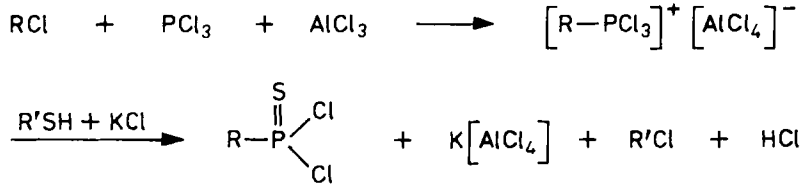


109



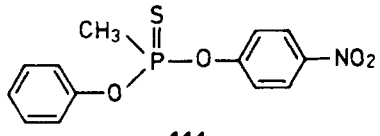
110

From the beginning of the 1960s, alkanephosphonothioate and alkanephosphonodithioate esters also gained importance. The alkanephosphonodichlorothioates required for their preparation are most suitably obtained by treating the respective alkyl halide with phosphorus trichloride in the presence of aluminium trichloride, and reacting the intermediate complex formed with alkyl mercaptan in the presence of potassium chloride (Kinnear and Perren, 1948; 1952; Karavanov and Ivin, 1965).



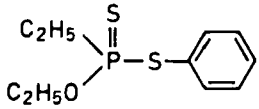
Elemental sulfur can also be used as thionating agent (Komkov *et al.*, 1958).

O-Phenyl-O-*p*-nitrophenyl-methanephosphonothioate **(111)**, introduced under the code number Monsanto CP 40 294 (Colep®) is known for its specific range of action which differs somewhat from that of other phosphorus esters (Chupp and Newallis, 1962).



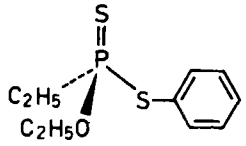
111

The esters of phosphonodithioic acids generally have a stronger insecticidal effect than the esters of the respective phosphorodithioic acid. Thus, for example, O-ethyl S-phenyl ethanephosphonodithioate, known by the name fonofos **(112)**, has an LD_{50} of 5 ppm for houseflies while its phosphonodithioate analogue has an LD_{50} of 56 ppm. With the increase of the insecticidal effect, the toxicity to warm-blooded animals also increases, but to a lesser extent (Menn and Szabó, 1965).



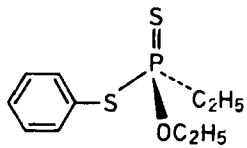
112

Chirality at the phosphorus atom of alkanephosphonodithioate esters has a significant effect on their biological activity (Fukuto and Metcalf, 1959; Wustner and Fukuto, 1973). Lee and associates (1978) found the dextrorotatory isomer of fonofos **(112a)** to be more toxic to houseflies and a more potent cholinesterase inhibitor than its $(S)_p$ enantiomer **(112b).**



$(S)_p$-fonofos

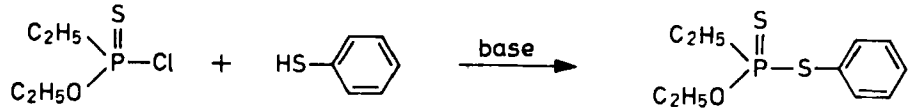
112a



$(R)_p$-fonofos

112b

Fonofos is prepared from O-ethyl-ethanephosphonothiochloridate and thiophenol in the presence of an acid-binding base.

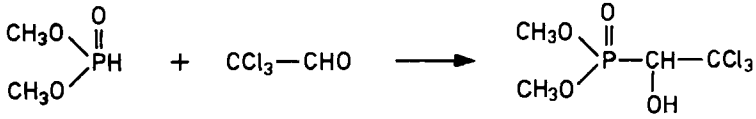


112

Szabó (1967) found that, when the two alkyl radicals of the phosphonic esters are different, the compounds have a stronger insecticidal action than in the case of identical alkyl radicals. This is in agreement with a similar finding of Melnikov (1963) in relation to parathion derivatives. This fenomenon is evidently due to the fact that asymmetry increases the polarisation of the central phosphorus atom, resulting in an increased phosphorylating ability.

In the group of phosphonic acid derivatives, O,O-dimethyl-(1-hydroxy-2,2,2-trichloro)ethane phosphonate, known under the name trichlorfon (Dipterex®, **68**), occupies a special place both chemically and biologically. It is prepared by the addition of dimethyl phosphonate to chloral (Barthel *et al.*, 1954; Lorenz, 1953a).

Contrary to most phosphorus ester insecticides, trichlorfon is readily soluble in water as well as in organic solvents. On reaction with acids, first the O-methyl groups are hydrolytically cleaved. In alkaline media, dichlorvos (**67**) is formed by the rearrangement already discussed.



68

Trichlorfon is moderately toxic to warm-blooded animals, its LD_{50} for rats being 630 mg/kg. It is strongly toxic to insects, but the symptoms of poisoning are somewhat similar to those of the chlorinated hydrocarbons. Trichlorfon is used in plant protection mainly against chewing insects as an effective stomach poison (Unterstenhöfer, 1957). As it penetrates the leaf tissues, it can be used also against mining insects. For hygienic purposes it is very efficient against flies *(Dipterae)* and, it has an extremely high knockdown effect as stomach poison.

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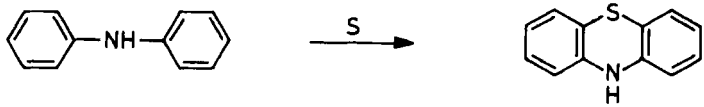
1.6 Various insecticides

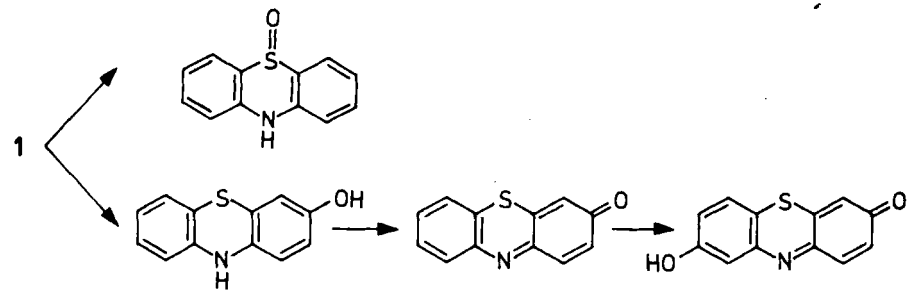
Compounds which do not belong to any of the three types already discussed play a relatively subordinate role among the insecticides.

Campbell *et al.* (1934) compared the insecticidal effect of several organic sulfur compounds, and found phenothiazine **(1)** most effective. It is readily formed by heating diphenylamine **(2)** and sulfur in the presence of aluminium chloride or iodine.



2 **1**

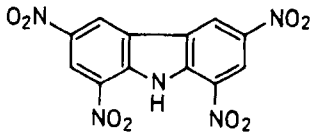
It is toxic to several insect pests, but its activity varies within wide limits, which is evidently due to its high sensitivity to oxygen and light. It is oxidised partly to its sulfoxide and partly to chinoidal derivatives (De Edds and Eddy, 1938).



Introduction of a chlorine atom or a cyano group in position 2 of the ring resulted in a sharp increase of activity as compared with the parent compound (Ghizdavu and Ghizdavu, 1978).

Phenothiazine can be considered as the forerunner of modern organic insecticides. Due partly to its sensitivity and the uncertain effect arising from it, and partly to the appearance on the market of DDT, its practical importance decreased in the 1940s.

Two derivatives of carbazole, 1,3,4,8-tetranitro-carbazole (nirosan, **3**) and 1,8-dichloro-3,6-dinitro-carbazole (nirosit, **4**) played an important role in the 1940s as insecticides used in vineyards (Pfaff *et al.*, 1939; Martin and Shaw, 1946). They are prepared by nitration and chlorination, respectively, of carbazole.



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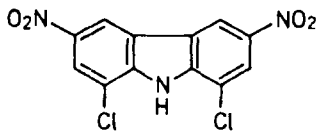
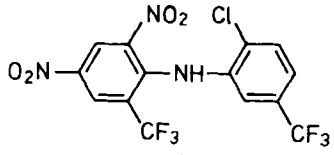


4

Nirosan and nirosit are characteristic stomach poisons, so that their action is highly selective against chewing insects. They are nonhazardous for bees and the natural enemies of insect pests. Their toxicity to warm-blooded animals is low. Owing to these properties, they can be considered, in spite of their outdatedness, as insecticides meeting modern requirements regarding environmental protection.

Diphenylamine (**2**) also has insecticidal properties, and attained limited importance in the 1930s, not primarily in plant protection but in veterinary medicine. Its substituted derivative 2-chloro-2′,4′-dinitro-5,6′-di(trifluoromethyl)-diphenylamine was recently introduced in plant protection under the name famaflur (**5**).

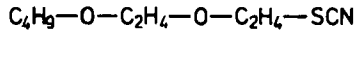


5

Since the 1920s several research workers have investigated the insecticidal effect of various thiocyanates. The action of these compounds is characterised by the knock-down effect and by the contact character of action. They have therefore mostly been used in combination with other insecticides, such as rotenone, pyrethrum and DDT. From the end of the 1940s onwards their use was gradually discontinued, due mainly to their disagreeable odour and their phytotoxic and skin-irritating properties.

The best known examples of this type of insecticide are β-butoxy-β′-ethoxy-ethyl thiocyanate (**6**), known under the name lethane 384, and isobornyl thiocyano-

acetate (7), known under the name thanite. They are prepared by the reaction of the respective chlorine derivative with alkali thiocyanate (Murphy and Peet, 1932; Borglin, 1938). The LD_{50} for rats of lethane 384 is 90–250 mg/kg, and that of thanite 1600 mg/kg.



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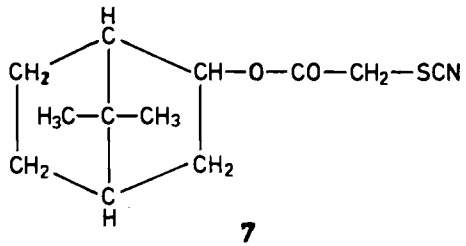
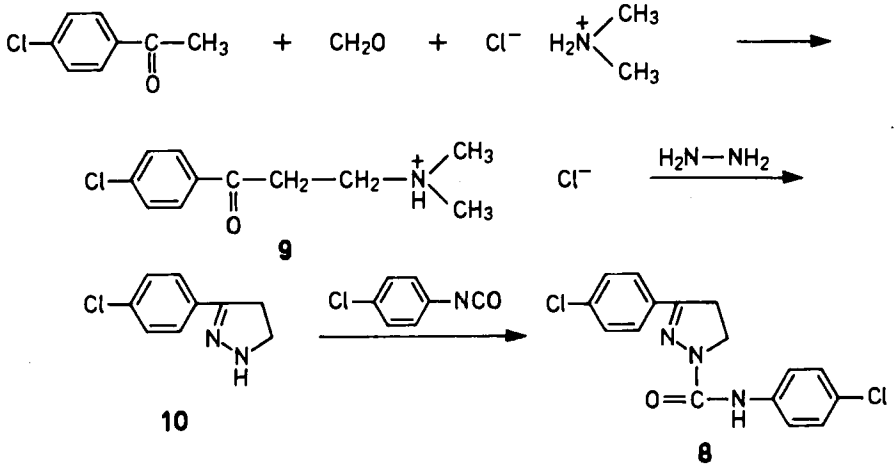


7

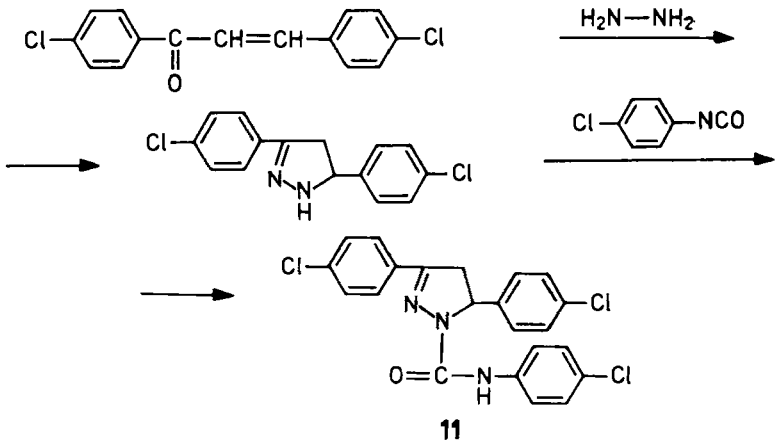
Wellinga and associates reported the development of 3-aryl-2-pyrazolines acting as powerful stomach insecticides. From the point of view of biological activity and economic aspects 3-(4-chlorophenyl)-1-(4-chlorophenylcarbamoyl)-2-pyrazoline (PH 60–41, **8**) appeared to be the most promising (Mulder *et al.*, 1975; Wellinga *et al.*, 1977).

Its synthesis is based on the cyclisation of the keto Mannich base salt **9** with hydrazine hydrate to yield 3-(4-chlorophenyl)-2-pyrazoline **(10)**, which is then carbamoylated with 4-chlorophenyl-isocyanate, as shown is Scheme 1.16.



Scheme 1.16

Introduction of a further phenyl ring at position 5 of the pyrazoline ring yielded products with comparable or enhanced insecticidal effect. 3,5-Bis(4-chlorophenyl)-1-(4-chlorophenylcarbamoyl)-2-pyrazoline **(11)** is regarded by the authors as the most promising compound of this series. It has been prepared according to the reaction shown in Scheme 1.17, but 4,4'-bis(chlorobenzalacetophenone) was used in the cyclisation reaction (Scheme 1.17) (Van Hes *et al.*, 1978).

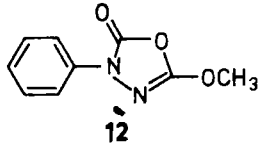


11

Scheme 1.17

The LD_{50} of compound **11** to mice exceeds 1000 mg/kg, thus it can be classified as an insecticide of low mammalian toxicity.

A further insecticide containing a five membered ring with two adjacent nitrogen atoms is 5-methoxy-3-(2-methoxyphenyl)-1,3,4-oxadiazol-2(3H)-one (oxadimeter, **12**) (Ambrosi *et al.*, 1979). In the investigations on oxadiazoles conducted by the research team of the Rhône-Poulenc Co., this product proved to be the most active.



12

The major agricultural pests susceptible to oxadimeter are aphids, planthoppers and leafhoppers. It is of particular interest for the control of ricehoppers which became resistant to carbamate and organophosphorus insecticides.

Its oral LD_{50} for mice is 75, and for rats 220 mg/kg. Administered percutaneously it is nontoxic to rats at 2000 mg/kg. In mammals it has a moderate anticholinesterase activity.

On plants it reveals a short persistence, its half-life time being 2 days, which permits its application on vegetables and other crops when insecticide treatment close to harvest is necessary.

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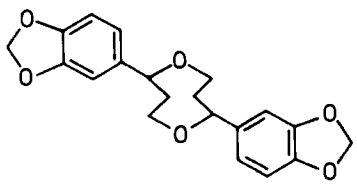
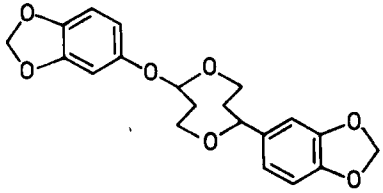
1.7 Insecticide synergists

Eagelson (1938) found that the insecticidal activity of pyrethrum against mosquitoes and flies is considerably increased in the presence of sesame oil, which is inactive in itself. This discovery, which permitted considerable economy in formulations, was the first example of synergism in the field of insecticides. Following this finding, Haller *et al.* (1942a; 1942b) and later Beroza (1954; 1955) established that sesame oil contains active substances comprising a methylenedioxyphenyl group, sesamin (**1**) and sesamolin (**2**).

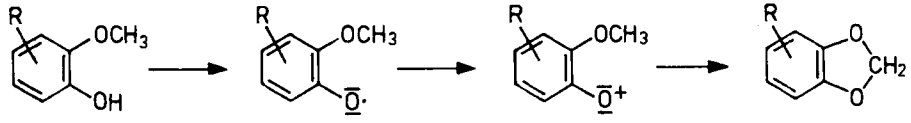


1

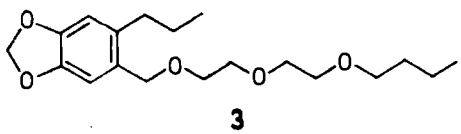


2

In the biosynthesis of the characteristic methylenedioxyphenyl group a decisive role is attributed to the oxenium ion, which is formed from the properly substituted *o*-methoxy-phenol by the loss of two electrons and is cyclised by insertion.



Following the discovery of the synergistic active substances of sesame oil, several synthetic analogues have been developed. Some of these contain a polyethyleneoxide side-chain as, for example, piperonylbutoxide (**3**), sesamex (**4**), tropital (**5**) and bucaprolate (**6**) (Wachs, 1947; 1949; Mitchell, 1952; 1959; Beroza, 1956; Hopkins and Maciver, 1956; Fales *et al.*, 1957).



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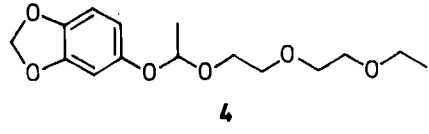

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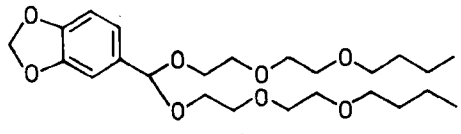

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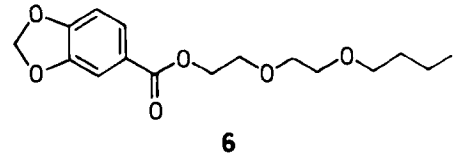
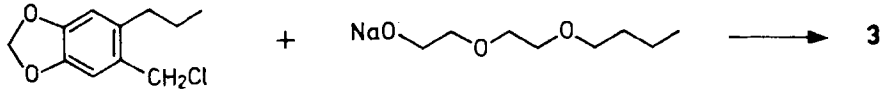
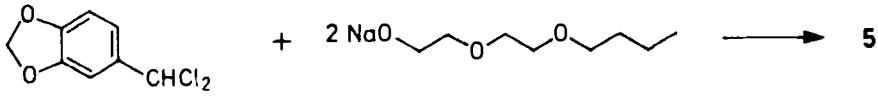


6

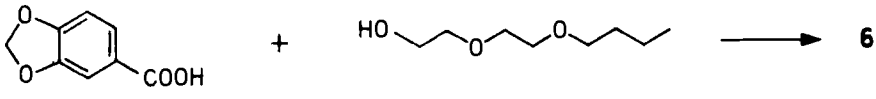
Piperonylbutoxide (**3**), tropital (**5**) and bucaprolate (**6**) are prepared by the reaction of diethyleneglycol-monobutylether or its sodium salt with chloromethylated dihydrosafrol (**7**), piperonal dichloride (**8**) or 2,3-methylenedioxybenzoic acid (**9**), respectively.



7 + NaO⟋⟍O⟋⟍O⟋⟍ → 3

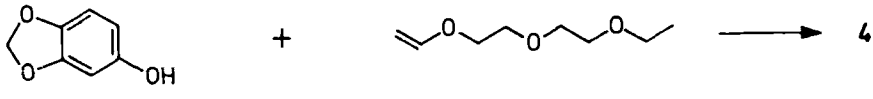


8 + 2 NaO⟋⟍O⟋⟍O⟋⟍ → 5



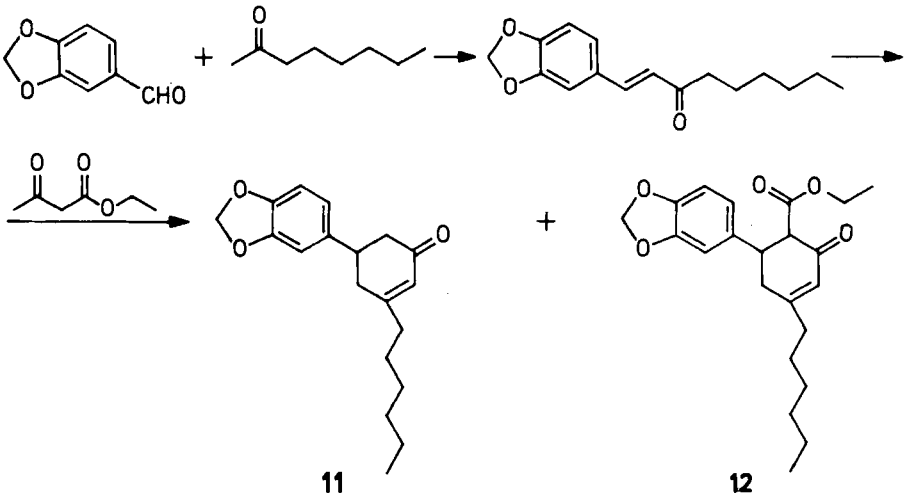
9 + HO⟋⟍O⟋⟍O⟋⟍ → 6

Sesamex (**4**) is generally prepared by the addition of sesamol (**10**) to vinylethyldiethyleneglycol ether:



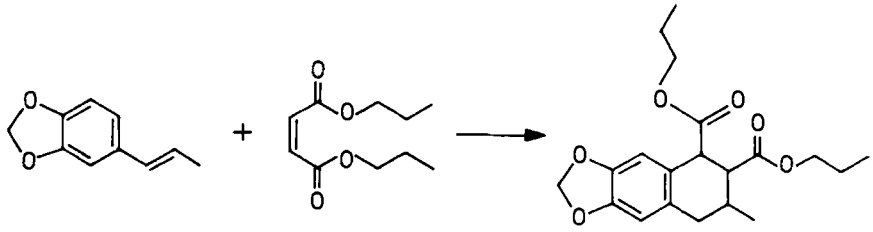
10 + ⟍O⟋⟍O⟋⟍O⟋⟍ → 4

The polyethyleneglycol chain is not a necessary condition of the action: synergists are known which have the methylenedioxyphenyl group attached to other moieties. If the ketone formed in the reaction of piperonal with methylhexyl ketone reacts with ethyl acetoacetate, a mixture known by the name piperonylcycloene containing two main components (**11** and **12**) is formed (Hedenburg and Wachs, 1948; Moburg and Hedenburg, 1948; Wachs and Hedenburg, 1948).



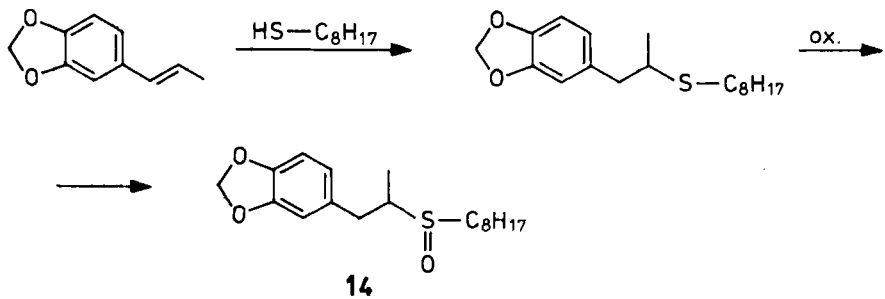
11 12

The product of the Diels–Alder reaction of isosafrol and dipropyl maleinate is dipropyl 7-methyl-5,6,7,8-tetrahydronaphtho-[2,3d]-1,3-dioxol-5,6-dicarbonate, known by the name propyl-isome (**13**).



13

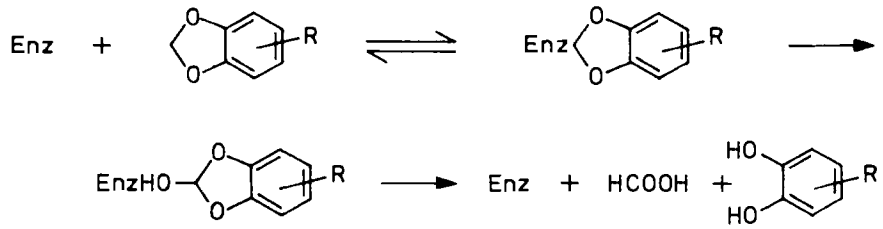
The preparation of sulfoxide (**14**) also utilises the readiness of the unsaturated side-chain of isosafrol to addition reactions. The sulfur atom ot the thioether, formed by the reaction of isosafrol with octylmercaptane, is oxidised to a sulfoxide group (Synerholm, 1944, 1946; Synerholm and Cullman, 1947; Synerholm and Hartzell, 1945).



14

The above compounds have been used as synergists of pyrethrum and synthetic pyrethroids, such as allethrin, cyclethrin and others. Later investigations showed that these compounds can also synergise other insecticides, primarily carbamates and DDT. Piperonylbutoxide and sesamex proved to be the most efficient in this respect; however, the latter is unsuitable for practical use because of its sensitivity to light and humidity.

Only assumptions can be made about the mode of action of the insecticide synergists discussed above. It seems certain that their action is based on the inhibition of oxydases responsible for the oxidative decomposition of the insecticides. The exchange of one of the hydrogens of the methylenedioxy group for other substituents or for deuterium results in a marked decrease in the synergising action. This permits the conclusion that the linkage to the enzyme occurs at this atomic group. When the linkage with the enzyme has been established, the methylenedioxy group is hydroxylated, and the substrate–enzyme complex breaks up into enzyme, formic acid and catechol derivative:

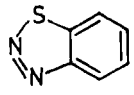


The methylenedioxy derivative can act in this way as the alternative substrate of the enzyme performing the microsomal hydroxylation, but the catechol formed may also contribute to the effect (Moore and Hewlett, 1958; Metcalf *et al.*, 1966; Casida, 1970; Casida *et al.*, 1966; Hennessy, 1965; 1969; Hennessy and Whalen, 1966; Kuwatsuka, 1970). However, this does not explain the strength and duration of synergism produced by methylenedioxyphenyl compounds. Experimental results of Franklin (1974) indicate that during oxidative metabolism these compounds form an intermediate which strongly binds to cytochrome P-450 and thereby prevents further participation of the enzyme in oxidative metabolism.

As regards the synergistic effect, not only the methylene group of the methylenedioxybenzene nucleus is sensitive to structural changes. At other sites of the molecule too, only a few modifications can be made without a sharp decrease or complete loss of the synergising activity. Exchange of one of the oxygen atoms for sulfur, resulting in only a slight decrease of efficiency, is one of the few exceptions (Wilkinson *et al.*, 1966).

In view of the strict structural requirements for the synergistic effect, the finding of Felton *et al.* (1970) that 1,2,3-benzthiadiazole **(15)** and a few of its substituted derivatives **(16, 17, 18)** are very effective synergists is of importance. These compounds represent the first major deviation from the methylenedioxybenzene structure to constitute another ring system having the same activity. These

compounds too, like methylenedioxybenzene derivatives, are inhibitors of phenolase systems.



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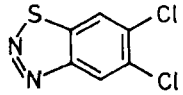

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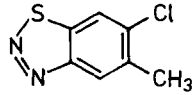

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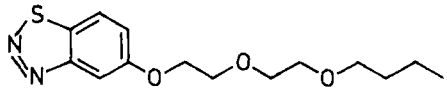
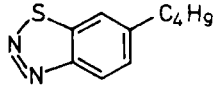


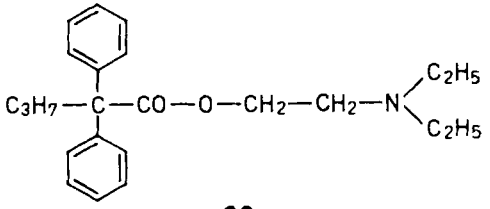
18

In a detailed structure–activity study Gil and Wilkinson (1977) found that of 47 substituted 1,2,3-benzothiodiazoles the 6-butyl derivative **19** is the most active inhibitor of microsomal oxidation. Regression analyses have shown that the activity of the 5-, 6- and 5,6-substituted compounds can be satisfactorily described in terms of the hydrophobic bonding constant π and the Hammett constant τ whereas that of the 4-substituted derivatives depend on π and the Taft's steric parameter E_s.



19

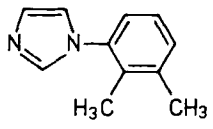
The dual effects of synergistic action and inhibition of oxidative enzymes is manifested also by other compounds which differ greatly from one another. Thus, for example, 2'-diethylaminoethyl-2,2-diphenylvalerate (**20**), known under the name SKF-525-A, has proved to have a synergistic action (Hewlett *et al.*, 1961; Bates *et al.*, 1965). This compound is also known for its inhibiting effect on microsomal hydroxylation and, owing to this property, it is able to prolong the action of active substances exposed to oxidative decomposition in warm-blooded animals (Axelrod *et al.*, 1954).



20

Wilkinson *et al.* (1973) established similar relationships for imidazole derivatives. They found that the 1- and 4-substituted derivatives of imidazole and their 2-substituted derivatives, already described earlier as synergists by Adolphi *et al.*

(1967), are potent inhibitors of microsomal epoxidase and hydroxylase and, at the same time, effective synergists of carbaryl *in vivo*. Compounds investigated by these workers, such as 1-(2′,3′-dimethylphenyl)imidazole **(21)**, (1′-naphthyl)imidazole **(22)** and 4-(2′-bromophenoxymethyl)imidazole **(23)**, bind powerfully to cytochrome P-450, and the spectral dissociation constants parallel the inhibition values.



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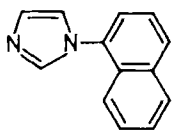

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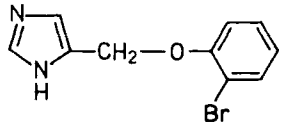
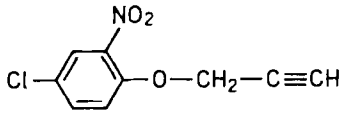


23

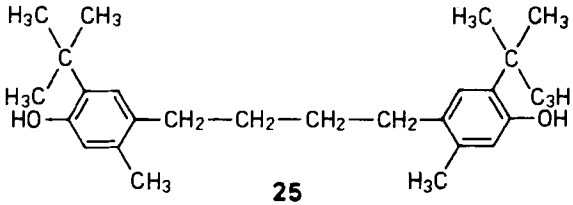
The above relationships seem to prove that the ability of the compounds discussed to synergise the activity of insecticides results from their inhibiting action on the microsomal enzymes responsible for the detoxication of foreign compounds (Wilkinson *et al.*, 1973; Wilkinson, 1974).

Felling and co-workers (Felling and Rachlin, 1968; Barnes and Felling, 1969; Felling *et al.*, 1970) found an interesting group of synergists of the carbamate type insecticides, the phenyl 2-propynyl ethers. The most active member of this series is the 2-nitro-4-chloro derivative **(24)**.



24

In contrast to these synergists acting on the enzyme level, Yamaguchi *et al.* (1979) published the nonenzymatic potentiation of synthetic pyrethroids by 4,4′-butylene-bis(6-*t*-butyl-3-methylphenol) **(25)** and 2,2′-methylene-bis(6-*t*-butyl-4-ethylphenol) **(26)**. These compounds are known as antioxidants and the antioxidant property seems to be the factor responsible for decreasing decomposition of the insecticide, thus resulting in a stabilised slow release product.



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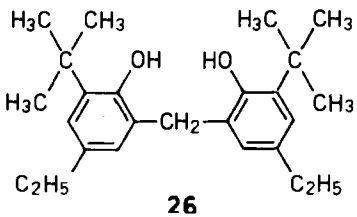

26

The synergists are used mainly in combination with pyrethroids. The ratio of the synergist to the active substance generally varies between 1 : 2 and 1 : 20. The synergists can also potentiate the action of other insecticides, such as chlorinated hydrocarbons, organophosphates and carbamates. However their use for this purpose is rather limited, even though the potentiation of dangerous pesticides, and thus a reduction in the quantities used, would be desirable from the point of view of human toxicology and environmental protection. Most of the synergists used have a very low toxicity for warm-blooded animals. Thus, for example, the acute oral LD_{50} of piperonylbutoxide for rats is > 7500, that of tropital > 4000, of sesamex > 2000 and of sulfoxide 15000 mg/kg.

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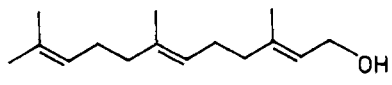
1.8 Insect growth regulators

1.8.1 Juvenile hormones and juvenile hormone mimics

As early as 1934 Wigglesworth showed that the evolutionary differentiation of insects is regulated by a centre in the brain. In 1956 Williams obtained from *Cecropia* moth a highly active extract which produced anomalies in the metamorphosis of experimental insects. Following this first description of the action of juvenile hormone, Gilbert and Schneiderman (1958), then Williams *et al.* (1959) described the juvenile hormone action of lipid extracts obtained from different mammalian organs. The pure active substance was isolated first by Schmialek (1961) from feces of the yellow mealworm, *Tenebrio molitor*, and identified as farnesol (**1**), known as an intermediate product in steroid biosynthesis. Six years later, Roeller and co-workers (1967) elucidated the structure of the juvenile hormone isolated from the male of *Cecropia*. The hormone was ascribed the structure methyl (*E,E*)-3,11-dimethyl-10,11-epoxy-7-ethyl-2,6-tridecadienoate (**2**), and was called C_{18}-JH. Independent of these workers, Meyer *et al.* (1968) isolated also from *Cecropia* another juvenile hormone, (*E,E*)-10,11-epoxyfarnesenate (**3**), called C_{16}-JH.



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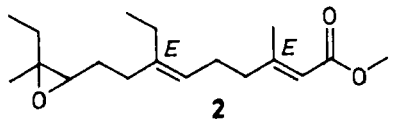

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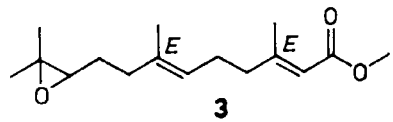
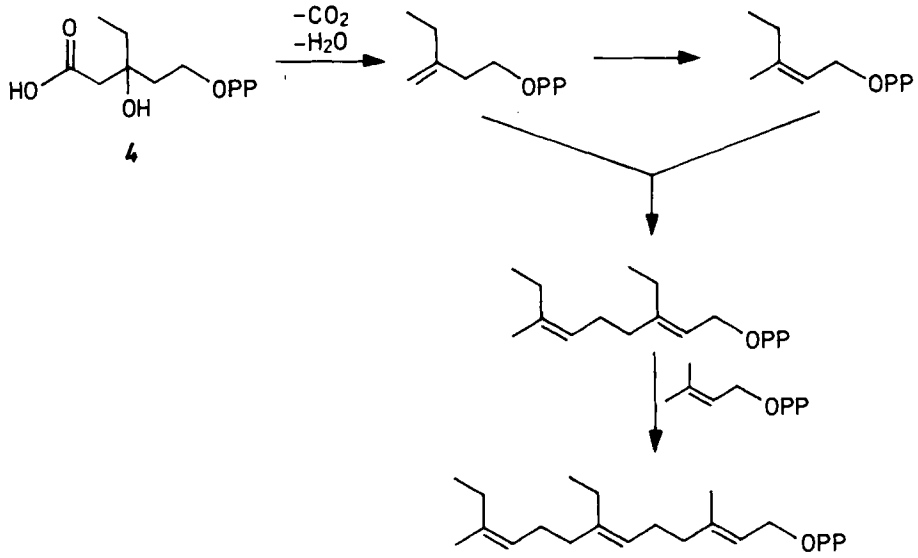


3

The biosynthesis of the juvenile hormones is not yet fully known. Their similarity to farnesol, an intermediate product in the biosynthesis of steroles in mammals, leads one to assume that their formation is analogous to that of farnesol. This obvious assumption seems to be supported by publications that have appeared in the early 1970s. Barnes and Goodfellow (1971) showed that isoprenoid biosynthesis in the larva of *Sarcophaga bullata* proceeds with the participation of mevalonate kinase. This enzyme regulates the formation of mevalonic acid pyrophosphate, an important intermediate product in steroid biosynthesis of mammals. Isopentenyl pyrophosphate, the C_5 unit of isoprenoid biosynthesis, is formed from mevalonic acid pyrophosphate by decarboxylation and, with the participation of ATP, by dehydration.

Schmialek (1963) obtained radioactive farnesol and farnesal from silkworm moth treated with [2-^{14}C]-mevalonic acid. The experiments of Sridhara and Bhat (1965), Happ and Mainwald (1966), Karlson (1970), Meyer *et al.* (1970) also prove that isoprenoid biosynthesis in insects proceeds via mevalonic acid as intermediate product, i.e. it is analogous to the early stages of mammalian steroid biosynthesis prior to the formation of the sterane skeleton. Early intermediates include acetate (Schooley *et al.*, 1973), acetyl-CoA (Baker and Schooley, 1978), (3*S*)-HMG-CoA (Bergot *et al.*, 1979) and (3*R*)-mevalonate (Schooley *et al.*, 1973; Lee *et al.*, 1978; Feyereisen *et al.*, 1981).

Ogura *et al.* (Ogura *et al.*, 1970; 1972; Koyama *et al.*, 1972) showed that not only isopentenyl pyrophosphate, but also its ethyl homologue, 3-butenyl-3-ethyl pyrophosphate, can serve as substrate for farnesyl pyrophosphate synthetase, which is responsible for the biosynthesis of the triterpene chain. This has been



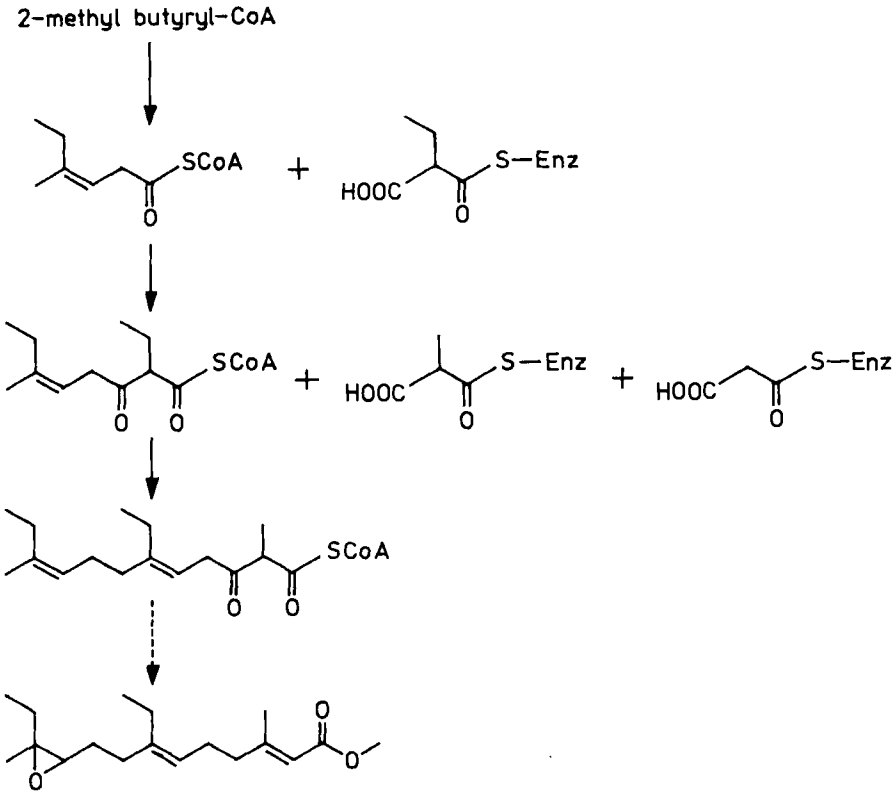
Scheme 1.18

confirmed by Schooley and associates (Schooley *et al.*, 1973; Lee *et al.*, 1978) and Siddall *et al.* (1974), thus it seems that the homoterpenoid ethyl branches of JH originate probably from propionate incorporated specifically *via* the intermediate homomevalonic acid pyrophosphate (**4**), the ethyl homologue of mevalonic acid pyrophosphate.

According to this theory, the terpenoid chain would be formed as shown in Scheme 1.18

At the same time, several findings have been published in the literature which indicate that juvenile hormone synthesis does not follow the seemingly obvious path. Metzler *et al.* found that of the presumed precursors of juvenile hormones only acetate and the ester methyl group arising from methionine are incorporated, while mevalonate, farnesol and farnesyl pyrophosphate are not (Metzler *et al.*, 1971; Rodé-Goval *et al.*, 1975).

The publication of Ajami (1974) gives rise to the strongest doubt. This worker found that isoprene precursors such as mevalonate, 3-methyl-2-pentenol, farnesol, the bis-ethyl homologue of farnesol (bis-homofarnesol) are not incorporated into



Scheme 1.19

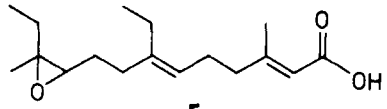
JH but, at the same time, the incorporation of acetate, propionate, glucose, alanine, leucine, isoleucine, threonine and fractions furnished by methionine can be demonstrated. Ajami concludes from this that JH is biosynthesised *via* a fatty acid route, according to Scheme 1.19

As regards the role of propionate, an interesting finding has been published by Peter and Dahm (1975), who established that the 1-C carbon atom of propionate only appears at the site of carbon atoms 7 and 11 of the carbon chain, while the 2-C and 3-C atoms of propionate also appear at the site of the other carbon atoms of the JH molecule. They conclude from this that, prior to its participation in the biosynthesis of JH, propionate is broken down into acetate, with the exception of the ethyl side chains, which are formed from intact propionate.

Conflicting schemes for the biosynthesis of JH may be partly explained by the fact that under the conditions of *in vivo* experiments the incorporation of the individual substances does not depend only on their fitting into the synthesis paths, but also on other factors, such as transport.

Up to the present, the last steps in the biosynthesis of juvenile hormone are those most satisfactorily established. It can be considered as proven that the ester methyl grouping is formed with the participation of methionine (Reibstein and Law, 1973), and this is followed by the formation of the 10,11-epoxy group (Pratt and Tobe, 1973; 1974; Tobe and Pratt, 1974). Presumably the epoxy group plays a role in the binding to the respective carrier protein of the haemolymph.

The two main steps of JH metabolism are the hydrolysis of the ester bond by esterase and the microsomal oxidation of the epoxy group into a dihydrodiol group effected by the enzyme epoxyhydrase. Either of these metabolic processes brings about complete disappearance of activity, and **5** and **6**, the proposed metabolic intermediates are inactive (Slade and Zibitt, 1971; Slade and Wilkinson, 1973; Ajami and Riddiford, 1973; Yu and Terrière, 1978).



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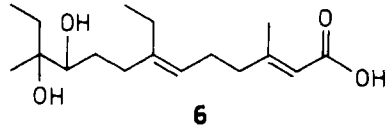
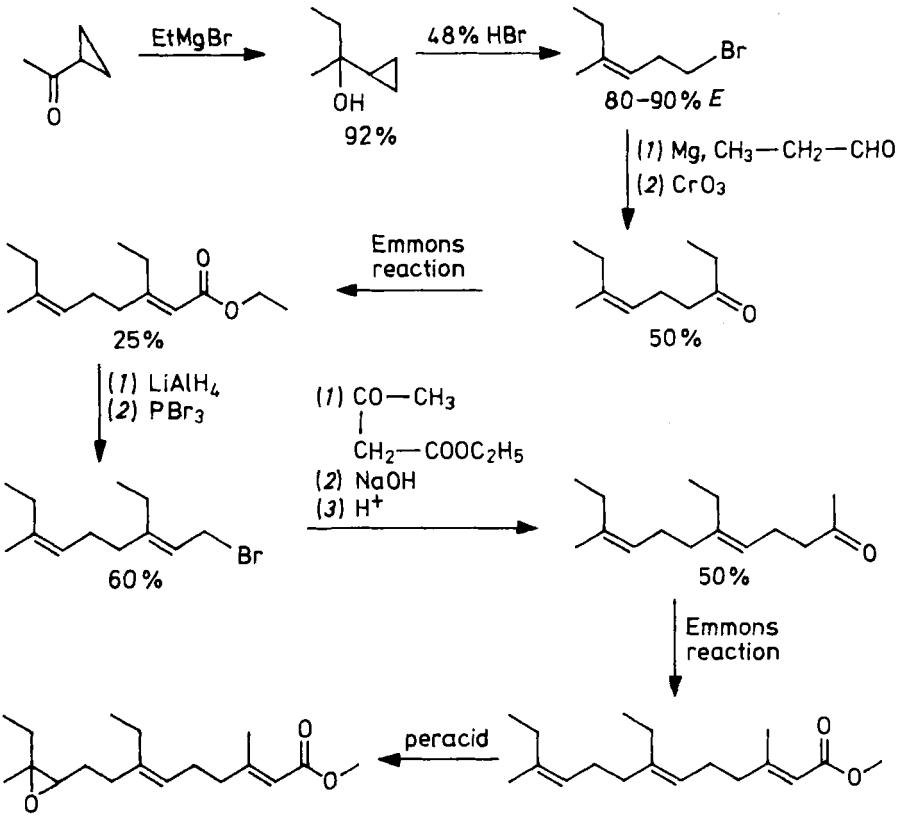


6

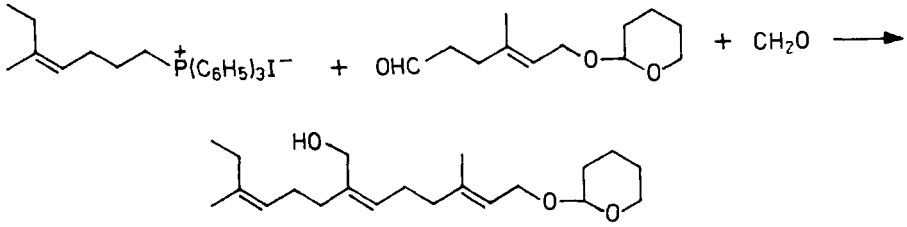
The synthesis of the juvenile hormones has been performed independently by several research groups (Dahm *et al.*, 1967; 1968; Johnson *et al.*, 1968; Corey *et al.*, 1968; Corey and Yamamoto, 1970; Findlay, 1971; Mori *et al.*, 1967; 1972a, 1972b; Kondo *et al.*, 1972).

The earliest was the nonstereospecific method of Dahm and co-workers (1967; 1968), shown in Scheme 1.20.

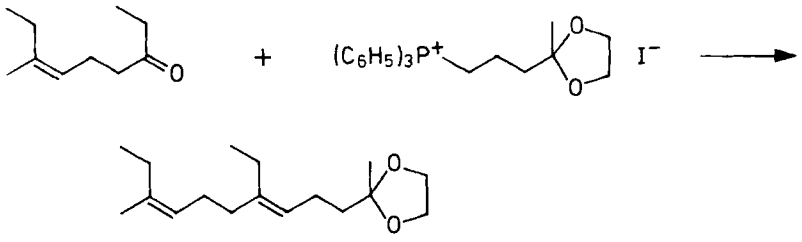


Scheme 1.20

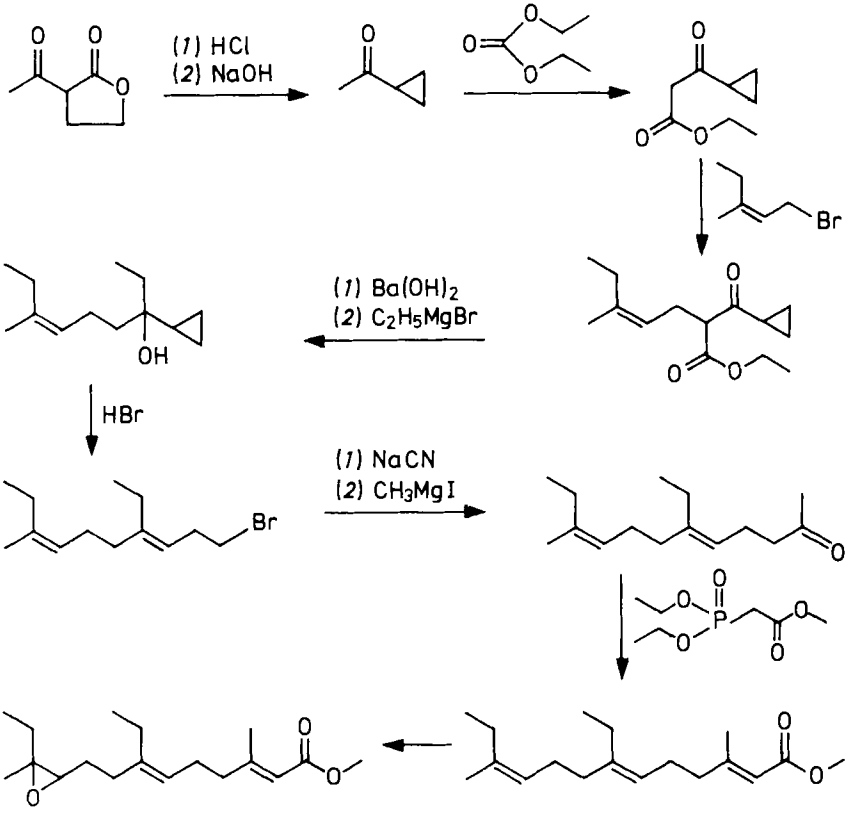
Corey and associates (1970) worked out a stereospecific synthesis route for the preparation of juvenile hormone. The essential element of their method is the use of phosphonium-ylides for the stereospecific linkage of three structural units in a single synthesis step.



The synthesis route of Findlay (1971) is also based on the use of phosphonium-ylides, its characteristic step being the coupling of two isoprenoid units:

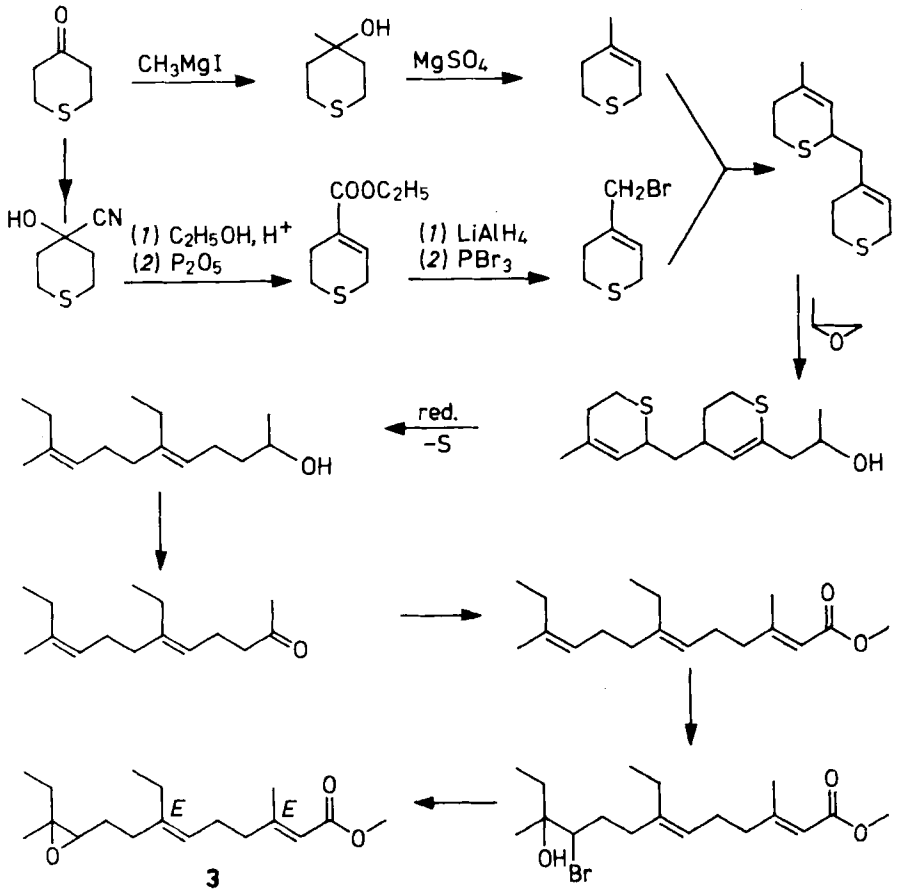


The nonstereospecific synthesis route of Mori *et al.* (Mori, 1971; Mori *et al.*, 1972a; 1972b) is shown by Scheme 1.21.



Scheme 1.21

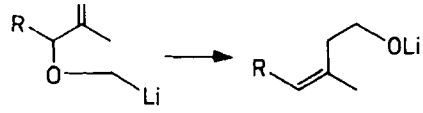
Kondo *et al.* (1972) used 4-methyl-Δ^3-dihydro-thiapyrane as structural unit in the stereospecific synthesis of juvenile hormone, the sulfur atom being removed by reductive desulfuration (Scheme 1.22).



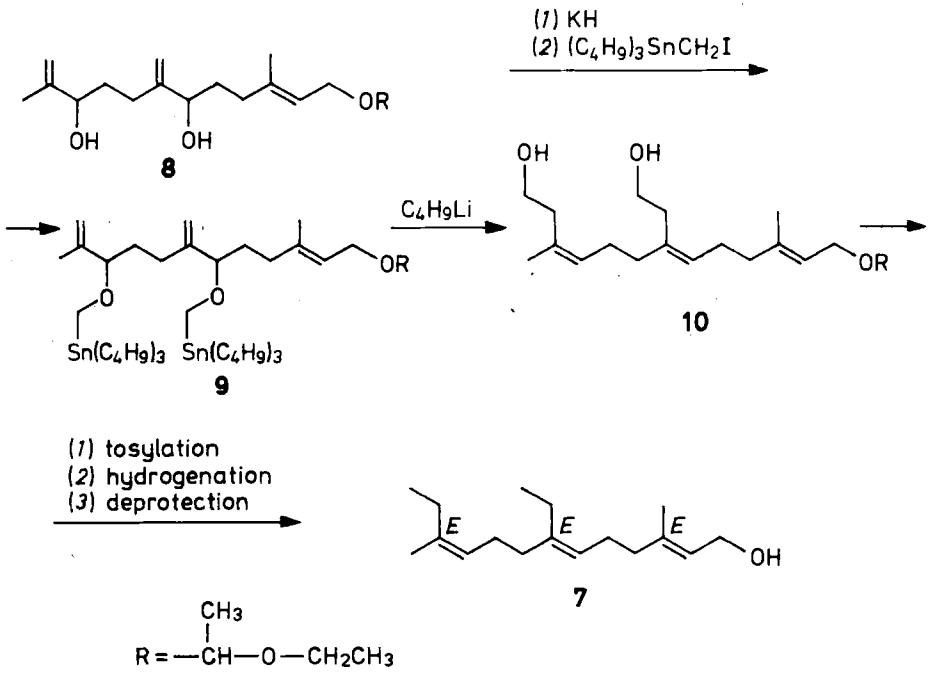
Scheme 1.22

In obtaining all-*trans* bis-homo-farnesol (**7**), needed for the synthesis of C_{18}-JH, Still and co-workers (1979) made use of their former finding (Still and Mitra, 1978) on the [2,3]-sigmatropic rearrangement of alkoxyorganolithium reagents, which provides an efficient method for the preparation of *Z*-homoallylic alcohols.

The crucial steps in the synthesis route developed by them are the alkylation of the monoprotected tris-allylic alcohol **8** with iodomethyltributyltin, to yield **9**,



which then underwent highly stereoselective rearrangement to the bis-homoallylic alcohol **10** on treatment with *n*-butyllithium. Tosylation, reduction and deprotection yielded **7** as shown in Scheme 1.23.

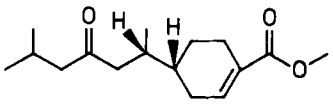


Scheme 1.23

Experimenting with the insect *Pyrrhocoris apterus*, Williams and Sláma (1966) observed that the insects failed to metamorphose normally in Petri dishes lined with paper of American origin. In elucidating the reason for this chance discovery, they established that *Pinaceae* used in America as raw material for paper manufacture contain "paper factor", a substance of morphogenetic action. This compound, which they called (+)-juvabione **(11)**, was isolated by Bowers *et al.* (1966) and, independently, by Cerny *et al.* (1967). The members of this latter research group isolated a still more effective derivative, dehydrojuvabione **(12)** from pinewood.

(+)-Juvabione proved to be identical to methyl todomatuate already previously known.

Ayyar and Rao (1967), and Mori and Matsui (1967) synthesised both compounds. The stereoselective synthesis was solved by Birch *et al.* (1969).



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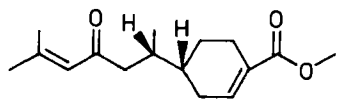
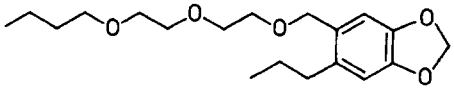


12

Bowers and co-workers (Bowers, 1968; 1971) investigated whether piperonyl butoxide (**13**), known as an insecticidal synergist, could also synergise JH and found that, when it was investigated for control purposes only, it also exhibited a juvenile hormone activity. In subsequent systematic investigations of other known insecticide synergists sesamex (**14**) proved to be the most efficient.



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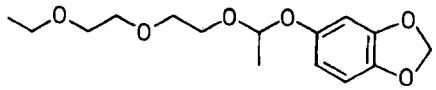
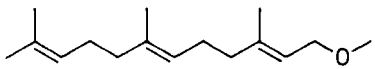


14

These two findings, the elucidation of the juvenile hormone effect of juvabione and of piperonyl butoxide, constituted a marked turn in the further course of research of compounds with juvenile hormone action. It became clear that not only endogenous compounds produced by insects are able to exert a juvenile hormone effect, but also compounds of an entirely different structure and origin. The detrimental properties of the traditional insecticides, the environmental contamination caused by their application and the public pressure for their banning necessitated the search for safer methods of insect control. Discoveries connected with insect hormones seemed to open up new prospects in this respect, and interest in a directed chemical interference with insect metamorphosis has been greatly intensified. At the end of the 1960s a search for synthetic juvenoids began with great intensity, and not only farnesol and juvenile hormones of insect origin, but also juvabione and methylenedioxyphenyl synergists served as lead compound in designing new structures.

Starting from the JH effect of farnesol, several workers attempted to obtain more effective derivatives by structural modification of this readily available compound. Schmialek (1963) found farnesyl methyl ether (**15**) and farnesyl diethylamine (**16**) to be more effective than farnesol, though none of these was as effective as *Cecropia* JH.

Bowers and Thompson (1963), after having established that the completely saturated hexahydrofarnesol (**17**) is also effective, investigated several saturated, nonbranched alcohols and their methyl ethers. Of these, dodecanol and dodecyl methyl ether (**18**) were active. Similar results were reported by Schneiderman *et al.* (1965), who found that molecular dimensions play a decisive role in the exertion of the action.



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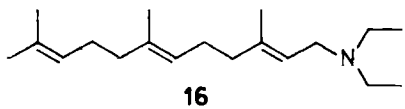

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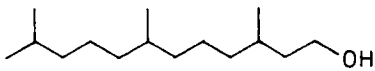

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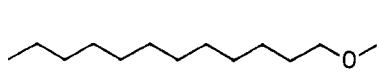
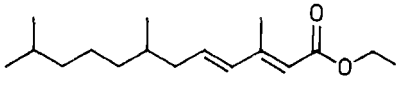


18

However, the JH activity of these compounds was relatively low as compared with that of the natural juvenile hormones. Significant progress was made by the research team of the Zoecon Corporation (Henrick *et al.*, 1973; 1975a; 1975b). They prepared a series of compounds differing from the natural juvenile hormones in that they possess a conjugated double bond system instead of the isolated double bonds at the carboxylic end of the molecule. Of these, compounds **19, 20, 21** and **22** were developed under the name hydroprene, methoprene, triprene and kinoprene, respectively.



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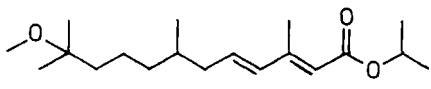

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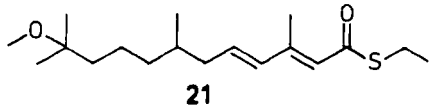

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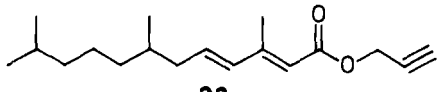
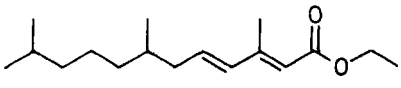


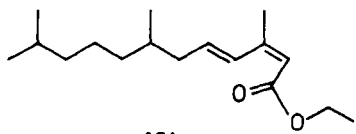
22

Methoprene was the first insect growth regulator to receive formal regulatory status from the US Environmental Protection Agency. Field trials at rates of 30–100 g/acre in an area infested with the eastern hemlock looper, *Lambdina fiscellaria*, resulted in an economic reduction of pupae and adults (Menn and Pallos, 1975).

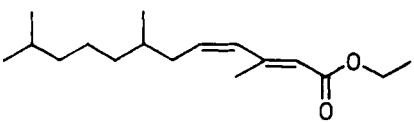
Henrick and co-workers (1973; 1975a; 1975b) performed the stereospecific synthesis of all four stereoisomers of hydroprene **(19a, 19b, 19c, 19d)**.



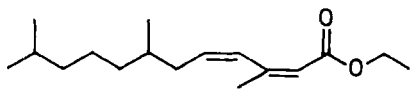
19a



19b



19c



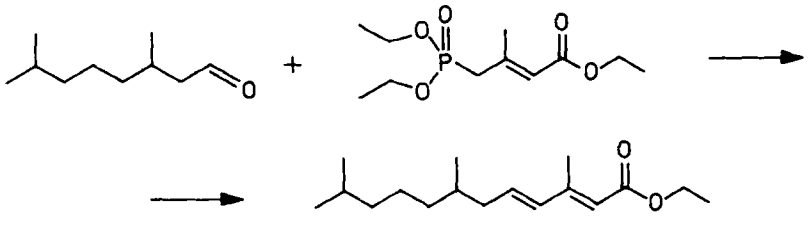
19d

Of these stereoisomers, compound **19a**, of configuration 2*E*,4*E*, proved to be the most effective, indicating that the presence of an (*E*)-2-ene double bond is essential for morphogenetic activity (Henrick *et al.*, 1976).

There is a chiralic centre at C-7 in these compounds and the (*S*)-(+)-enantiomers of alkyl (*E*,*E*)-3,7,11-trimethyl-2,4-dodecadienates are more effective than the

(*R*)-(−)-enantiomers. From this finding Henrick and co-workers (1978a; 1978b) concluded that a chiralic receptor is involved in their activity.

The synthesis of these products rests on a reaction of the corresponding aldehyde with trialkylphosphonoacetate, as exemplified by the reaction of dihydrocitronellal with triethylphosphonoacetate, to yield hydroprene **(19)** (Henrick *et al.*, 1973). However, specific synthesis routes had to be elaborated to obtain the stereoisomers in pure form (Henrick *et al.*, 1975a; 1975b).



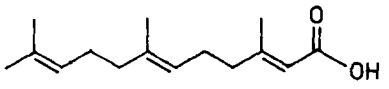
19

Hydroprene is metabolised in insects by both microsomal oxidase and esterase, while methoprene is metabolised by microsomal oxidase only (Terrière and Yu, 1973; 1977; Yu and Terrière, 1975). Methoprene is readily decomposed in the soil (Schooley *et al.*, 1975).

The advantage of both hydroprene and methoprene is their increased chemical stability, as compared with the natural juvenile hormones and most of their synthetic analogues. This is probably connected with the delocalisation of the π electron orbital in the conjugated double bond system, thus resulting in a lowering of energy level. An increased chemical stability is of special importance in the case of the juvenoids. Since the juvenile hormone action can assert itself only in the developmental periods sensitive to juvenoids, strict timing of treatments to the developmental cycles of the insects can be avoided only by using chemically stable derivatives.

Law *et al.* (1966) obtained by the addition of hydrochloric acid to farnesoic acid **(23)** in an alcoholic medium a mixture of several reaction products with strong JH activity. One of the most effective components of the reaction mixture has been isolated by Romanuk and co-workers (1967), and identified as the methyl ester of (*E*)-7,11-dichloro-3,7,11-trimethyldodecenoic acid **(24)**. One nanogram of the compound is sufficient for disrupting the metamorphosis of some insects.

Insertion of a cycloalkane ring into the terpenoid chain was carried out by Polish, Czechoslovak and American authors. Kocór *et al.* (1974) prepared by a modified



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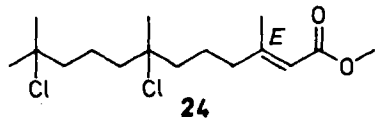
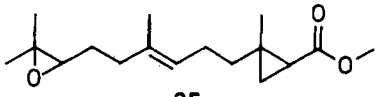


24

Simmons–Smith reaction 2,3-methylenefarnesol, which gave on oxidation, esterification and subsequent functionalisation of the C-10,11 double bond the 2,3-methylenefarnesenic acid derivatives **25** and **26**.



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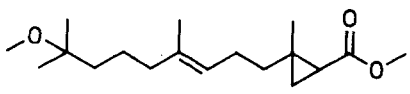
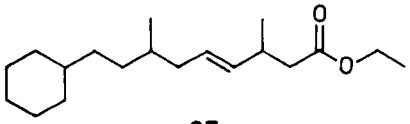


26

Members of the Czechoslovak research group (Sehnal *et al.*, 1976) prepared several alkyl esters of 3,7-dimethyl-2-nonenoic acid with a cyclohexane moiety at the end of the chain. Compounds **27** and **28** showed a marked biological activity.



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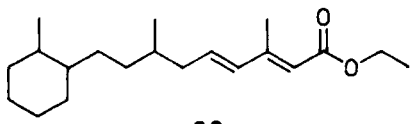
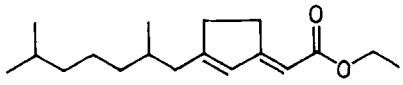


28

According to expectation based on pharmacological analogies, fixation of part of the molecule by a relatively rigid cyclic structure enhanced the species specificity, as compared with acyclic juvenoids. Thus, compounds **27** and **28** seem to be the most potent juvenoids presently available against *Blattodea* and *Lepidoptera*. At the same time, they are but moderately effective against their dipterous and hymenopterous parasites, honey bees and other useful insects.

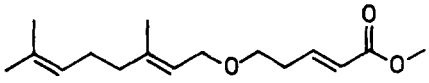
Active compounds have been obtained by Henrick *et al.* (1978a) who incorporated a cyclopentene ring into the juvenoid skeleton (**29**).



29

This compound can be regarded as a cyclic analogue of hydroprene (**19**) prepared by the same authors.

Sorm *et al.* prepared several oxygen analogues of JH, such as compounds **30** and **31**. Their potency varies considerably, depending on the length of the chain, and the number and position of the oxygen atoms (Sorm, 1971; Jarolim *et al.*, 1970).



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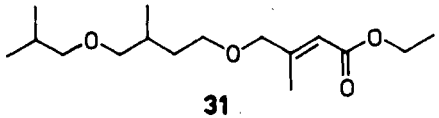
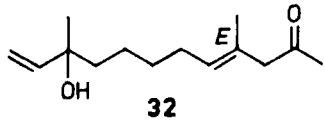


31

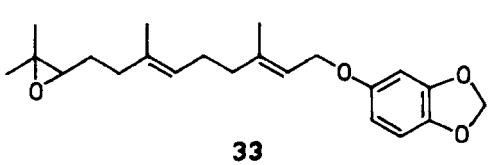
In spite of its great difference from the structural features of natural juvenile hormones, (*E*)-4,10-dimethyl-10-hydroxy-4,11-dodecadien-2-one (**32**), isolated by Jacobson and Redfern (1974) from the root of *Echinacea angustifolia*, exhibited a strong morphogenetic action.

After the discovery of the JH effect of piperonyl butoxide (**13**), Bowers (1969) prepared several derivatives in which the polyoxyethylene chain of the molecule is substituted by the whole or part of the terpenoid chain of juvenile hormone.



32

Derivative **33**, containing the complete JH chain, had a moderate effect, while derivatives **34, 35** and **36**, reduced by one terpenoid unit, proved to be very potent. This finding is in accordance with the experience of other authors that a chain of approximately the same length as that of JH is important from the point of view of activity.



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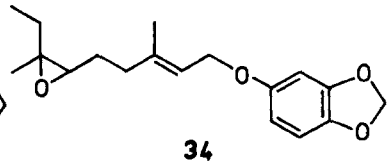

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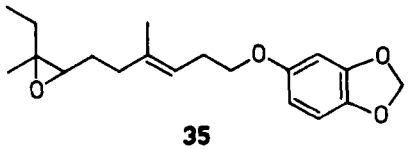
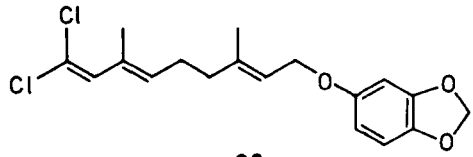
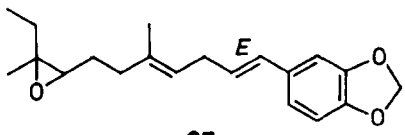


35



36

A similar potency is shown by the derivatives prepared by Chang *et al.*, where the terpenoid chain is attached through a vinylidene group to the methylenedioxyphenyl group (Chang and Tamura, 1971a; 1971b; Chang *et al.*, 1972). The most effective of these are compounds **37** and **38.**



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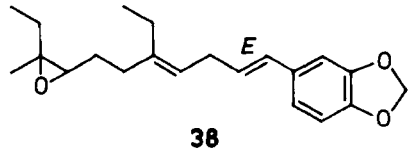
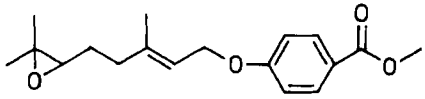


38

These findings, first of all the strong JH activity of compounds **34, 35** and **36** contributed to the development of a number of JH-analogues where one or two terpenoid units of the molecule were replaced by a benzene ring. Part of the products synthesised within this type carries an esterified carboxylic group in the *para*-position on the aromatic ring, thus showing structural features both of the natural juvenile hormones (**2, 3**) and of juvabione (**11**). Characteristic representatives of this class are terpenoid ethers of *p*-hydroxybenzoic acid, such as compounds **39, 40** and **41** (Bowers, 1969; 1971; Romanuk *et al.*, 1969).

The chain terminal ethoxy group of compound **41** has been introduced by means of the solvomercuration-demercuration method (Brown, 1967; Brown and Min-Hon Rei, 1969). This process, based on the mercuration of olefin with mercuric



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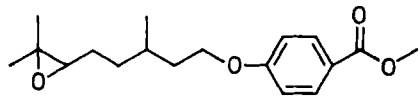
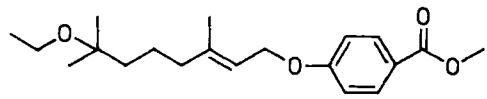
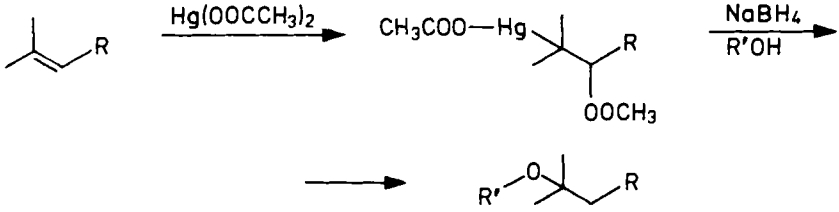


40

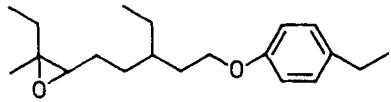


41

acetate and subsequent reductive demercuration in an alcoholic medium, obtained widespread application in the synthesis of JH analogues.



Further investigations on the structural requirements of activity have shown that alkyl substitution in the *para*-position on the benzene nucleus may also yield active derivatives, ethyl being optimal (Pallos *et al.*, 1971). This finding led to the development of a number of active derivatives, such as **42, 43, 44** and **45** (Hangartner *et al.*, 1976; Piccardi *et al.*, 1977; McGovern and Redfern, 1979).



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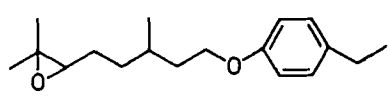

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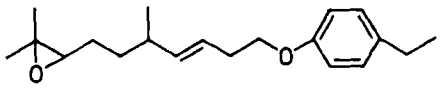
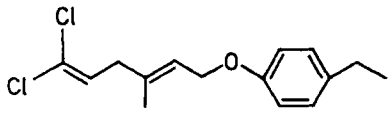


44

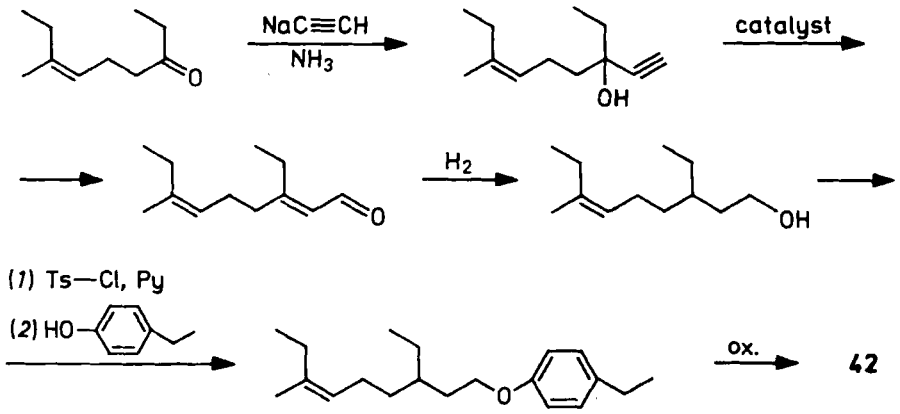


45

The chain terminal dichlorovinyl group of compounds **36** and **45** resulted in enhanced field stability as compared with the epoxidised analogues.

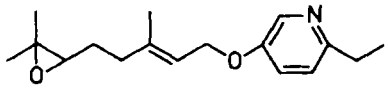
Compound **42**, developed by the Swiss company Hoffman–La Roche under the name epofenonane obtained commercial importance. The most characteristic part

of its synthesis, which is illustrated in Scheme 1.24, is a new process for the isomerisation of acetylenic carbinols using a vanadyl *n*-propylate and silanyl catalyst composition (Pauling, 1972; Hindley and Andrews, 1974).



Scheme 1.24

In agreement with the finding that within a series of terpenoid *p*-alkylphenyl ethers the *p*-ethylphenyl derivatives are the most effective, Solli *et al.* (1976) prepared a great number of pyridyl terpenoid ethers and found that optimal activity is obtained when the ether bond is in position 3, the alkyl group in position 6 of the heterocyclic nucleus and the substituent is ethyl. Accordingly, the most active representatives of this class are compounds **46** and **47.**



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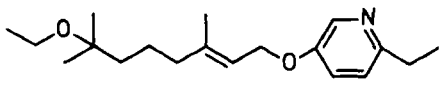
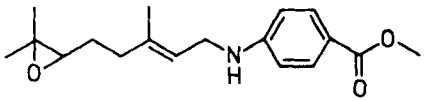
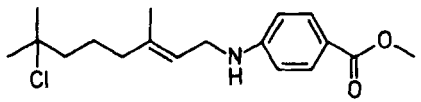


47

The development of *p*-aminobenzoic acid derivatives in which one or two diterpenoid chains are attached to the nitrogen atom is linked with the Czechoslovak research group (Dolejs *et al.*, 1969; 1970a; 1970b). The most active compounds of this type are the derivatives **48, 49** and **50**. Their activity is limited to the family of *Pyrrhocoridae*, however.

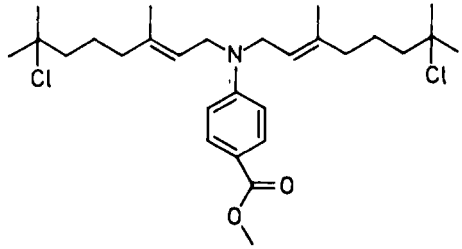


48



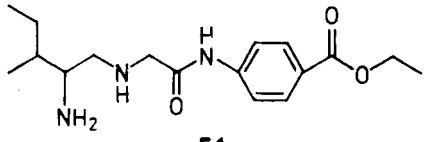
49

A complete departure from the terpenoid character of the natural juvenile hormones is the development of those *p*-aminobenzoic acid derivatives in the molecule of which a peptide chain is attached to the nitrogen atom on the benzene



50

ring (Zaoral and Sláma, 1970; Poduska *et al.*, 1970; 1971; 1973). Following the synthesis of ethyl L-isoleucyl-L-alanyl-*p*-aminobenzoate and the establishment of its activity, several other still more potent derivatives, novel also with respect to their range of action, have been prepared by modern methods of peptide chemistry. Derivatives with a hydrophobic acyl group attached to the terminal amino group proved to be particularly active. The most active members of this type in the order of increasing activity are: **51** < **52** < **53** < **54** < **55.**



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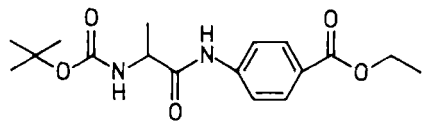

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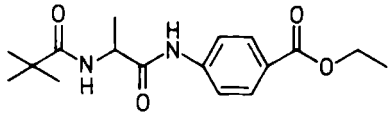

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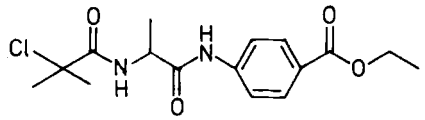

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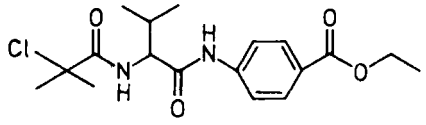
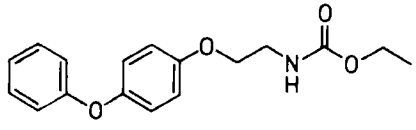


55

Effective doses of these derivatives against *Pyrrhocoris apterus* and *Dysdercus cingulatus* are **51:** 0.5, **52:** 0.01, **53:** 0.000 04, **54:** 0.000 01 and **55:** 0.000 002 μg/insect. The latter derivative is the most potent juvenile hormone analogue known so far. Only the isomers of *S*-configuration of this type are active, while those containing

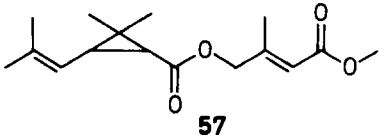
the *R*-amino acid part are inactive. Omission of the side-chain of the central amino acid moiety, or its substitution for an aromatic group, results in inactive products.

Ethyl N-[2-(*p*-phenoxyphenoxy)ethyl]carbamate (Ro 13-5223, fenoxycarb, **56**), a compound possessing high juvenile hormone activity, has gained practical importance in the control of various lepidopterous species, scale insects, fire ants and stored product pests (Fischer *et al.*, 1980; Masner *et al.*, 1981; Dorn *et al.*, 1981). It completely inhibits the population growth of the California red scale, *Aonidiella aurantii* in a concentration as low as 0.03%. It interrupts the development during morphogenesis and thus prevents eclosion of adults.



56

Punja *et al.* (1973) prepared several new esters of chrysanthemic acid, combining structural features of the pyrethroids with those of juvenile hormones. Of these, the JH effect of the most potent derivatives, **57**, **58** and **59**, was nearly the same as that of the natural juvenile hormones.



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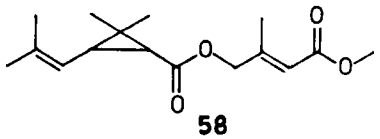
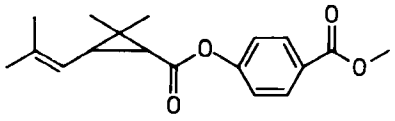


58

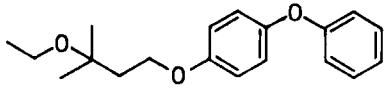


59

In spite of the fact that these compounds are structurally very different from *Cecropia* juvenile hormone, they possess structural features common to the natural hormones and to the active mimics, i. e. a terminal esterified carboxylic group conjugated with a double bond held *trans* to a long alkyl chain and a *gem* dialkyl group at the opposite end of the chain. Punja and co-workers compared Dreiding's molecular models of the active chrysanthemates **57**, **58** and **59** with C_{18}-JH (**2**) and with juvabione (**11**) and found that in each case the terminal ester and the *gem* dialkyl group coincide. They inferred from this that the relative positions of the terminal groups are of more importance from receptor fit than is the configuration in the centre of the molecule.

Karrer *et al.* (1974) synthesised C_{18}-JH analogues in which two of the three isoprene units are replaced by phenyl groups connected by a short linkage. In the compounds prepared by them first both the central isoprene unit and that

containing the methoxycarbonyl function of the natural juvenile hormone are replaced by phenyl groups. Of these, derivatives **60** and **61** have been found to be most active.



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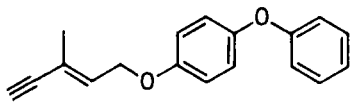
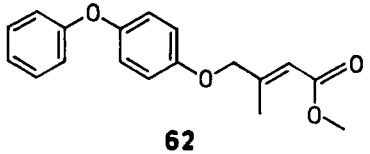


61

After having established the strong JH-activity of these compounds, Karrer *et al.* prepared a series of derivatives in which the two phenyl groups replace the central and the epoxide carrying isoprene units of C_{18}-JH. Compounds **61, 62, 64** and **65** were particularly active members of this group. The activity of all of them surpassed that of C_{18}-JH.



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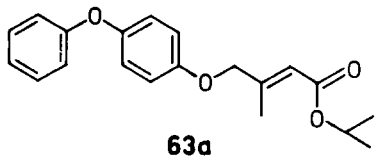
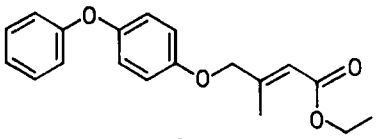
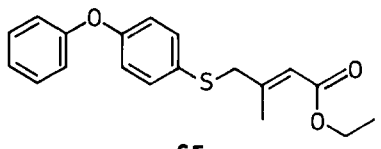


63a

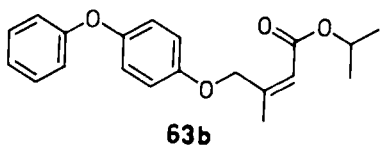


64



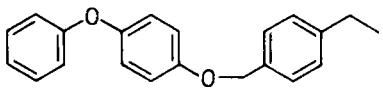
65

In this case too, bioactivity depends on the steric structure of the molecule. Compound **63b,** possessing a *Z*-configuration showed a considerably weaker biological activity than its highly active stereoisomer **63a** with an *E*-configuration.



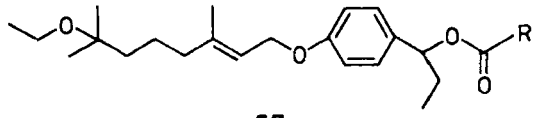
63b

Their recent findings (Karrer and Farooq, 1981) indicate that even the third isoprene unit of the JH terpenoid skeleton can be replaced by a benzene nucleus, provided that two of the three benzene rings are linked by a methyleneoxy grouping, as exemplified by **66.**



66

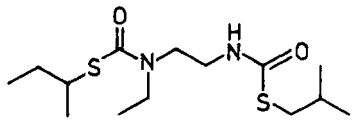
Sláma and associates (Sláma and Romanuk, 1976; Sláma *et al.*, 1978) prepared esters of juvenoid alcohols formed with long chain fatty acids. These compounds, which they call juvenogens, can generate products with JH activity as a result of ester hydrolysis in the insect. The activity of these juvenogens is determined only by that of the juvenoid alcohol, thus permitting a variation of polarity and other characteristics by changing the biologically unimportant acyl moiety. Typical representatives of this class are compounds characterised by formula **67** where R represents different long alkyl chains.



67

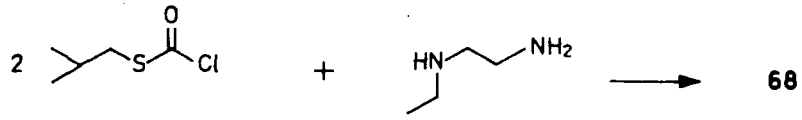
Pallos *et al.* (1974; 1976) found compounds of strong morphogenetic action in the group of the bisthiolcarbamates, representing further departure from the terpenoid skeleton. They suggested, on the basis of the structural features of known juvenoids, a generalised molecular model for activity. The structure of the proposed template is

A series of bisthiolcarbamates were prepared which structurally adhere to the template and display high morphogenetic activity. The most active member of this class was compound **68.**

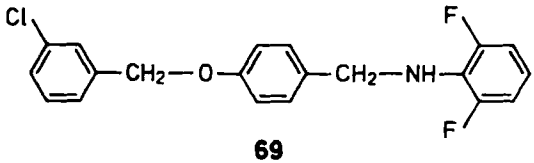


68

In accordance with the general scheme of preparation of thiolcarbamates this compound can be obtained by the reaction of S-isobutyl chlorothiocarbonate with N-ethyl-ethylenediamine.

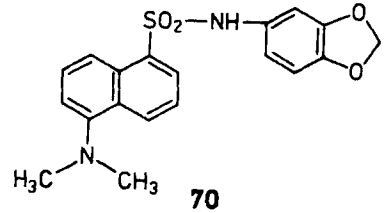


The N-[4-(benzyloxy)benzyl]anilides obtained by DeMilo and Redfern (1979) proved to be highly effective juvenile hormone mimics, though their structure does not reflect even the intention of preparing terpene inspired juvenoids. The most effective member of this class was N-[4-(3-chlorobenzyl)oxy]benzyl-2,6-difluoro-aniline **(69).**



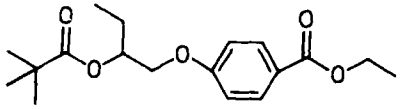
69

5-[[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]amino]-1,3-benzodioxole (DNSAB, **70**), prepared by Mayer *et al.* (1976), shows insect juvenile hormone activity, and at the same time it fluoresces in the visible region of the spectrum. This property of the compound permits the use of fluorescence and absorbtion detection methods in the study of juvenile hormone activity.



70

Ethyl-4-[2-(*t*-butylcarbonyloxy)butoxy] benzoate (ETB, ZR-2646, **71**) occupies an intermediate position between the juvenile hormone mimics and the anti-juvenile hormones to be discussed later. It acts as an anti-JH at low doses and as a JH mimic at high doses. The nature of this JH agonist/antagonist action is not understood, yet its interference with the induction of juvenile hormone esterase seems to elucidate at least partly its action on insects (Staal, 1977; Sparks *et al.*, 1979).



71

The mode of action of the synthetic juvenoids exerted at the molecular level is still essentially unknown.

Sláma *et al.* (1974) classified current theories of the mechanism of action of juvenile hormones and juvenoids into the following three groups:

(1) specific influence on nucleic acid metabolism and gene inactivation;

(2) interference with the intracellular balance of potassium and sodium ions, and

(3) effects on membrane permeability.

Williams and Kafatos (1971) and Karlson (1971) assume, in good agreement with their experimental results, that juvenoids act by specific changes in gene activation, thus interfering into developmental programmes.

According to Minks (1967), juvenoids stimulate the Na/K pump, inducing a decrease in intracellular Na and an increase in intracellular K. This results in a stimulation of phosphorylation through a decrease of ATPase activity. On the

other hand, Lezzi and Friegg (1971) claim that the action of juvenile hormones results in an increase of the intracellular Na/K ratio.

The theory based on the influence on membrane permeability is supported by the finding of Baumann (1968) that certain juvenoids influence the conductivity of lipid-protein membranes, as well as by the fact that isoprenoids form complexes with proteins.

It cannot be decided on the basis of experimental results available so far whether the action of the synthetic juvenoids is a hormonomimetic effect exerted according to the same mechanism as that of endogenous juvenile hormones. The fact that compounds with a very different structure from that of natural juvenile hormones also display morphogenetic activity seems to suggest that at least an important part of synthetic juvenoids acts according to another mechanism. According to Bowers (1968), the morphogenetic activity of certain insecticide synergists cannot be traced back to the stimulation of juvenile hormone biosynthesis, but both morphogenetic activity and their synergising ability presumably result from the inhibition of oxidative enzymes. These enzymes are responsible on the one hand for converting the plant sterols consumed by the insects into ecdysone and, on the other hand, for the oxidative detoxication of insecticides. Slade and Wilkinson (1973) drew similar conclusions from their *in vitro* investigations. Accordingly, several synthetic juvenoids act by inhibiting the enzyme system responsible for the degradation of the endogenous hormone, thus causing its stabilisation (Slade, 1974; Slade and Wilkinson, 1973). Staal (1975) is of the opiniion that this theory can be valid only for some juvenoids. Several weakly active juvenoids can synergise more active ones (Redfern *et al.*, 1972; Riddiford *et al.*, 1971; Sonnet *et al.*, 1973). From these and other experimental findings Slade (1974) concluded that these effects are based on competition for the same metabolic enzymes.

Juvenile hormones and molting hormones (ecdysones) discussed below together form the hormone system regulating the development and reproduction of insects. For transformation from one larval stage into the other the simultaneous action of juvenile hormone and ecdysone is needed. Larval-pupal and pupal-adult ecdysis proceeds with the participation of ecdysone alone. Finally, juvenile hormone again attains an important role in reproduction, as it initiates the development of the ovaries (Bowers, 1971). Any deviation from the hormone levels required for the development of the insect and from their appropriate timing leads to serious disturbances in the metamorphosis and reproduction of insects, such as mixed morphological patterns of different developmental stages, extra larval, pupal or adult forms, disruption of embryogenesis, female sterility, etc. All these effects may result in the death of the insect or an arrest of reproduction, and this fully justifies the positive expectations of the use of synthetic juvenile hormones in plant protection.

According to data available so far, synthetic juvenoids are only slightly toxic to mammals, birds and fish, their acute oral LD_{50} for mice being higher than 4000 mg/kg. Therefore, their use should have considerable advantages with regard to human toxicological and environmental aspects compared to conventional

insecticides. The fact that they affect a hormone system functioning only in insects precludes the possibility of hazards to other organisms.

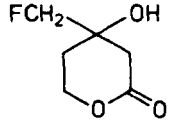
Notwithstanding this, their use in plant protection has so far brought modest results. This is due mainly to their narrow range of anti-insect activity, the necessity of critical timing in their application, insufficient persistence, lack of immediate action, and the possibility of reinvading population.

In recent years, it has been reported in an increasing number of publications that juvenoids are also subject to the development of resistance. Strains of insects resistant to insecticides have shown cross-resistance to juvenoids (Vinson and Plapp, 1974).

1.8.2 Anti-juvenile hormones

Earlier attempts to develop compounds with anti-juvenile action remained unsuccessful. Sláma *et al.* (1974) tested about 200 compounds structurally related to juvenoids but lacking JH activity. None of them revealed anti-juvenile activity, in spite of the fact that they can be considered as potential antimetabolites of juvenile hormones.

Similarly, the experiments of Matolcsy *et al.* (1974a; 1974b; 1975), in which several metabolite analogues of mevalonic acid and homomevalonic acid have been tested for anti-juvenile action, were unsuccessful. Support for the rationale that these metabolite analogues would block the formation of juvenile hormone at the mevalonate level was provided by the successful inhibition of cholesterol biosynthesis by mevalonate analogues in humans. Yet, a fluorinated mevalonate analogue, 4-fluoromethyl-4-hydroxy-tetrahydro-2H-pyran-2-one (FMev, **72**) was found to act as a potent inhibitor of JH biosynthesis by Quistad and co-workers (1981).

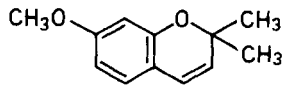


72

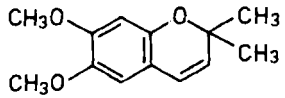
Hammock and Mumby (1978) surveyed several known anti-oxidants, mixed function oxidase inhibitors, and related compounds as potential inhibitors of the NADPH dependent epoxidation of methyl farnesoate to JH III (methyl-10,11-epoxyfarnesoate) *in vitro*. Several compounds were active in this respect, the most effective inhibitor being *o*-bromophenoxymethylimidazole (**23** in Chapter: Insecticide synergists). In the experiments of Wilkinson *et al.* (1973) this compound proved to be highly active also as an inhibitor of microsomal epoxidase and insecticide synergist (see Chapter: Insecticide synergists), suggesting that the same mechanism is also involved in the epoxidation in juvenile hormone biosynthesis. However, none of the inhibitors were active as morphogenetic agents and they failed to cause precocious metamorphosis, characteristic anti-juvenile hormone

action. According to the authors the results obtained *in vivo* suggest the possibility of obtaining pest control chemicals acting by blocking the chain terminal epoxidation or other steps in JH biosynthesis.

The most significant discovery in this field was the finding of Bowers *et al.* (1976). They isolated two substances from the lipid extract of the ornamental plant *Ageratum houstorianum* which exhibited a marked biological effect on several insect species, causing precocious metamorphosis on hemimetabolous larvae. Characterisation studies showed the two active principles to be 2,2-dimethyl-7-methoxychromene (precocene I, **73**) and its 6,7-dimethoxy analogue (precocene II, **74**). They proved to be identical with the ageratochromes isolated earlier by Alertsen (1955) and subsequently synthesised by Huls (1958).



73



74

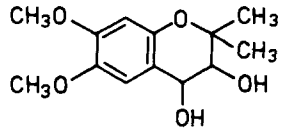
Larvae of the large milkweed bug, *Oncopeltus fasciatus* treated with precocene II undergo precocious metamorphosis and moult into diminutive forms with adult characters. Freshly hatched females treated with precocene II remain sterile and their *corpora allata* loose their ability to secrete juvenile hormone even when transplanted into an untreated body (Müller *et al.*, 1979; Masner *et al.*, 1979; Pener *et al.*, 1978).

The action of precocenes on the molecular level is not understood. Pratt and Bowers (1977) demonstrated the inhibition of the final steps in juvenile hormone biosynthesis, including epoxidation of farnesenic acid, following administration of precocene II to the test insects. Based on their experimental findings, members of the Bristol research group hypothesised that precocene and its derivatives are epoxidised to 3,4-epoxides having alkylating properties. The formation of these epoxides competes with the epoxidation step in JH biosynthesis, thus destroying the ability of *corpora allata* to synthesise JH.

However, other authors concluded that the effect induced by precocenes is a consequence of their antifeeding or general toxic action (Sláma, 1978; Kelly and Fuchs, 1978; Rembold *et al.*, 1979). Arguments favouring this hypothesis are the growth disruption of insects caused by some antifeedants (Ruscoe, 1972), the observation that precocene had no effect on the development of insects that are resistant to some antifeedants due to adaptation (Sláma, 1978), and by the lack of morphological abnormalities on honey bee following administration of precocene II (Rembold *et al.*, 1979).

Kelly and Fuchs (1978) found an inhibition of trypsin synthesis after treatment of insects with precocene II and concluded that the retarded ovarial maturation is but a consequence of a general toxic state.

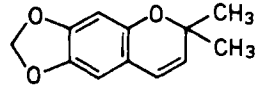
The principal metabolite of precocene II in the test insects was found to be 6,7-dimethoxy-2,2-dimethyl-chroman-3,4-diol (**75**), which is then readily conjugated (Ohta *et al.*, 1977; Burt *et al.*, 1979).



75

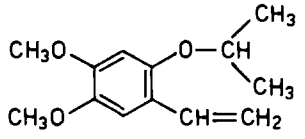
Structure–activity studies carried out by Bowers (1977) have shown that the most important position for the methoxy substitution in the aromatic ring is the position 7 while 6,7-substitution results in higher specificity. Outside of the 6,7-position, all dimethoxy substitutions of the aromatic ring were inactive, as was the 6,7-dimethyl derivative. Exchange of the methyl groups in position 2 for ethyl groups decreased activity and substitutions either in the 3 or 4 positions destroyed it (Soderlund *et al.*, 1981). The corresponding chromans lacking the 3,4-double bond are completely inactive (Bowers, 1977).

Brooks and co-workers (1979) have shown that compound **76**, the methylenedioxy analogue of precocene II, is a specific inhibitor of the oxidative conversion of precocene II to its active epoxide. This action rests on an inhibition of monooxygenase activity responsible for bioactivation of precocene, a mechanism analogous to the inhibition of oxidative degradation of insecticides by the methylenedioxybenzene type synergists.



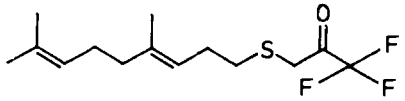
76

Matolcsy *et al.* (1980; 1981) reported that 1,2-dimethoxy-4-isopropoxy-5-vinylbenzene (**77**) a compound derived formally by opening the dihydropyrane ring of precocene II, possesses a precocene type anti-juvenile hormone activity. This finding indicates that compounds lacking the chromene ring structure can also be active.



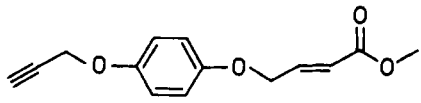
77

Hammock and co-workers (Hammock *et al.*, 1982; Abdel-Aal, 1984; Prestwich *et al.*, 1984) prepared several 3-alkylthio-1,1,1-trifluoro-2-propanones with juvenile hormone-like side chains. These compounds were designed as possible transition-state analogue inhibitors of JH esterases. The most active analogue **(78)** showed a dose-dependent delay in pupation and a selective inhibition of JH esterase of the cabbage looper, *Trichoplusia ni.*



78

In the search for chemicals inhibiting the enzymes O-methyl transferase and methyl farnesoate epoxidase, responsible for the methyl ester formation and for the terminal epoxidation in juvenile hormone biosynthesis, Brooks and co-workers (1984) prepared a number of acetylenic esters and 1,3-benzodioxole derivatives. These groupings are of particular interest in the context of JH biosynthesis inhibition. The acetylenic derivative **79** showed the strongest inhibitory action on both enzymes.



79

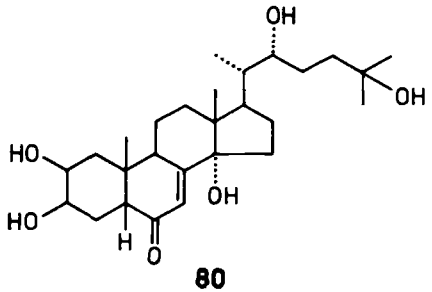
No prediction can be made as yet on the future role of anti-juvenile hormones in insect control. However, the results obtained hitherto demonstrate the possibility of developing anti-insect agents acting to disrupt rather than mimic endocrine function.

1.8.3 Ecdysones, ecdysoids and anti-ecdysones

In 1917 the Polish biologist Kopec tied up the middle part of a caterpillar with a thin thread. The head section of the caterpillar moulted and pupated normally, but its hind end remained an unaltered caterpillar (Kopec, 1922). He concluded from this that the moulting and pupation of insects is regulated by a brain-controlled hormone.

Butenandt and Karlson (1954) isolated the moulting hormone and called it α-ecdysone **(80).** The elucidation of its structure is associated with the name of Karlson *et al.* (Karlson *et al.*, 1963; Huber and Hoppe, 1965; Hoppe and Huber, 1965).

α-Ecdysone has been shown to be hydroxylated to ecdysterone (β-ecdysone, **81**), which is regarded by many authors to be the real moulting hormone. This process is catalysed by the enzyme ecdysone 20-monooxigenase (Robbins *et al.*, 1971; Nigg *et al.*, 1976; Bollenbacher *et al.*, 1977; Feyereisen, 1977; Weirich *et al.*, 1984). Further product of the hydroxylation series is 20,26-dihydroxyecdysone **(82).**



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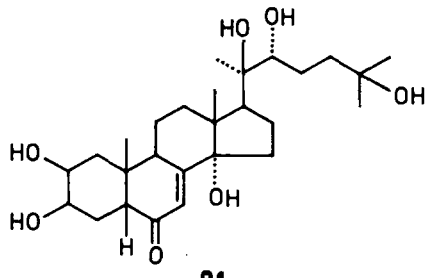

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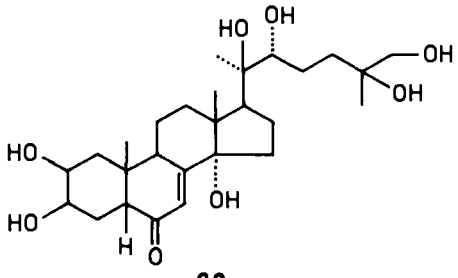
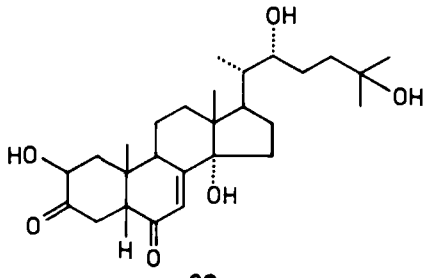


82

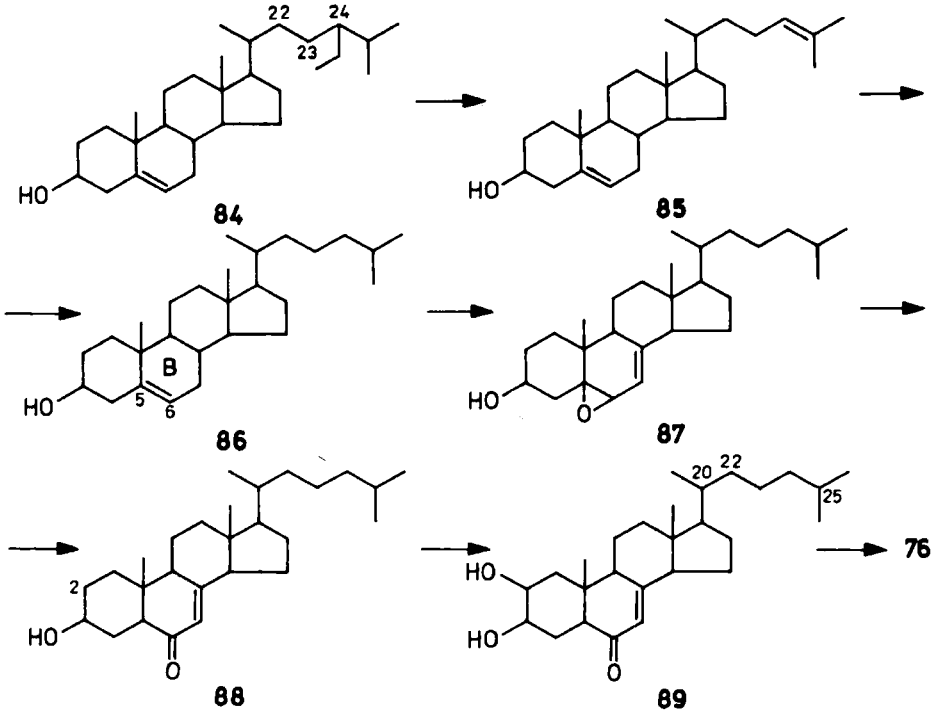
However, ecdysone may also undergo oxidation leading to inactivation, such as the oxidation to 3-dehydroecdysterone **(83)** by the enzyme ecdysone oxidase (Koolman and Karlson, 1978).



83

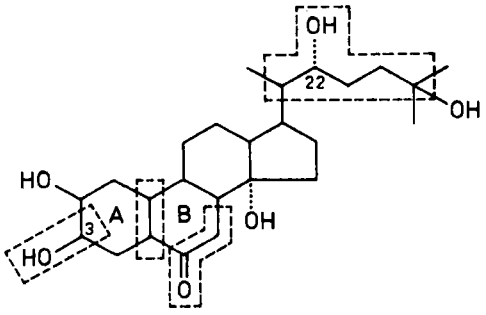
The biosynthesis of α-ecdysone has been extensively investigated by Svoboda *et. al.* (Svoboda and Robbins, 1967; 1968; Svoboda *et. al.*, 1969; 1975; Kaplanis *et al.*, 1969; 1973; Thompson *et al.*, 1972). They found that the insect is unable to build up the steroid skeleton, so that it is dependent upon dietary sterol for normal growth. Thus, phytophagous insects must be able to convert phytosterols, such as sitosterol **(84)** into desmosterol **(85)** which is then converted into cholesterol **(86).** This conversion proceeds by the mediation of the Δ^{24}-sterol reductase enzyme system. Following this, the 5,7-diene system in ring B is converted to 5,6-monoepoxide **87,** which is rearranged to give the 6-keto derivative **88.** Hydroxylation at position 2 of the ring **(89)** and hydroxylations of the side chain at positions 20, 22 and 25 are

effected by an enzyme system not yet identified. The main route of ecdysone biosynthesis may be illustrated by Scheme 1.25.

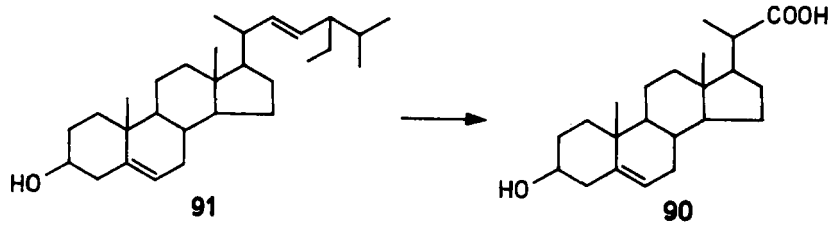


Scheme 1.25

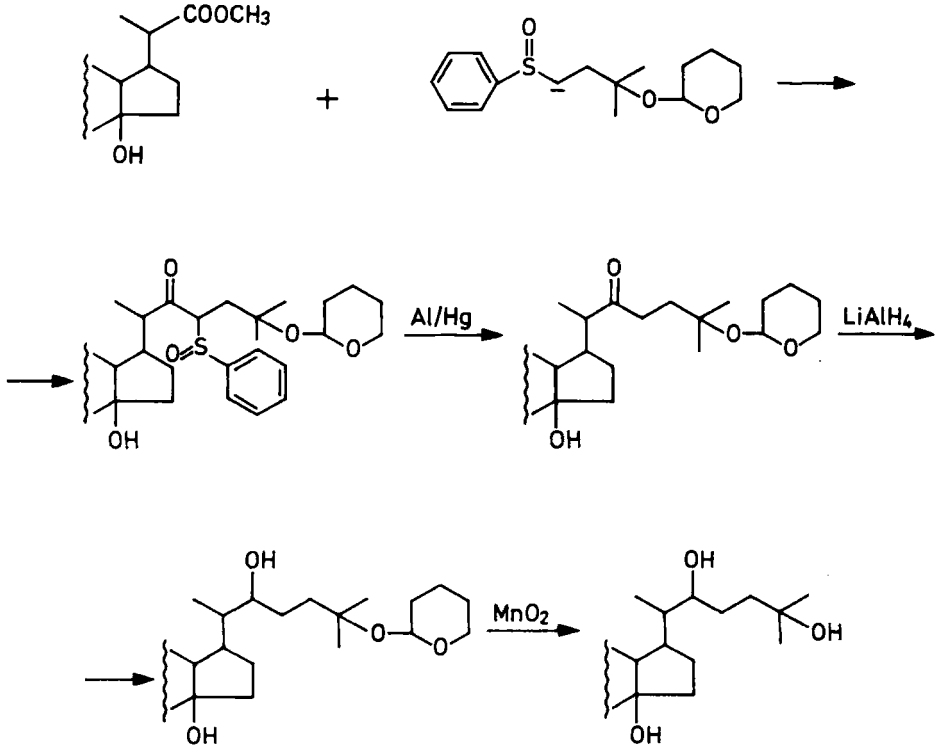
From a comparison of the biological action of ecdysones of insect origin and of several ecdysoids of plant origin, Sláma *et al.* (1974) summarised the following indispensable structural requirements for high moulting-hormone activity: (*1*) Z-fusion of rings A and B; (*2*) β-hydroxylic function at position 3; (*3*) keto group at position 6 in conjugation with a Δ^7 double bond, and (*4*) steroid side chain with an appropriately *R*-orientated hydroxyl function at position 22:



The synthesis of α-ecdysone was developed almost at the same time by several research groups working independently. The processes of Kerb *et al.* (Kerb *et al.*, 1966; Wiechert *et al.*, 1966) and Siddall *et al.* (1966) both start from 23,24-dinorcholenic acid **(90)**, obtained by the oxidative cleavage of the side chain of stigmasterol **91.**

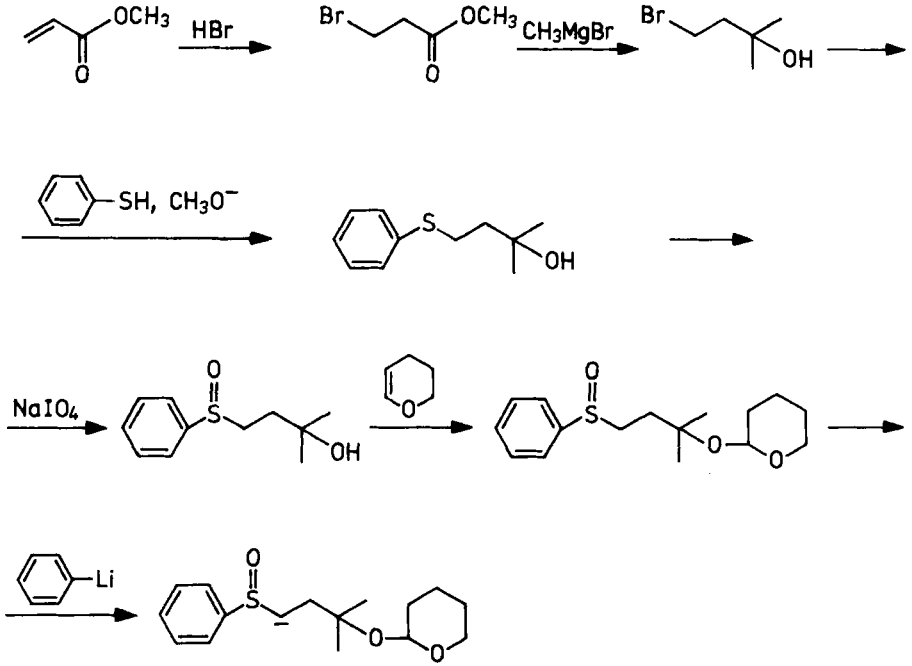


One of the crucial synthesis steps, the introduction of the side chain, was solved by Siddall and co-workers with the aid of a sulfinyl-stabilised carbanion alkylating agent, as shown is Scheme 1.26.



Scheme 1.26

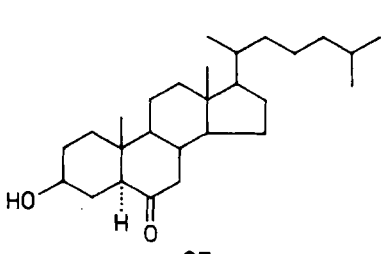
The alkylating agent has been synthesised according to Scheme 1.27.



Scheme 1.27

Several active, related derivatives of ecdysterone **(81)** can be isolated from insects as well as from several plants and from the marine crab, *Callinectes sapidus*. Most of them differ with respect to the side chain. Characteristic examples of this type are ponasterone A **(92)**, inokosterone **(93)**, pterosterone **(94)**, makisterone A **(95)** and cyasterone **(96)** (Scheme 1.28).

A few steroid compounds, which only partly meet the indispensable structural requirements for moulting hormone activity were found to inhibit post-ecdysial hardening and sclerotisation of the insect cuticle (Horn *et al.*, 1966; Velgová *et al.*, 1968). Characteristic examples of this type are compounds **97** and **98**.



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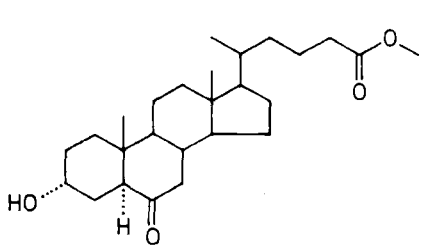

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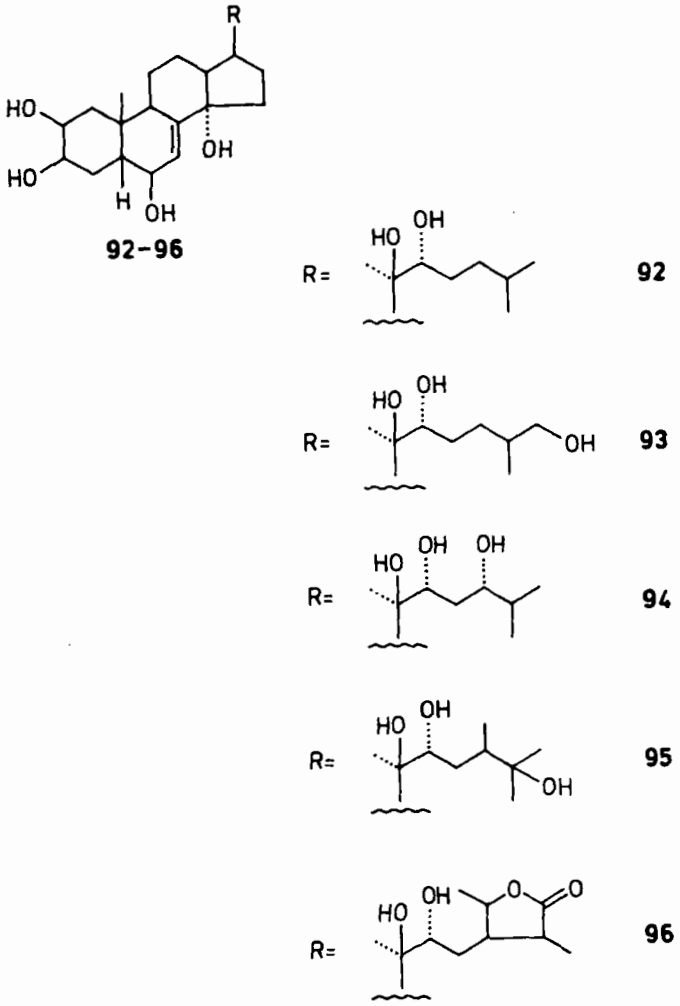
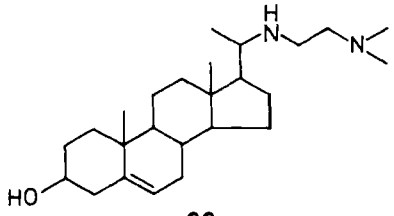


Scheme 1.28

Svoboda and co-workers (Svoboda and Robbins, 1967; 1968; Svoboda *et al.*, 1967; 1969) found that triparanol, 2-(4-chlorophenyl)-1-[4-(2-diethylaminoethoxy)phenyl]-1-(4-tolyl) ethanol and 22,25-diazacholesterol **(99)** inhibit Δ^{24}-sterol reductase and also disrupt the normal growth and development of the larvae of tobacco hornworm, *Manduca sexta*. Both compounds are known as inhibitors of steroid biosynthesis in vertebrates. 22,25-Diazacholesterol is a hypocholesterolaemic agent acting as a competitive antagonist of cholesterol. A similar activity was found later for 25-azacholesterol **(100)**. For the determination of the minimum structural requirements of activity, Svoboda and Robbins synthesised and tested

compound **101**, which lacks the steroid nucleus, and even more simple open-chain aliphatic amines **102, 103, 104.**

Compounds **101, 102, 103** and **104** were found to be active, though their activity was less than that of the azasteroid inhibitors **99** and **100** (Robbins *et. al.*, 1975). Since nonsteroidal compounds also possess activity, it becomes questionable whether azasteroids exert their action as cholesterol antimetabolites; the possibility that they act specifically as lipophilic amines cannot be excluded.



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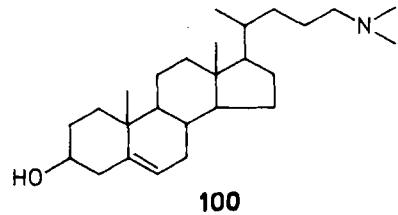
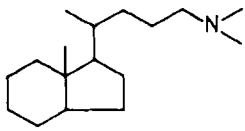


100



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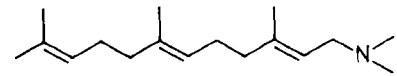

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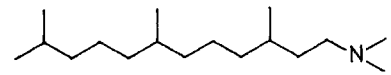

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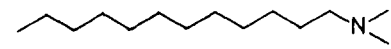


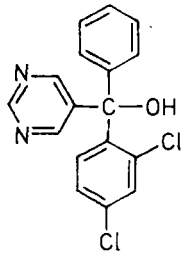
104

Matolcsy *et al.* (1974a; 1974b) tested for anti-ecdysone activity several compounds known to act as inhibitors of steroid biosynthesis in other organisms, such as hypocholesterolaemic agents used in human therapy, and fungicides acting by the inhibition of ergosterol biosynthesis. The fungicide triarimol, 2,4-dichloro-α-pyrimidin-5-yl-benzhydrol **(105),** proved to the most active. Its activity could be reversed by simultaneous administration of ecdysterone.

Based on the same hypothesis, Hammock *et al.* (1978) bioassayed analogues of the hypocholesterolaemic agent ethyl α-(4-chlorophenoxy)-α-methylpropionate (clofibrate, **106**), tested earlier by Matolcsy *et al.* (1974a, 1974b), and found that the acute symptoms on the test insects were similar to those induced by precocene II **(74).**

Funatsu *et al.* (1972) postulated a correlation between the secretion of ecdysone and the activation of a latent phenol oxidase complex. In an attempt to inactivate this metal-dependent enzyme by chelation and to overcome at the same time the

poor lipophility of the known chelators, Maekawa and Matolcsy (1975) introduced the lipophilic hydroxydiphenylmethyl group into the molecule of 8-hydroxyquinoline, known as a metal-binding agent. Compound **107** which they prepared inhibited the action of phenol oxydase isolated from prepupae of the housefly, and it showed at the same time an inhibitory effect on metamorphosis.



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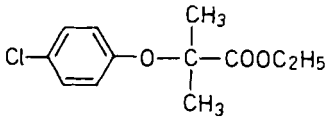

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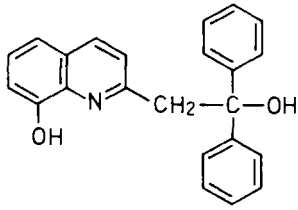
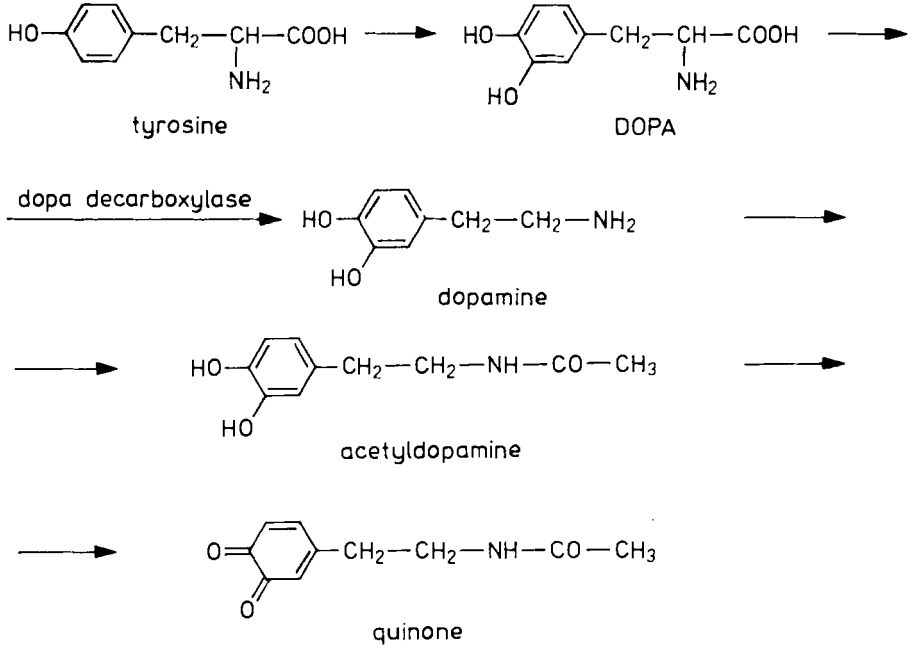


107

The effect of ecdysones and ecdysoids has been studied most extensively by Karlson *et al.* (Karlson, 1960; 1966; Karlson and Schmied, 1955; Karlson and Sekeris, 1962). They found that besides exerting their action by other routes ecdysone hormones act by interfering with tyrosine metabolism. Tyrosine in the insect haemolymph is converted in several steps to "quinone", as shown in Scheme 1.29.



Scheme 1.29

"Quinone" causes tanning and hardening of the larval cuticle, which is a precondition of moulting. This process, known as sclerotisation, is a result of the reaction between the "quinone" and the cuticle proteins. One of the basic steps of quinone formation is the decarboxylation of DOPA into dopamine, effected by DOPA decarboxylase. Presumably, the messenger-RNA responsible for DOPA decarboxylase synthesis is formed by the action of ecdysone.

Adenyl cyclase has been shown to be stimulated by β-ecdysone **(81)** in pupal epidermis, resulting in a sharp increase in cyclic AMP. The latter acts as a messenger in the induction of the specific response. In this respect, juvenile hormone acts as an antagonist of ecdysone, probably by suppressing the genetic information connected with metamorphosis.

In addition to its role in puparium formation, ecdysone also regulates reproduction by stimulating metamorphosis of the gonads.

Although ecdysone is present in almost all parts of insects, its action is exerted only on epidermal cells and the cells of a few other tissues. This is due presumably to the fact that ecdysone is bound to a specific protinaceous receptor at the target cell (Gilbert *et al.*, 1971).

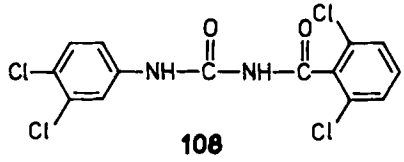
In principle, the practical application of the ecdysones and ecdysoids known so far should be made possible by their property of disrupting insect development or reproduction when applied in sufficiently high dosages. However, their use is impeded by the high cost of their preparation.

From the point of view of agricultural use, compounds destined to inhibit the formation or the function of ecdysones are considerably more promising. Initial results attained in this field cannot yet be directly utilised, but they have shown that this is a realistic approach.

1.8.4 Inhibitors of chitin synthesis

In their search for new urea-type herbicides, the research workers of the Philips Duphar Co. established as an unexpected side-effect the insecticidal action of 1-(2,6-dichlorobenzoyl)-3-(3,4-dichlorophenyl)urea **(108).** The manifestations of the effect differed radically from those produced by insecticides known earlier, and led to the conclusion that the compound acts on the moulting process. On the basis of the synthesis of a number of related derivatives, the authors established that other compounds also possessing the 1-(2,6-dihalogenbenzoyl)-3-arylurea structure show similar insecticidal properties. The most potent of several analogue derivatives were 1-(2,6-difluorobenzoyl)-3-(4-chlorophenyl)urea (diflubenzuron, **109**) and to a lesser extent its 2,6-dichlorobenzoyl analogue, PH 60–38 **(110)** (Van Daalen *et al.*, 1972; Mulder and Gijswijt, 1973; Wellinga *et al.*, 1973a; 1973b; Busvine *et al.*, 1976).

The preparation of this type of compound is illustrated by the synthesis of PH 60–38, in which 2,6-dichlorobenzamide **(111),** used also in the synthesis of the herbicide dichlobenil, reacts with *p*-chlorophenylisocyanate.



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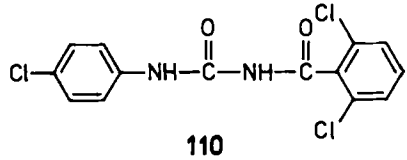

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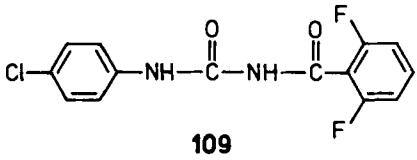

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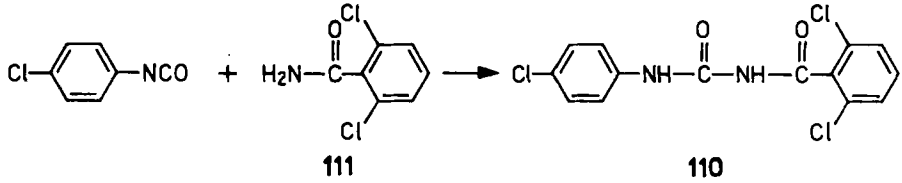
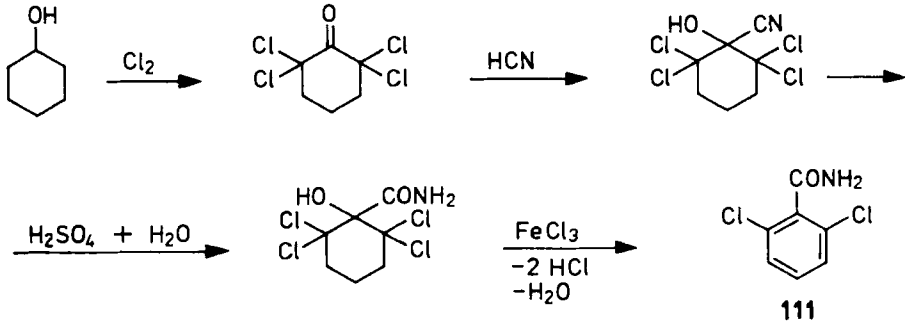


111 110

Several processes are known for the preparation of 2,6-dichlorobenzamide (**111**). The most important process start from cyclohexanol and proceed according to the following reaction route (Anonym, 1967).



Post *et al.* (1974) found disturbances in the endocuticular structure of insects treated with these derivatives. A characteristic symptom of the effect is the abortion of moult. These authors as well as Deul *et al.* (1978) concluded from their experiments involving the incorporation of labelled glucose in treated larvae, that 1-(2,6-dihalogenbenzoyl)-3-arylureas affect chitin synthesis in the insect cuticle by disrupting the process of connecting the N-acetylglucosamine units to the chitin chain. Thus diflubenzuron was proved to produce the same effect on the insect cuticle as Polyoxin-D, a known inhibitor of chitin synthetase.

Ishaaya and Casida (1974) investigated the insect cuticle chitin, as well as chitinase and phenoloxidase activity in housefly larvae treated with diflubenzuron, and observed a marked increase in activity of both enzymes. They concluded that

increased chitinase activity results in a softening of the endocuticle, and at the same time, increased phenoloxidase activity causes a hardening of the exocuticle. Phenoloxidase is known to convert orthodiphenols into quinones, which are responsible for the sclerotisation of cuticle protein.

Yu and Terrière (1977) concluded from their experiments on housefly larvae that the disruption of chitin formation by diflubenzuron is due to the inhibition of enzymes responsible for ecdysone metabolism.

Ascher and Nemny (1974; 1976) found that diflubenzuron acts mainly through the stomach, but when it is dissolved in a suitable solvent, such as tetrahydrofurane, it is able to penetrate the cuticle of housefly prepupae. At the same time, the compound showed a strong ovicidal action. The finding of these authors also showed that neither are moult-disturbing substances of dihalogenbenzoylurea type exempt from one of the greatest disadvantages of insect growth regulators, retarded action. Larvae between moults can cause considerable damage on plants, since they are not injured until they moult.

Diflubenzuron controls beetles, flies, rust mites and weevils. Insects that are susceptible to diflubenzuron can be controlled by low doses such as 30–120 g/hectare. The particle size greatly influences its activity and the rate at which it breaks down.

It is very stable on foliage. This means, on the one hand, that few applications are needed, but, on the other hand, residues can remain on foodcrops until the end of the growing season. This disadvantage is, however, counteracted by the fact that diflubenzuron seems to be the least hazardous insecticide yet developed (Marx, 1977). Orally administered to cattle and sheep it is extensively metabolised and almost totally excreted. The major metabolites result from hydroxylation of both benzene rings and by cleavage between the carbonyl and amide groups (Ivie, 1978). Its LD_{50} for mammals and birds is in the range of 4.5–10 g/kg.

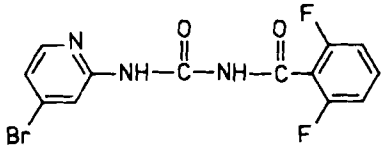
Several authors attempted to develop new and more effective compounds related chemically to diflubenzuron. Early quantitative structure–activity relationship analyses seemed to show that while the aniline moiety can be varied within wide limits, the benzoyl moiety is stringent in this respect and the 2,6-dihalogen substitution was thought to be indispensable for activity. The most active benzoylureas were those containing a 2,6-difluorobenzoyl moiety combined with a 4-chloro-, 3,4-dichloro-, 3,5-dichloro-, 2,4-difluoro-, 4-trifluoromethyl- or 4-nitro-substituted anilide moiety (Wellinga *et al.*, 1973a; 1973b Yu and Kuhr, 1976; Becher *et al.* 1983).

Diflubenzuron and its analogues aroused the interest of researchers engaged in quantitative structure–activity relationship (QSAR) studies. Thus, Verloop and Tipker (1977; 1978) demonstrated on a number of diflubenzuron analogues the feasibility of STERIMOL parameters in QSAR analyses, permitting a refined insight into the shape of the substituents. Bordás *et al.* (1979) carried out a retrospective study of activity data on diflubenzuron derivatives, by using Free–Wilson analysis, factor analysis and principal component analysis. The factors extracted by principal component analysis and factor analysis were used as

independent variables in the Free–Wilson analysis. The authors suggested that in this way it might be possible to predict both overall and selective activity of the designed compounds against different insect species.

Nakagawa *et al.* (1984) found that the oxidative metabolism of benzoylphenylurea insecticides, a factor significant in determining the activity, is favoured by electron-donating substituents at the anilide moiety. However, when the metabolic factor is eliminated, the activity is enhanced by electron-withdrawing and hydrophobic substituents and lowered by bulky groups.

Miesel (1976) obtained active analogues of diflubenzuron by replacing the *p*-chloroaniline moiety by substituted aminopyrazines. As an extension of their earlier work DeMilo *et al.* (1978) have synthesised and tested a series of new analogues where the aniline portion of the diflubenzuron molecule has been exchanged for various substituted heterocycles such as isoxazoles, thiazoles, thiadiazoles, pyridines, pyrimidines, *s*-triazines and bicyclic heterocycles. The most active derivatives were the 4-bromo- **(112)** and 4-chloro-2-pyridinyl analogues **(113)** but none was as active as diflubenzuron.



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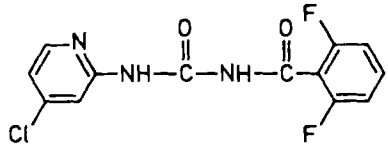
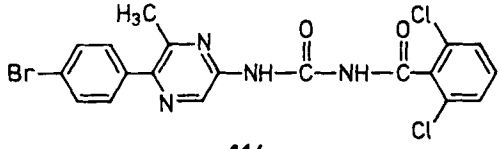


113

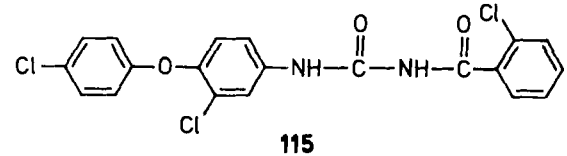
Retnakaran (1979) described the product known as EL-494 **(114)**, a compound containing a substituted pyrazine ring as the aniline part of the molecule. It showed a high degree of moult inhibitory action against the spruce budworm, *Choristoneura fumiferana*.



114

Some reports published after the mid seventies indicated that the assumption on the necessity of the 2,6-dihalogenbenzoyl group is valid only within certain structural limits and activity is to be expected also from compounds lacking this moiety. Thus, Stirrenberg *et al.* (1977) patented an interesting type of diflubenzuron analogues in which the 2,6-dihalogenbenzoyl group is replaced by a 2-chlorobenzoyl moiety. Typical representatives of this class are compounds **115** and **116** which killed *Plutella maculipenuis* in a concentration of 0.001%.

A further representative of the 2-monohalogenbenzoyl derivatives is compound **117**, known as BAY SIR 8514 (Hajjar and Casida, 1978; Schaefer *et al.*, 1978). It is a potent inhibitor of the terminal polymerisation step in chitin formation and effectively inhibits mosquito larval development.



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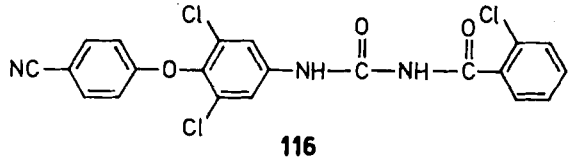

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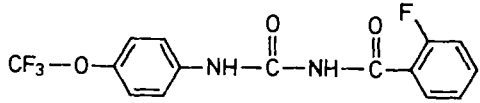

117

The future significance of insect growth regulators cannot be foreseen as yet. The latest achievements corroborate expectations, and the drawbacks which retarded their widespread practical use, such as lack of immediate action, insufficient persistence, high cost, arising of resistance and others, do not raise doubts on their feasibility but create topics for continuous research in this promising field.

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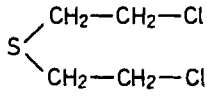
1.9 Chemosterilants

In 1887, Victor Meyer reported on the toxic effect of sulfur mustard, bis(2-chloroethyl)sulfide **(1)**: on laboratory animals, and in 1898 Ehrlich described the toxic properties of ethyleneimine **(2)** (Himmelweit, 1956). The effects described by these authors have not yet been traced back to the alkylating properties of these compounds, but these were the forerunners of later purposeful research which finally led to the discovery of the carcinogenic activity of alkylating agents (Gilman and Philips, 1946; Goodridge *et al.*, 1960; 1963; Ross, 1962; Wheeler, 1962; Warwick, 1963; Emmelot, 1964; Montgomery *et al.*, 1970). Some of the compounds belonging to this class, such as sulfur mustard **(1)** and nitrogen mustard, bis(2-chloroethyl)methylamine **(3)**, have also been used as chemical warfare agents. These completely different biological actions represent different manifestations of the ability of biological alkylating agents to combine with nucleophilic centres, such as thiolate anions of proteins, nitrogen atoms of polypeptide chains or of nucleobases, phosphate anions of nucleotides, etc.

In addition to abnormal cellular metabolism one of the characteristics of cancer cells is an increased rate of mitosis, and as a result an increased sensitivity to inhibitors of cell division. Therefore, the fact that DNA is the cell component most sensitive to alkylating agents may explain to a certain extent the increased reactivity of cancerous tissues towards these substances.



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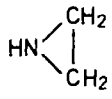

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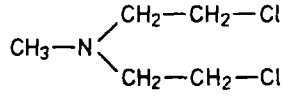

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On the other hand, from the middle of the 1950s, important results were achieved in the chemotherapy of cancer from treatment with compounds which exert their antimitotic activity as antimetabolites of nucleic acids, folic acid, and purine- and pyrimidine-containing cofactors.

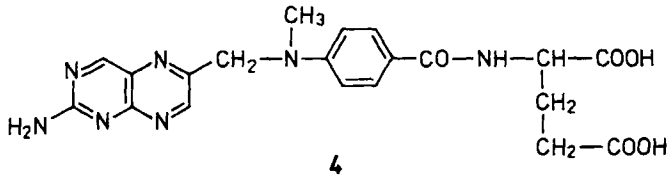
In the following years, alkylating agents, antimetabolites and a few compounds belonging to other groups were developed which showed antitumour activity and some of which attained clinical importance in the chemotherapy of cancer.

Research work on the mode of action of these compounds furnished the theoretical basis for the chemical control of insects by means of chemosterilants, and most of the compounds showing such action were first described as antitumour agents. In no other field is the interaction between plant protection and human therapy so close as that between the chemotherapy of cancer and insect control by chemosterilants. The capacity of these substances to interfere with the biosynthesis of DNA served as the common theoretical basis. In addition to other effects such as antitumour and antimitotic effects, deactivation of viruses, etc., a characteristic outcome of this interference is the mutagenic effect and, closely related to this, inhibition of reproduction (Bořkovec, 1962).

Knipling (1938) was the first to put forward the idea that by sterilisation of one section of the insect population the individuals of the population can be exterminated more rapidly than by the use of conventional insecticides (Knipling, 1955). The application of the method called "sterile male-release technique" gave good results against the screw worm, *Cochliomyia hominivorax*, by gamma irradiation of captured males and their subsequent release (Baumhover *et al.*, 1955; Knipling, 1960). In the sterilisation of insects by chemical means, pioneer work was done by Goldsmith *et al.*, who established that amethopterine, N-{*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl}glutamic acid (**4**), can sterilise female insects by retarding ovarian development (Goldsmith *et al.*, 1948; Goldsmith and Frank, 1952). This compound, used against leucaemia and tumours, is known as an antimetabolite of folic acid. Shortly afterwards, Mitlin and co-workers (Mitlin *et al.*, 1954; Mitlin and Baroody, 1958a) reported that ovarian development is inhibited by several antimetabolites such as ethionine (**5**), the ethyl analogue and antimetabolite of methionine, and by β-2-thienylalanine (**6**), an

antimetabolite of phenylalanine. Ascher (1957) established the ovarian inhibitory activity of 1,1-bis(*p*-chlorophenyl)-2,2,3,3,3-pentafluoropropanol (7).

When light was shed by the work of these researchers on the possibilities of chemical sterilisation of insects, the Agricultural Research Service of the United



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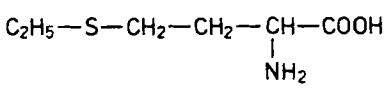

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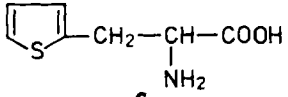

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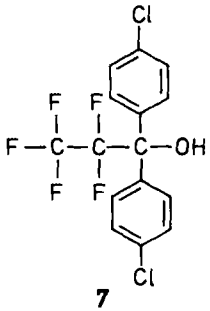

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States Department of Agriculture investigated within the compass of a wide screening programme the effect of numerous compounds on houseflies as test insects. A considerable number of the chemosterilants known today have been developed within the scope of that programme.

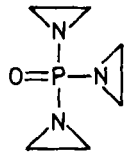
Usually, three groups of chemosterilants are distinguished: alkylating agents, antimetabolites and miscellaneous compounds.

1.9.1 Alkylating agents

The best known and most important members of this group are the aziridine derivatives. The carrier of the alkylating property is the strained, and therefore reactive, three-membered aziridine (ethyleneimine) ring. However, only those aziridine derivatives have a sterilising effect in which an electron-attracting group is attached to the nitrogen atom of aziridine, thus decreasing the basicity of the nitrogen atom. Although monofunctional aziridines also possess a certain amount of anticancer and insect sterilising activity, the truly effective derivatives contain at least two aziridine groups. These conditions are met by derivatives in which the nitrogen atom of the aziridine ring is linked to a phosphorus atom, a carbonyl group or to the carbon atom of the azomethin group of a heterocyclic ring. Major

credit is due to LaBrecque and associates for the discovery of the sterilising activity of these compounds.

Of the derivatives containing a phosphorus atom, the most important are tris(1-aziridinyl)phosphine oxide (TEPA, **8**), its thio analogue (thio-TEPA, **9**), tris(2-methyl-1-aziridinyl)phosphine oxide (metepa, **10**) (Buckley *et al.*, 1951; Burchenal *et al.*, 1952; LaBrecque *et al.*, 1960; 1963; LaBrecque, 1961), O-methyl bis(1-aziridinyl)phosphorothioate (ENT-50 765, **11**) (Chang and Bořkovec, 1966; Fye, 1967), N,N′-ethylene-bis[P,P-bis(1-aziridinyl)]-N-methyl-phosphinamide (aphamide, **12**) and 2,2,4,4,6,6-hexa-(1-aziridinyl)-triazatriphosphorine (apholate, **13**) (Ross, 1962; Rötz and Grundmann, 1957; LaBrecque, 1961). They are prepared by the general method of synthesis of phosphoroamidates and phosphorothioamidates.



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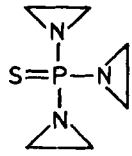

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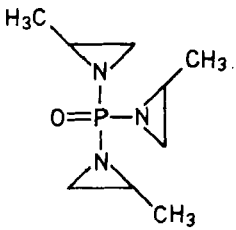

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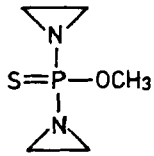

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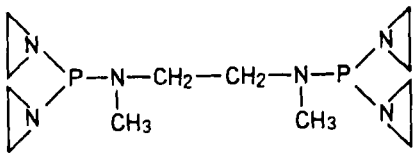

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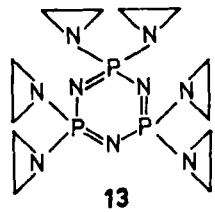

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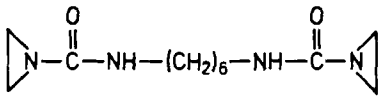
Oral LD_{50} values for metepa, TEPA and apholate for rats are 136, 37 and 98 mg/kg, respectively (Gaines and Kimbrough, 1964).

Characteristic examples of derivatives in which the nitrogen atom of the aziridine ring is linked to a carbonyl group are N,N′-hexamethylene-bis(1-aziridinecarboxamide) (**14**), N,N′-*p*-phenylene-bis(1-aziridinecarboxamide) (ENT-50 848, **15**) and N,N′-1,5-naphthylene-bis(2-methyl-1-aziridinecarboxamide) (ENT-50 664, **16**) (Ham, 1964; Crystal, 1963; 1967; Hendry *et al.*, 1951; Fye, 1967; Fye and LaBrecque, 1967).



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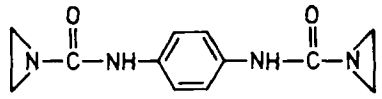

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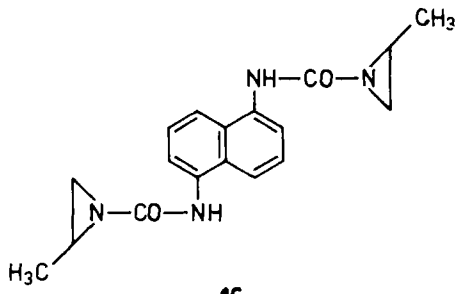

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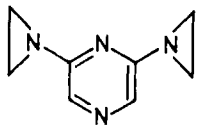
Aziridine derivatives where the aziridine groups are linked to nitrogen-containing heterocyclic carrier groups are 2,6-bis(1-aziridinyl)pyrazine (ENT-50 457, **17**), 4,8-bis(1-aziridinyl)pyrimidino-[5,4d]-pyrimidine (ENT-50 792, **18**) and 2,4,6-tris(1-aziridinyl)-*s*-triazine (triethylene-melamine, tretamine, **19**).



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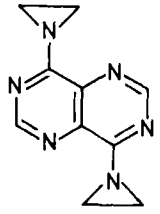

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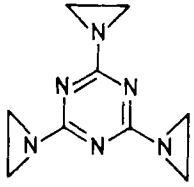

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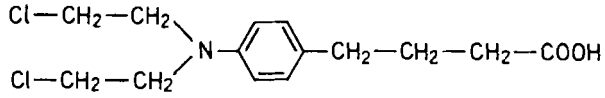
These compounds can be prepared by the reaction of the respective halides, such as 2,6-dichloropyrazine, 4,8-dichloro-pyrimidino-[5,4d]-pyrimidine and cyanuric chloride, respectively, with ethyleneimine.

Chang and co-workers (Chang *et al.*, 1964; Chang and Bořkovec, 1965) prepared a series of compounds in which the aziridinyl groups of TEPA (**8**) were gradually replaced by dimethylamino groups. As a result of these structural modifications, a gradual decrease on sterilising potency was observed. However, hexamethyl-

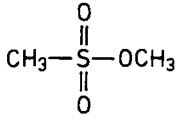
phosphoramide (hempa, **29**) is still an effective male housefly chemosterilant, like hexamethylmelamine (hemel, **30**) which can be derived from tretamine (**19**) in an analogous way.

Of considerably less importance than the aziridine derivatives are the alkylating agents of the mustard nitrogen type. The bis(2-chloroethyl)amino moiety is characteristic of most of these compounds. Nitrogen mustard (**3**) itself is too toxic to be of practical value but some of its aromatic analogues are promising both as anticancer agents and as insect chemosterilants. The most important representative of this group is [bis(2-chloroethyl)amino]phenylbutyric acid (chlorambucil, **20**) (Ross, 1953; 1958; Shaw and Sanchez Riviello, 1962).



20

A third important group of alkylating agents are the sulfonic acid esters. Fahmy and Fahmy (1961) reported on the sterilising activity of methyl- (**21**) and ethyl-methanesulfonates (**22**), the anticancer effect of which has been described by Ross and Davis (1957) and by Roberts (1958). As with the aziridine and nitrogen mustard derivatives, in this group too bifunctional derivatives proved to be the really effective ones. Thus, 1,4-butylene-bis(methanesulfonate) (busulfan, **23**) showed a greater antitumour and sterilising activity compared to the mono-functional derivatives **21** and **22** (Haddow and Timmis, 1953; LaBrecque *et al.*, 1960).



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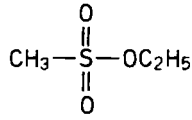

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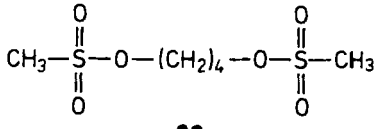

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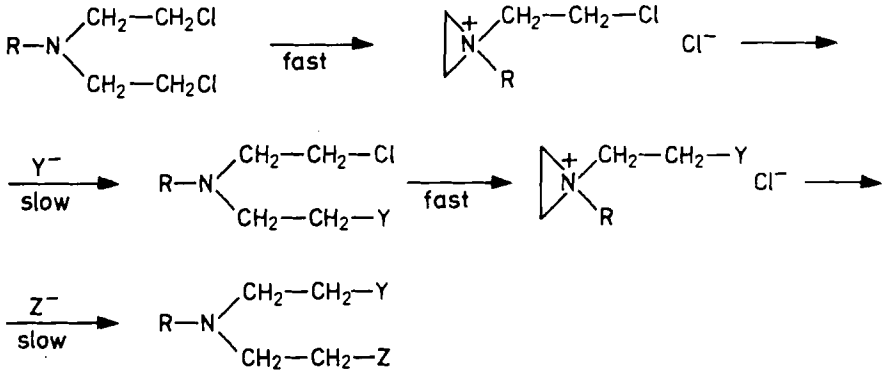
Although aziridine derivatives and nitrogen mustard derivatives differ in structural respects, they presumably act in the same way. Nitrogen mustards readily form a cyclic aziridinium ion which reacts in the subsequent rate-controlling step in an S_N2 process with an available nucleophilic Y^-. This process is repeated with a second chloroethyl group and a second nucleophilic Z^- (Bartlett *et al.*, 1947; Montgomery *et al.*, 1970).



Ring-opening reactions of aziridines with nucleophiles proceed in a similar manner, but are slower than those of their aziridinium counterparts (Montgomery *et al.*, 1970).

Of the various *in vivo* reactions of alkylating agents, presumably the direct alkylation of the 7-position of guanine, resulting in the deletion of this nucleobase from DNA (depurination), is the most important (Ross, 1962; Wheeler, 1962). This may lead to anomalous base pairings and to alteration of the template for DNA replications (Brookes and Lawley, 1961). This mechanism must at least be partly responsible for the decreased DNA content of nonviable eggs deposited by apholate-treated flies (Kilgore and Painter, 1964).

At the same time this method of insect sterilisation involves the hazard of various toxic side-effects, as interference in DNA synthesis may lead to teratogenic, mutagenic and carcinogenic effects or sterilising effects on mammals (Klassen and Chang, 1966; Hayes, 1964; Palmquist and La Chance, 1966; Barnes, 1964).

The uptake and metabolism of aziridine derivatives have been studied by different workers. Plapp *et al.* (1962) found that metepa **(10)** is rapidly excreted from mice, partly in the form of unaltered metepa and partly as inorganic phosphate. Thio-TEPA **(9)** is excreted from albino rats, TEPA **(8)** being the main urinary metabolite (Parish and Arthur, 1965).

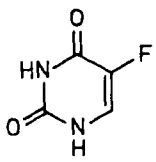
1.9.2 Antimetabolites

Antimetabolites can be defined as compounds derived from metabolites by a minimum structural change, mostly by isosteric replacement in their structure. Owing to this structural similarity, an antimetabolite can partially replace the corresponding natural metabolite, resulting in the inhibition of enzymes responsible for the transformation of the melabolite, or in the incorporation of the antimetabolite as a foreign building unit in biopolymers.

Amethopterin **(4)**, as mentioned already, is an antimetabolite of folic acid, and can be derived from the latter by the isosteric replacement of its hydroxyl group by an amino group and methylation at N-10. It acts as an inhibitor of folic acid

reductase and, consequently, of DNA synthesis (Seeger *et al.*, 1949; Bertino *et al.*, 1965).

LaBrecque *et al.* (1960), Kilgore and Painter (1964), and Crystal (1963, 1967) established the insect sterilising potency of several known nucleobase-antimetabolites, such as 5-fluorouracil **(24)**, 5-bromouracil **(25)**, 6-methyluracil **(26)**, 5-fluoroorotic acid **(27)** and 2,6-diaminopurine **(28)**.



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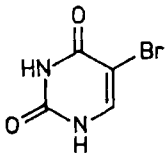

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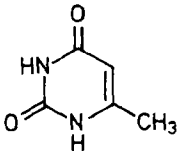

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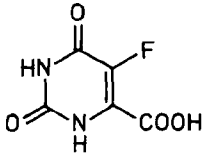

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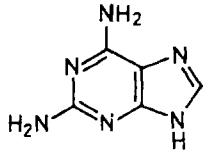


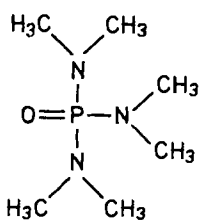
28

With these antimetabolites teratogenic, mutagenic and other toxic side effects must be taken into consideration in the same way as with alkylating agents because, these compounds albeit by a different mechanism, also exert their action by interfering with nucleic acid biosynthesis.

In contrast to alkylating agents, antimetabolites act almost without exception as female sterilants, disrupting the reproductive process of female insects.

1.9.3 Miscellaneous compounds

The possible mutagenic and carcinogenic properties of the insect sterilants belonging to the alkylating agents and antimetabolites have limited their application and prompted the search for sterilants acting by other mechanisms. A significant achievement in this field was the development of hempa **(29)** and hemel **(30)**. Mentioning them among alkylating agents is only justified by their structural relationship with the aziridine derivatives TEPA **(8)** and tretamine **(19)** (Chang *et al.*, 1964; Chang and Bořkovec, 1965).



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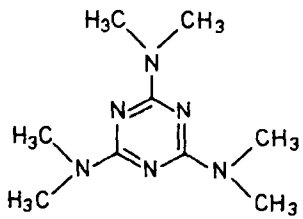
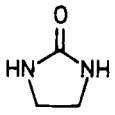


30

These two compounds are not alkylating agents. Hence, the fact that they possess sterilising potency justifies either the assumption of another mechanism of action, or the revision of theories of the mode of action of aziridine derivatives. Oxidative conversion of the dimethylamino groups to aziridine groups may serve as a further explanation.

Several authors established the sterilising activity of urea and thiourea derivatives such as 4-imidazolidin-2-one **(31)** (Flint *et al.*, 1968; Simkover, 1964), 4-imidazolin-2-one **(32)** (Schaeffer and Tieman, 1967), thiourea and 1-(1-naphthyl)-2-thiourea **(33)** (LaBrecque *et al.*, 1963; Mitlin and Baroody, 1958b).



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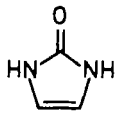

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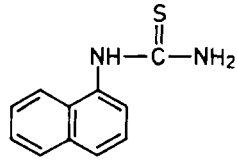
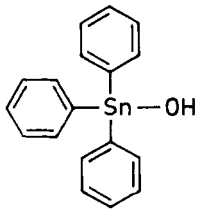


33

Ascher *et al.* (1967) found that triphenyltin hydroxide (fentin hydroxide, **34**) and triphenyltin acetate (fentin acetate, **35**), already known for their fungicidal and insect antifeedant effect, also show insect sterilising activity. They assumed that the sterilisation of male insects is brought about by a slow poisoning of the sperm.



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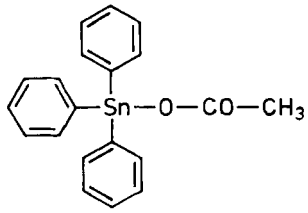
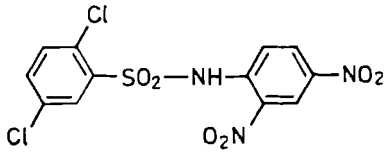


35

DeMilo and co-workers (1974) reported on the male sterility of houseflies induced by 2,5-dichloro-N-(2,4-dinitrophenyl)-benzenesulfonamide **(36)**. In subsequent studies aimed at optimalisation of the sterilising effectiveness, they found the 3,4-dichloro-analogue **(37)** to be the most active within this group (DeMilo *et al.*, 1977).



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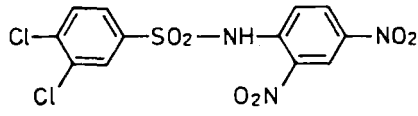

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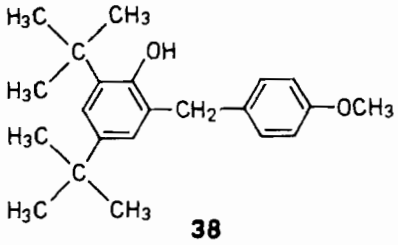
An interesting type of insect chemosterilants has been reported by Jurd *et al.* (1979). They found that benzyl derivatives of 2,4-di-*t*-butylphenol and of 1,3-benzodioxoles sterilise houseflies when fed at concentrations as low as 0.025% in the diet. The most active members of this group are 2,4-bis(1,1-dimethylethyl)-6-[(4-methoxyphenyl)methyl]-phenol **(38)** and 5-ethoxy-6-[1-(4-methoxyphenyl)-ethyl]-1,3-benzodioxole **(39).**



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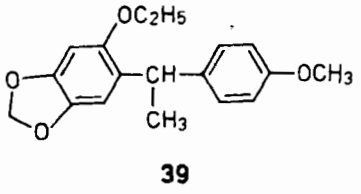

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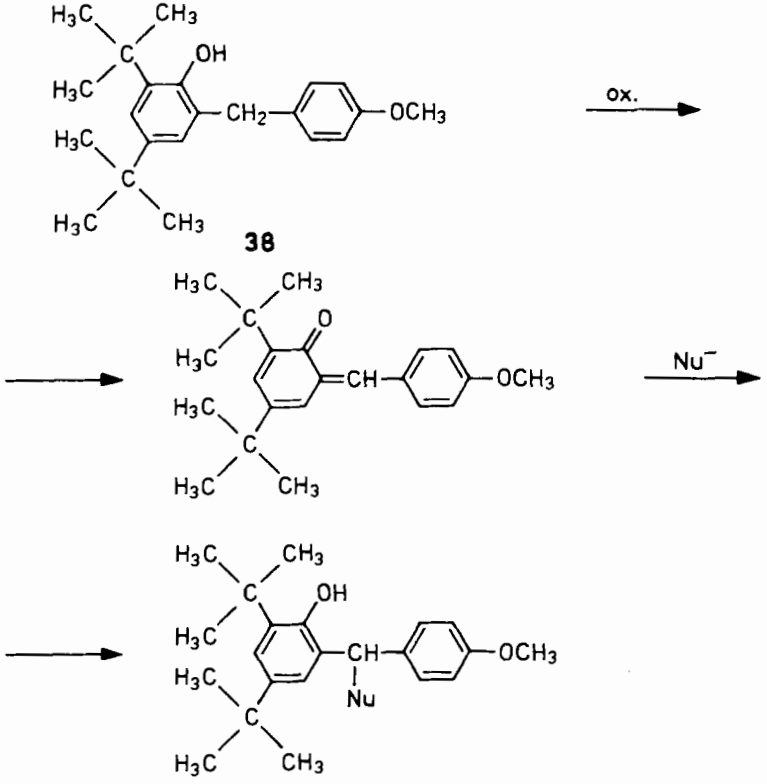
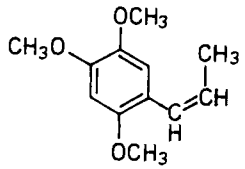
The authors correlated structural features with sterilant activity and concluded that in the insect organism these compounds are oxidised to quinone methide intermediates which then undergo nucleophilic attack by cell constituents participating in the reproductive process:



Saxena and co-workers (1977) reported on the female sterilant activity of β-asarone (**40**) isolated from the essential oil of the plant *Acorus calamus*. Its specific antigonadal action causes sterility in adult females. However, a clear-cut distinction in the mode of action is aggrevated by the fact that also an antifeedant action, verified by Sláma (1978) and Rembold *et al.* (1979) for precocene II (**74** in Section 1.8.2. Insect growth regulators) showing common structural features, may be involved in exerting biological activity.



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Males can be sterilised by insect chemosterilants in three ways: (*1*) sperm does not develop; (*2*) ripe sperm does not move; (*3*) mutations resulting in unviable progeny are produced in the hereditary substance (dominant lethal mutants). The latter effect is of practical importance (Jermy, 1967).

Several methods have been proposed for the practical application of insect sterilants, such as contact, oral ingestion and sterile male release method. This latter method involves capture of the males, their chemosterilisation and subsequent release which means considerable excess of work compared to the usual application of pesticides. Nevertheless it seems particularly advantageous because under appropriate conditions it permits almost complete control of undesirable insect populations in several generations.

However, several factors have prevented their extensive use. The most important of these is the possible hazard of mutagenic, teratogenic, carcinogenic and other side-effects as mentioned already. Other negative aspects are the possible development of resistance (Hazard, 1964; Klassen and Matsumura, 1966), and the lack of immediate effect. Sanchez Riviello and Shaw (1966) and Campion (1967, 1974) proposed to overcome the hazard to mammals by the combined application of chemosterilants and sex attractants, which would restrict the use of chemosterilants to localised bait-stations.

The number of compounds mentioned as insect chemosterilants in the literature is more than a thousand. However, only alkylating agents of aziridine and alkanesulfonate type and the nonalkylating phosphorus amides are on the verge of practical application (Bořkovec, 1974). At the same time, the use of chemosterilants offers great possibilities for plant protection. Thus, further research aimed at the elimination of undesirable side-effects by the development of compounds with more selective action seems to be necessary.

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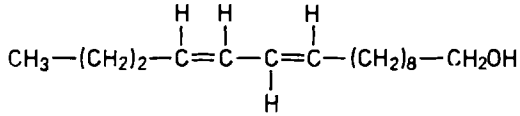
1.10 Pheromones

The opinion of biologists differed for a long time with respect to the mechanisms by which females of some insect species ready for copulation are able to induce an approaching reaction in males at great distance. According to one school of thought, volatile substances of high physiological activity act by material contact with the insect sensory organ, while others adhered to the theory that the stimulatory molecule transfers energy by radiation.

Research results in relation to olfaction contributed significantly to the elucidation of the problem and finally to the rejection of the radiation theory (Beets, 1964). In the case of insects, decisive proof in favour of the material contact theory was furnished by the findings of Butenandt *et al.* (1959). As a result of long research work, they isolated the sex attractant substance produced by the female of the silk worm, *Bombyx mori*, and identified it as (*E*)-10-(*Z*)-12-hexadecadienol (bombykol, **1**). Determination of the active structure was achieved by the synthesis and biological testing of the four possible isomers (Butenandt *et al.*, 1959).

Bombykol and the sex attractants of other insects discovered later are the most potent substances of all biologically active compounds. A concentration of 10^{-13} μg/ml bombykol, i. e., the presence of only 200 molecules in 1 ml of air, produces in male insects a state of excitation manifested by the trembling of the wings, and by an



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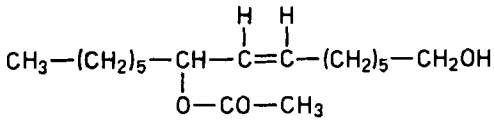
electrophysiological signal measurable on the sensory organ of the antennae. Although they are most important, sex attractants represent only one group of substances regulating the locating behaviour of insects, which together Butenandt called pheromones (from the Greek words for "carry" and "excite"). Some pheromones mediate in attracting insects to food sources and oviposition sites, others in aggregating for mutual defence.

The sex attractant of the gypsy moth, *Portheria dispar*, was erroneously identified by Jacobson *et al.* (1961) as (*Z*)-7-hexadecene-1,10-diol-10-acetate (gyptol, **2**). The synthesis aimed at proving the structure yielded an inactive product (Stefanovic *et al.*, 1963; Eiter *et al.*, 1967), showing that the structure of the natural pheromone had been identified erroneously. Ten years later, Bierl and Beroza (1970) identified the correct structure of the sex attractant of the gypsy moth as (*Z*)-7,8-epoxy-2-methyloctadecane (disparlure, **3**). The compound was prepared by Bestmann and Vostrowsky (1974) by the Wittig synthesis, by the reaction of isooctylidene-triphenylphosphoran with undecanal, and the stereospecific epoxidation of the (*Z*)-2-methyl-7-octadecene obtained. The synthetic product had a bioactivity equivalent to that of the natural pheromone (Beroza *et al.*, 1971).



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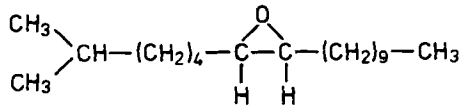

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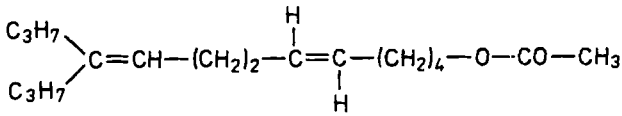
The isolation of the pheromone obtained from the female of the pink bollworm, *Pectinophora gossypiella*, and the determination of the structure and synthesis of the compound are also associated with the names of Jacobson and co-workers (Jones *et al.*, 1966). The synthetic (*E*)-10-propyl-5-tridecadienyl acetate (propylure, **4**) showed the same activity as the natural product.

Eiter *et al.* (1967) synthesised propylure by another route. However, the product was biologically inactive. To elucidate the cause of this inconsistency, Jacobson (1969) followed the procedure of Eiter and co-workers, and established by separation of the isomers that the *E*-isomer in the pure state is biologically active;



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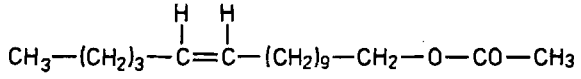
however this activity disappears completely in the presence of as little as 10% of the *Z*-isomer.

This finding, already known from other pheromones, called attention to the remarkable and so far inexplicable fact that the activity of the active isomers can be masked by inactive isomers present in much less than equivalent amounts. With this knowledge successful experiments were carried out in plant protection.

The major component of the sex pheromone of the cabbage army worm, *Mamestra brassicae*, was determined independently by Bestmann *et al.* (1978) and Nedopjekina *et al.* (1978) as (*Z*)-11-hexadecenyl acetate **(5).**

Novák *et al.* (1979) proved that the sex pheromone of the cabbage army worm contains also a minor component present in a concentration of 10% as compared to the major component. Its chemical structure is (*Z*)-11-heptadecenyl acetate **(6).** The activity of the minor component **6** is somewhat lower than that of the main component, yet its presence affords a two–three fold increase of pheromone efficiency. This is only one of the numerous examples which demonstrate the potentiation of pheromone activity by minor components.



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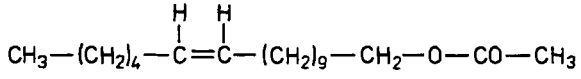
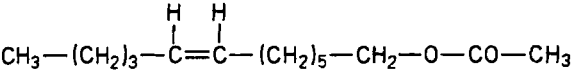


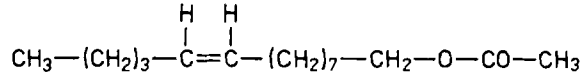
6

Also the sex attractant of the whiteline dart moth, *Scotia segetum*, was found to consist of two components. The major component was identified as (*Z*)-7-dodecenyl acetate **(7),** the minor one as (*Z*)-9-tetradecenyl acetate **(8)** (Tóth *et al.*, 1980).



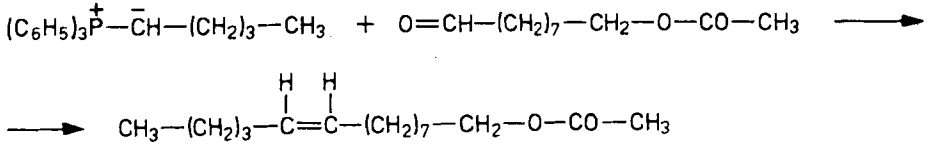
7

Unsaturated alcohols of *Z*-configuration, which form the major part of sex attractants, can be prepared almost isomer-free with a good yield by Witting's stereoselective *cis*-olefination. With this method, by the stereoselective reaction of 9-acetoxynonanal with pentylidine-triphenylphosphoran, Bestman *et al.* (1971)



8

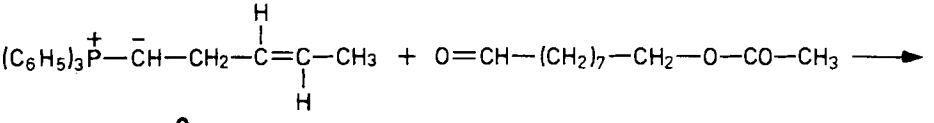
synthesised, along with a number of other pheromones, (*Z*)-9-tetradecenyl acetate **(8),** the sex attractant of the fall armyworm, *Laphygma frugiperda,* which damages maize and sorghum. Its structure was determined earlier by Sekul and Sparks (1967a, 1967b).



8

(*Z*)-11-Tetradecenyl acetate, which is the sex attractant of several insect pests of economical importance such as *Ostrinia nubialis, Argyrotaenia velutinana* and *Choristoneura rosaceana,* has been prepared in a similar way (Roelofs and Arn, 1968; Roelofs and Tette, 1970; Klun and Brindley, 1970).

Witting's *cis*-olefination could readily be used for the preparation of derivatives containing several double bonds of *Z*- and *E*-configuration. Thus, for example, the reaction of the unsaturated phosphoran **(9)** with 9-acetoxynonanal yields (*Z,E*)-9,12-tetradecadienyl acetate **(10)** (Vostrowsky *et al.*, 1973). This compound is the sex attractant of several storehouse pests.



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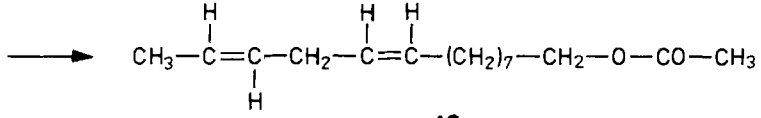
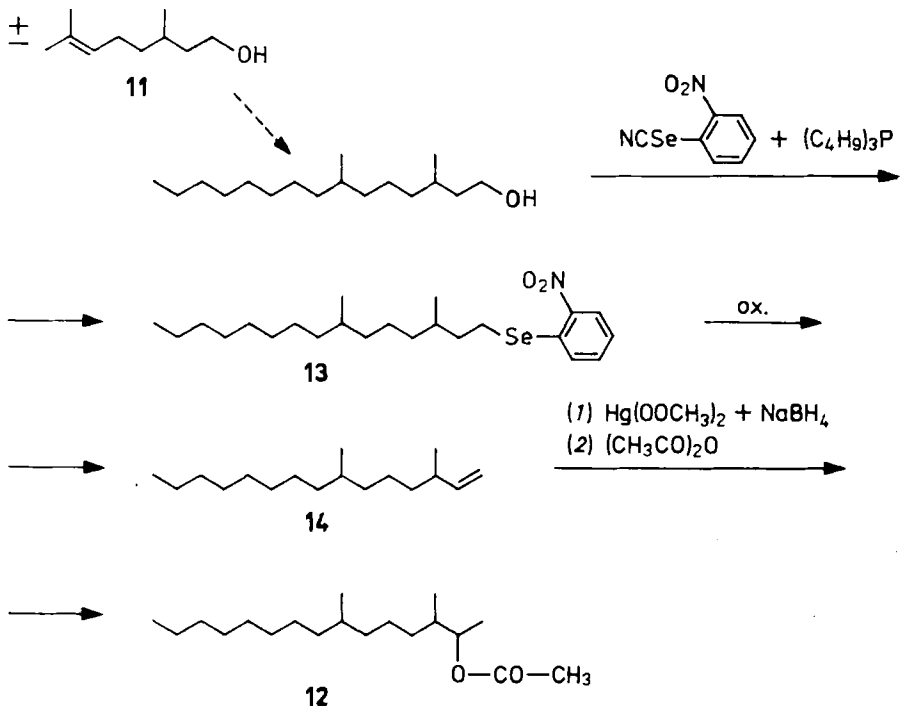


10

Mori *et al.* (1978) converted racemic citronellol to a stereoisomeric mixture of 3,7-dimethylpentadec-2-yl acetate **(12),** the sex pheromone of the pine sawflies, *Neodipirion lecontei* and *N. sertifer.* They treated (±)-citronellol **(11)** with *o*-nitrophenyl selenocyanate and tri-*n*-butylphosphine to yield the selenide **(13),**

which was then oxidised to the terminal olefin hydrocarbon **(14)**. The Markownikoff hydration of this olefin with mercuric acetate and sodium borohydride gave the stereoisomeric mixture of the sex pheromone **(12)**, as shown in Scheme 1.30.

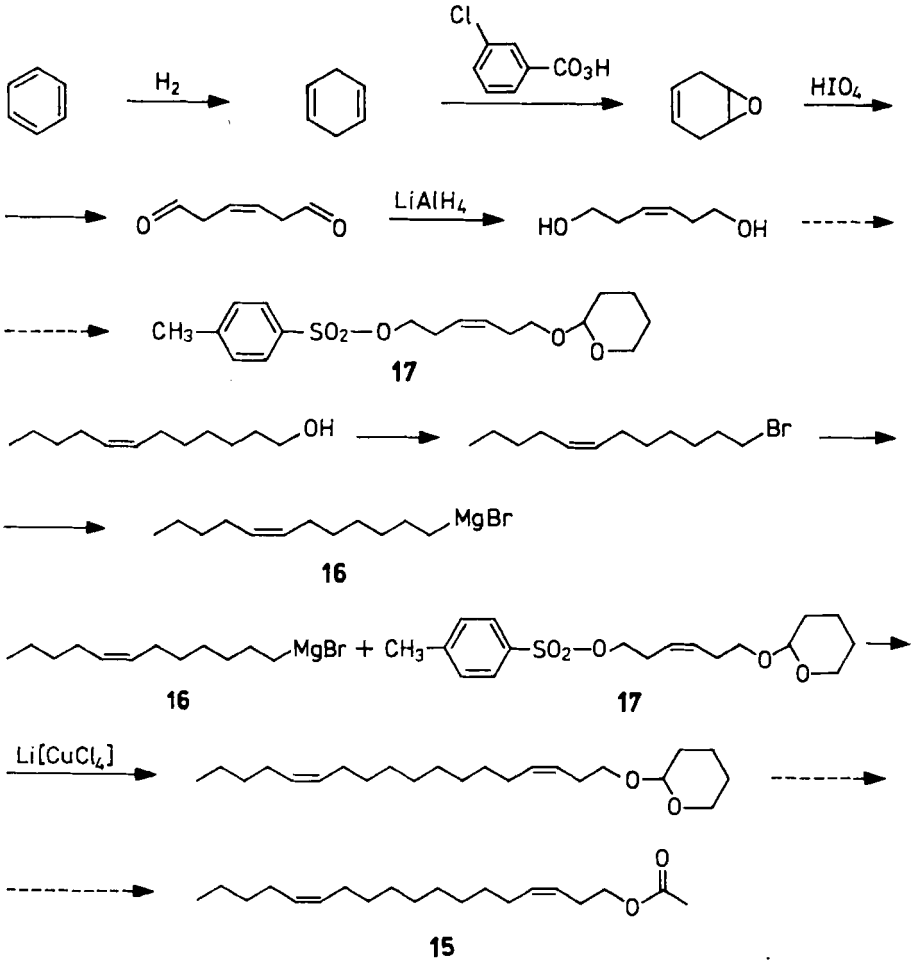


Scheme 1.30

The stereoselective synthesis of (*Z*,*Z*)-3,13-octadecadienyl acetate **(15)**, the sex attractant of the smaller clear wing moth, *Synanthedon tenuis*, was performed by Uchida *et al.* (1979) according to Scheme 1.31. The key step of this synthesis is the coupling of the Grignard reagent **16** with the intermediate **17** in the presence of lithium tetrachlorocuprate, as described by Fouquet and Schlosser (1974).

Tumlinson *et al.* (1977) were the first to demonstrate inhibition of response to a pheromone by its enantiomer. They synthesised stereospecifically the *Z*- and *E*-isomers of both enantiomers of (*Z*)-5-(1-decenyl)dihydro-2(3H)-furanone, the sex pheromone of the Japanese beetle, *Popillia japonica*. The purely synthetic (*R*, *Z*)-5-(1-decenyl)dihydro-2(3H)-furanone **(18)** was as effective as the natural isolated pheromone, but male response was strongly inhibited by small amounts of the *S*- and *Z*-isomer.

Results obtained in the elucidation of the structure of natural pheromones stimulated the search for related synthetic derivatives with pheromone action. Soon it became clear that, for males of a given insect species, the attractant produced by



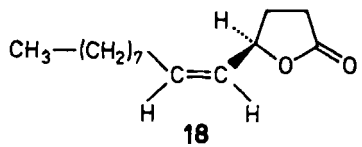
17

16

16 17

15

Scheme 1.31



18

females of the same species is the most effective. Structural changes, such as alteration of the chain length of the unsaturated alcohols and acetates, or transfer of the double bond, resulted in a decreased effect. Thus, for example, the shortening or the lengthening of the carbon chain by a methylene group decreased the effect by a factor of 3–10.

Structural changes carried out in the *n* section of unsaturated acetates of the following general formula result in a larger decrease in effect than the same changes made in section *m* (Vostrowsky *et al.*, 1973).

$$CH_3-(CH_2)_n-CH=CH-(CH_2)_m-CH_2-O-CO-CH_3$$

The identification of disparlure **(3)** by Beroza *et al.* (1971) prompted Elizarov and co-workers (1974) to investigate the influence of structural changes on attractant activity. They concluded that any change in the structure of disparlure results in a decrease in activity, and the measure of decrease increases in the following order: lengthening of the chain with one CH_2 group < shortening of the chain with one CH_2 group < transfer of the epoxy group to position 8–9 < transfer of the epoxy group to position 6–7 < introduction of a hydroxy or acetoxy group at the end of the chain < removal of the 2-methyl group < replacement of the epoxy group by an ether group < replacement of structure *Z* by structure *E*.

Structure–activity relationships elucidated so far for this type of compound serve as a good basis for a mathematical interpretation of the pheromone–acceptor interaction, and of a possible model for the insect pheromone receptor, based on the law of mass action and intermolecular binding energies (Kafka, 1974).

The search for related derivatives proved to be successful with respect to gyptol **(2)**, which was erroneously considered to be the sex attractant of the gypsy moth by Jacobson *et al.* (1961). Jacobson and Jones (1962) prepared an active homologue from ricinoleyl alcohol containing two additional methylene groups in the chain (gyplure, **19**).

$$CH_3-(CH_2)_5-\underset{\displaystyle O-CO-CH_3}{\underset{|}{CH}}-CH=CH-(CH_2)_7-CH_2OH$$

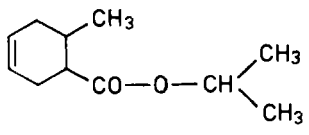
19

Modification of the propylure **(4)** molecule resulted in the synthesis of a mixture of geometrical isomers of 5,9-tridecadienyl acetate **(20)**. This product has an attractant effect on several agricultural insect pests (Warthon and Jacobson, 1967).

$$CH_3-(CH_2)_2-CH=CH-(CH_2)_2-CH=CH-(CH_2)_4-O-CO-CH_3$$

20

Also known are synthetic sex attractants of which the molecules show only a slight structural relationship with natural pheromones or none whatsoever. Of these, siglure **(21)** and trimedlure **(22)** should be mentioned (Beroza and Jacobson, 1963). The latter is a mixture of four stereoisomers, one of which is inactive whereas the other three are strongly active (McGovern and Beroza, 1966).



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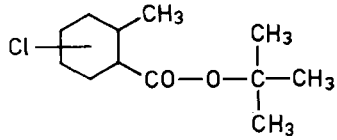


22

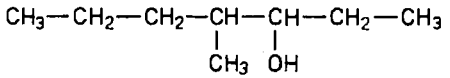
Conclusions drawn so far concerning pheromones are not free from inconsistencies. Possibly, in the light of future results, some of them will prove to be simplified, since the role of mutual interaction of substances participating in insect communication systems is disregarded.

Thus the fact that living females produce a higher pheromone activity than can be calculated from the female release rates, suggests the involvement of pheromone potentiators or pheromone precursors in the biological response (Steinbrecht, 1964; Shorey and Gaston, 1965; 1967).

An interesting example of the interaction of substances of various origin has been detected by researchers of the State University of New York. Their finding serves, at the same time, as manifestation of selective action within the same species with regard to steric structure. North American populations of the small European elm bark beetle, *Scolytus multistriatus*, which transmits the fungus causing Dutch elm disease by drilling into the bark of the tree for laying eggs, have been shown to release two pheromones, (3*S*, 4*S*)-(−)-4-methylheptan-3-ol **(23)** and (−)-α-multistriatin **(24a)**. The tree produces a tricyclic sesquiterpene, α-cubebene **(25)**, which acts as a potent synergist of the two pheromones produced by females of the insect (Anonym, 1974).

The absolute configuration of (3*S*, 4*S*)-(−)-4-methylheptan-3-ol **(23)** was determined by synthesis of its antipode (Mori, 1977).

The structure of (−)-α-multistriatin was found to be the structure (1*S*, 2*R*, 4*S*, 5*R*)-(−)-2,4-dimethyl-5-ethyl-6,8-dioxabicyclo-[3.2.1]-octane **(24a)** (Mori, 1976; Pearce *et al.*, 1976; Cernigliaro and Kocienski, 1977). However, populations of the beetle epidemic to forests in the Upper Rhine Valley did not aggregate in response to (−)-α-multistriatin; instead, another of its stereoisomers, (−)-δ-multistriatin **(24b)** exerted attractive action when combined with **23** and **25.**



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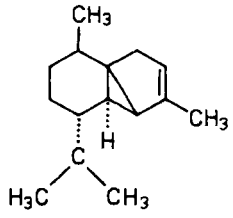

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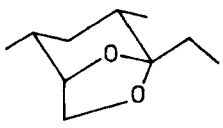
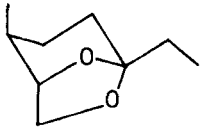
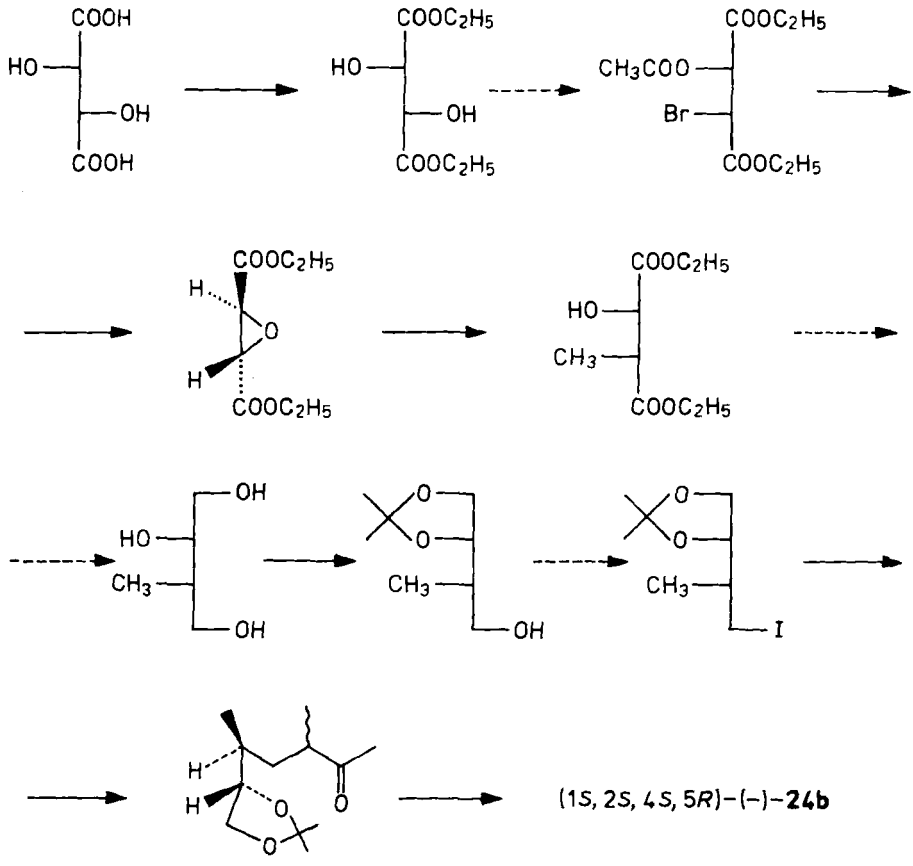


24a



24b

A stereoselective synthesis of optically highly pure enantiomers of δ-multistriatin **(24b)** has been developed by Mori and Iwasawa (1980). When using D-(−)-tartaric acid as a starting material, the synthesis route shown in Scheme 1.32 yielded (1*S*, 2*S*, 4*S*, 5*R*)-(−)-δ-multistriatin, while its antipode, (1*R*, 2*R*, 4*R*, 5*S*)-(+)-δ-multistriatin was formed from L-(+)-tartaric acid.



Scheme 1.32

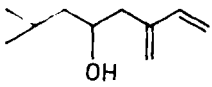
The devastating tree disease, which has wiped out elm trees in almost half of the United States, could not be controlled successfully with either insecticides or fungicides. It seems, however, that the problem can be resolved by the application of a synthetic mixture of the three compounds.

The biosynthesis and, in particular, the origin of insect sex pheromones is unclear. Hendry *et al.* (1975) have shown that a number of compounds known as sex pheromones originate from plants serving as a dietary source for the insects. They developed a theory according to which, upon emergence, the male codes the odour complex of the meconium and selects for a mate that conforms to the substances contacted during feeding.

Using deuterium labelling techniques Hendry *et al.* (1980) demonstrated that ipsenol **(26)** and ipsdienol **(27)** — the pheromones of the bark beetle *Ips paraconfusus* — are formed in the males from myrcene **(28)**, a constituent of its host plant *Pinus ponderosa*. Their finding suggests that the evolution of host plant

preferences in bark beetles can be traced back to host plant substances serving as intermediates in pheromone biosynthesis.

Little is known about the mechanism of pheromone action. In the response induced by pheromones, sensory cells on the sensilles of insect antennae play an



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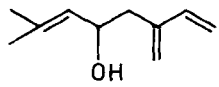

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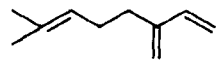

28

important role. Several pores are located on the walls of the sensilles. Presumably, pheromone molecules adsorbed on the wall diffuse through the pores to the membrane of the sensory cell, and interact with the flexible membrane protein serving as acceptor, generating a nerve impulse (Vostrowksy *et al.*, 1973).

The orientation of insects towards the pheromone source is presumably based, on the fact that they follow a concentration gradient from an area of low molecular density of areas of increasing densities (Shorey and Gaston, 1967).

In insect control pheromones can be used in different ways. As a survey tool, they can be used to warn of the spread of insects, thereby permitting the rational programming of control by conventional methods. This method is essentially a prognosis of insect gradation, based on the number of injurious insects captured in the pheromone-baited traps.

The most important ways of direct pheromone application are their combination with traps, and their joint application with insecticides, male sterilants or insect hormones on restricted parts of the area to be protected. This method of application permits a considerable reduction in the quantity of insecticide to be used which, besides its economical advantage, is important also from the aspect of environmental protection.

Use of pheromones in a contrary sense is also known. The "male confusion technique" involves essentially the inhibition of the orientation between sexes by the application of a high concentration of a natural pheromone. From this, the "male inhibition technique" differs only insofar as a synthetic derivative with a structure different from that of the natural pheromone, such as the inactive stereoisomer thereof, is spread, so that the male response to the natural pheromone is suppressed.

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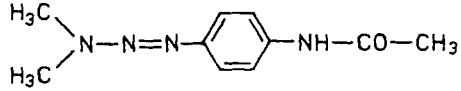
1.11 Antifeedants

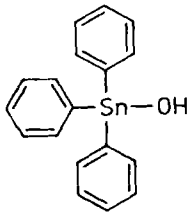
While insect repellents acting by driving or keeping insects away from the host plant have found little use in modern crop protection, the interest in anti-feeding compounds counteracting signals to initiate feeding has increased during the last two decades.

Wright (1963) reported on the antifeedant activity of several triazenes, the most active member of this class being 4-(dimethyltriazeno)acetanilide (**1**). Under field conditions it inhibits the feeding of surface-chewing caterpillars and beetles. It possesses a medium acute toxicity to rats, its oral LD_{50} being 510 ppm.



1

Ascher and co-workers (Ascher and Rones, 1964; Ascher and Nissim, 1964), as well as Murbach and Corbaz (1963) reported on the antifeedant activity of triphenyltins such as triphenyltin hydroxyde (**2**) and triphenyltin acetate (**3**) known as fungicides under the names Du-Ter® and Brestan®, respectively. Later these compounds were reported to show sterilising effect, too (see Section 1.9).



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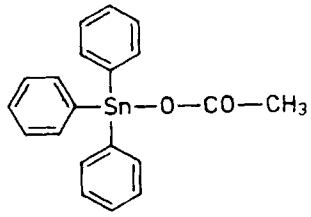
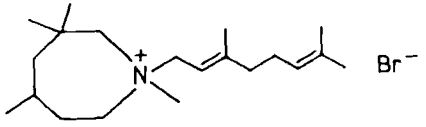


3

Darwish *et al.* (1980) described the insect antifeedant activity of quaternary derivatives of some commercially available heterocyclic secondary amines. The most active members of this series, tested against *Leptinotarsa decemlineata*, were compounds **4** and **5**.



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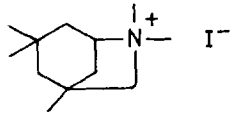
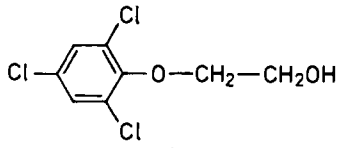


5

Jermy (1961) investigated the antifeedant activity of metal ions and found salts and complexes of copper(II) to be the most active.

In an attempt to overcome the limitation that only surface feeding chewing insects can be controlled by the known antifeedant compounds, Jermy and co-workers (Jermy and Matolcsy, 1967; Matolcsy *et al.* 1968) investigated the antifeedant activity of some substituted phenoxyethanols and phenoxyacetic acids which do not affect plant growth and which are known to possess systemic properties. 2,4,6-Trichlorophenoxyethanol (**6**) and 2,4,6-trichlorophenoxyacetic acid (**7**) have shown the highest antifeeding activity both under laboratory and field conditions.



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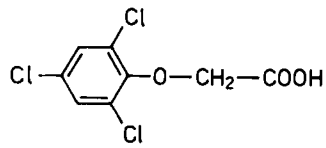
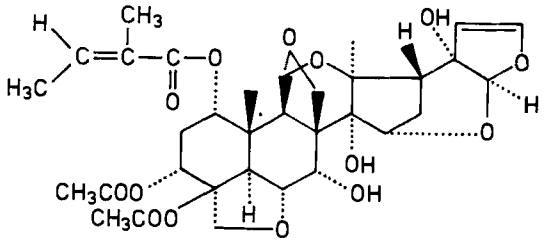


7

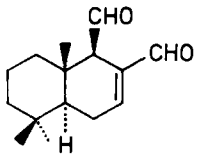
Much work has been done to find the specific plant substances evoking feeding responses and in some cases they were identified (Matsumoto and Sugiyama, 1960; Nayar and Fraenkel, 1963; Nayar and Thorsteinson, 1963). A two-way receptor mechanism seems to determine the host range, namely, on the one hand, the more or less specific response of some chemoreceptors to plant substances acting as feeding stimulants and, on the other hand, the sensitivity of other receptors to various substances inhibiting feeding (Jermy, 1966).

In the early seventies scientists of the International Centre of Insect Physiology and Ecology (ICIPE) in Nairobi, Kenia, launched a wide range programme aimed at investigating selected East African plants for secondary metabolites that might have antifeeding characteristics. These plant derived substances were regarded as built-in defense mechanisms, though this teleological interpretation was criticised by several authors. As part of this programme, azadirachtin **(8)**, an unstable, amorphous triterpenoid, has been isolated from seeds of the common Indian neem tree, *Azadirachta indica*. This compound revealed significant antifeedant activity in a concentration as low as 0.35 ppm (Nakanishi, 1975; Warthen *et al.*, 1978).



8

Further results from this screening programme were the isolation and determination of polygodial **(9)**, warburganal **(10)** and ugandensidial **(11)** from the bark of the plants *Warburgia stuhlmannii* and *W. ugandensis* (Kubo and Nakanishi, 1977; Nakanishi and Kubo, 1977; Meinwald *et al.*, 1978).



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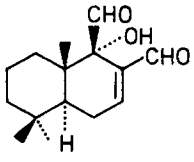

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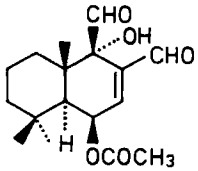
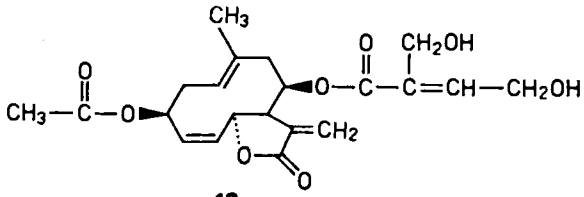


11

These and some other substances isolated in this programme turned out to be uniformly active against a great variety of insects while a part of them appeared to have species specificity in their antifeedant action.

Members of the same research team isolated two germacranolides, schkuhrin I **(12)** and schkuhrin II **(13)** from the African plant *Schkuhrina pinnata*. Both compounds revealed a high degree of antifeedant action on a number of insects. Their structure has been determined by spectroscopic and chemical methods (Pettei *et al.*, 1978).



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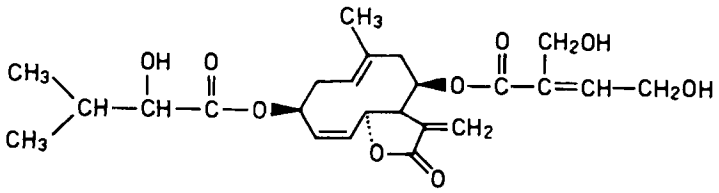
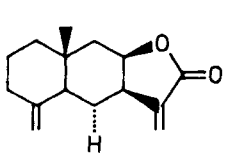


13

A characteristic part of the molecule of these substances is the α-methylene lactone ring. Compounds possessing this moiety are of great interest also as fungicidal, bactericidal and cytostatic agents.

The methylene lactone grouping is present also in some of the sesquiterpenes isolated from plants by Nawrot and co-workers (Nawrot *et al.*, 1983; 1984; Harmata and Nawrot, 1984), such as isoalantolactone **(14)** and bakkenolide A **(15)**. At the same time other highly active sesquiterpenes isolated by them, such as yatein **(16)**, bisabolangelone **(17)** and others lack this characteristic grouping, indicating that its presence is not a stringent requirement of antifeedant property within this type.



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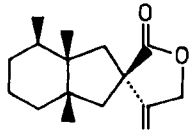

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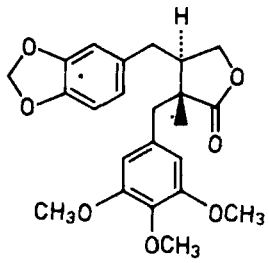

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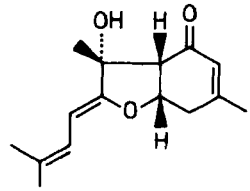

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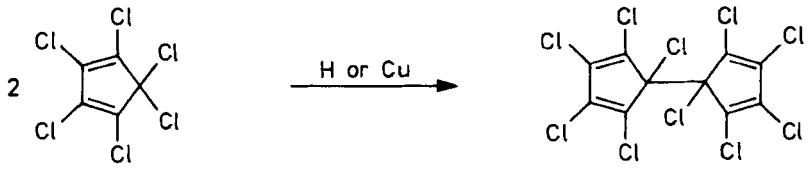
2. Acaricides

In addition to insects, mites (*Acaridae*), also belonging to the arthropodous animals (*Arthropoda*), may cause great losses in agricultural yield and quality. Their taxonomic difference from insects predisposes that the structural requirements of biological action against mites are often different from those against insects. A significant number of the compounds used as acaricides have no effect or only a minor effect on insects. Conversely, of the insecticides only some organophosphorus compounds and carbamates are also effective against mites, while insecticides of other types such as chlorinated hydrocarbons and others have virtually no useful acaricidal effect. Therefore, the use of insecticides resulted in many cases in an increased infection by mites, because the treatment also killed those natural enemies of mites which had previously limited their propagation. There is an interesting parallel between the action against powdery mildew and acaricidal action, i e. those fungicides which are effective against powdery mildew fungi can often be used with good effect also against mites.

Very little is known of the mechanism of acaricidal action and research in this field is insignificant compared to research aimed at the elucidation of the mechanism of insecticidal action. It is certain, however, that not only acaricides belonging to various types show differences in their mode of action. In addition, the action of a certain compound can be different at the various stages of development of the mites.

2.1 Chlorinated hydrocarbons

Most of the chlorinated hydrocarbon derivatives used as insecticides are practically ineffective against mites. At the same time, one example of chlorinated hydrocarbons, ineffective as insecticide, bis(pentachloro-2,4-cyclopentadien-1-yl) **(1)**, attained importance in the chemical control of mites. It was introduced in 1960 under the name dienochlor. It is prepared by the catalytic hydrogenation, or Wurtz reaction, of hexachlorocyclopentadiene (Ladd, 1952; Rucker, 1955a, b; Allen *et al.*, 1964).

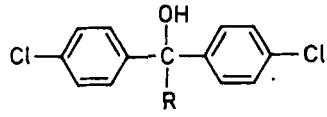


1

Dienochlor acts by interfering with oviposition. It is virtually harmless to mammals, the acute oral LD_{50} for rats being 3160 mg/kg.

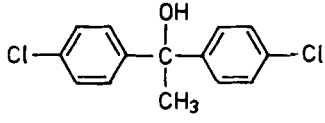
2.2 Diaryl carbinols

Metcalf *et al.* (Metcalf, 1948; Gunther *et al.*, 1956) investigated extensively the effect of those derivatives, structurally related to DDT, in which a hydroxyl group is attached to the carbon atom linking the two chlorophenyl groups. They found that the condition for acaricidal action is the presence of another group attached to this carbon atom. By changing this group they obtained the following order of decreasing efficiency:



$$R = CCl_3 > CH_3 > CHCl_2 > C_2H_5 > C(CH_3)_3 > H$$

The following members of this group attained practical importance: 1,1-bis(4-chlorophenyl)ethanol (chlorfenethol, **2**), 1,1-bis(4-chlorophenyl)-cyclopropyl-methanol (prochlonol, **3**) and 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethanol (dicofol, **4**).



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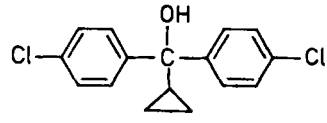

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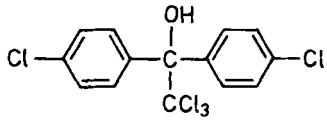
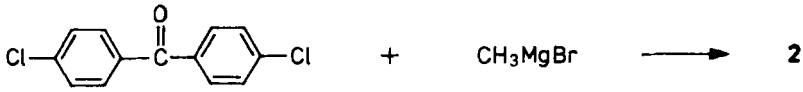
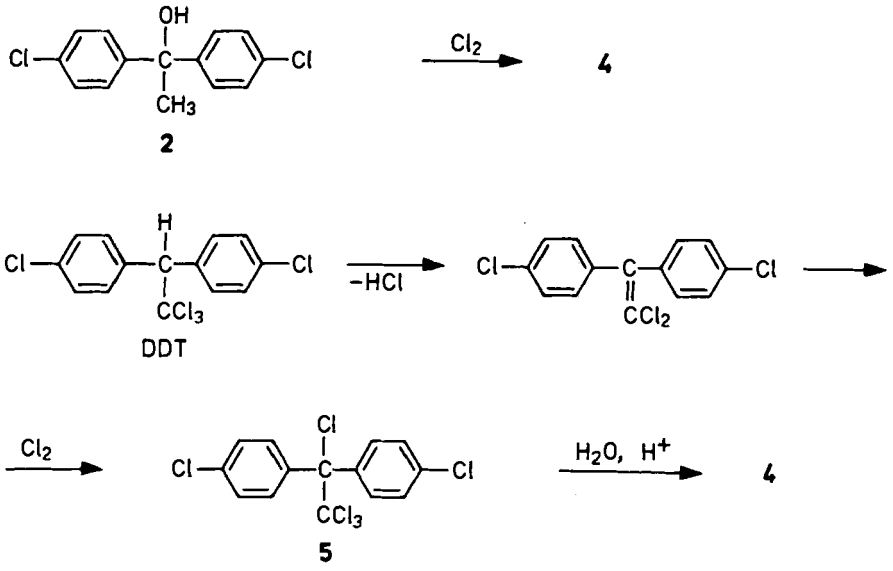


4

Chlorfenethol (**2**) is prepared from 4,4'-dichlorobenzophenone and methyl magnesium halogenide by the Grignard reaction (Grummitt, 1950). Prochlonol is obtained in an analogous way.

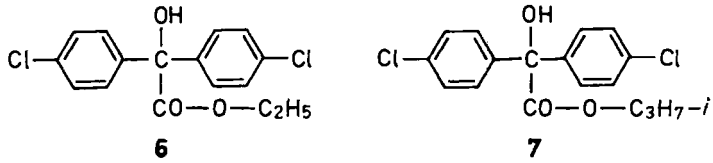


Dicofol (**4**) is prepared by the chlorination of chlorfenethol (**2**), or by the partial hydrolysis of 1,1-bis(4-chlorophenyl)-1,2,2,2-tetrachloroethane (**5**), obtained from DDT by dehydrochlorination and subsequent chlorination (Reuter and Ascher, 1956; Wilson *et al.*, 1955; Wilson and Wolffe, 1955).



Chlorfenethol, prochlonol and dicofol are powerful acaricides, but they differ with respect to their spectrum of activity. Characteristic of chlorfenethol (**2**) is its strong ovicidal action, while the effect of dicofol (**4**) is directed mainly to more developed stages. The most characteristic feature of prochlonol (**3**) is its rapid onset of action. Its activity against adults of *Tetranychus urticae* is about the same as that of dicofol (**4**); its residual ovicidal activity, however, proved to be markedly better. Prochlonol shows interesting plant growth stimulation, resulting in better performance of the leaves and bigger fruits (Busschots, 1967).

Gasser described in 1952 the acaricidal properties of the ethyl and isopropyl esters of 4,4′-dichlorobenzylic acid (**6**) and (**7**) respectively. The first was introduced under the name chlorobenzilate, the latter under the name chloropropylate, as nonsystemic acaricides, mainly effective against adult mites. Chlorobenzilate is prepared by the alkylation of 4,4′-dichlorobenzylic acid with diethyl sulfate, while chloropropylate is obtained by esterification of the dichlorobenzylic acid with isopropanol (Häflinger, 1951).

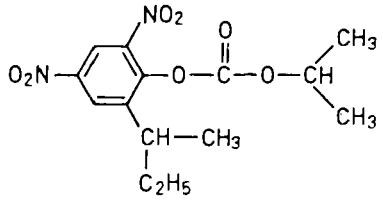


The acute oral LD_{50} of chlorobenzilate for rats varies between 700 and 3100 mg/kg, while that of chloropropylate is more than 500 mg/kg. In two-year feeding tests on dogs the no-effect concentration was 500 mg/kg for both compounds.

2.3 Aromatic nitro compounds

2-Alkyl-4,6-dinitrophenols and their esters possess the most general effect of all pesticides, including herbicidal, fungicidal, insecticidal and acaricidal activity. This also means that at the same time, they are relatively highly toxic to mammals. In spite of these general biocidal properties, a certain degree of selectivity can be achieved by appropriate selection of the time of treatment: for example, by winter application to prevent injury to the green parts of the plant, or by changing substituent groups which affect efficiency.

Of the carboxylic acid esters the most important are isopropyl 2-*s*-butyl-4,6-dinitrophenyl carbonate (dinobuton, **8**), methyl 2,4-dinitro-6-(1-ethylhexyl)phenyl carbonate **(9a)** and methyl 2,4-dinitro-6-(1-propylpentyl)phenyl carbonate **(9b).** The mixture of the two latter compounds has been introduced under the name dinocton-6 **(9)** (Pianka and Polton, 1963; Pianka and Smith, 1965).



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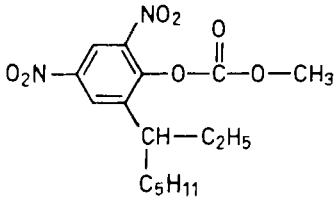

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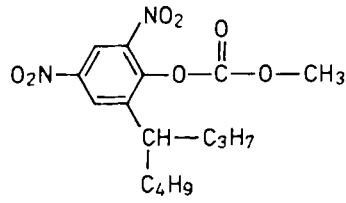


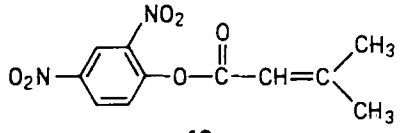
9b

These compounds are prepared by the reaction of the sodium salt of the respective dinitroalkylphenols with alkyl chloroformate.

The acute oral LD_{50} of dinobuton for mice is 2450 mg/kg, and for rats 140 mg/kg. The maximum no-effect level for dogs is 4.5 mg/kg/day. Dinocton-6 is less toxic, its acute oral LD_{50} for rats being 1250 mg/kg.

Of the esters formed with unsaturated acids, the most important are 2-(1-methyl-*n*-propyl)-4,6-dinitrophenyl-2-methyl crotonate (binapacryl, **10**) and the product known under the name dinocap **(11),** which is a mixture of 2,4-dinitro-6-(2-isooctyl)phenyl crotonate **(11a)** and 2,4-dinitro-4-(2-isooctyl)phenyl crotonate **(11b)** (Emmel and Czech, 1960).

They are prepared by acylation of the respective dinitroalkylphenols with crotyl and methylcrotyl chloride, respectively.



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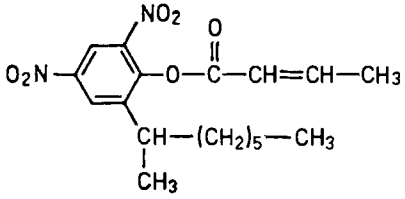

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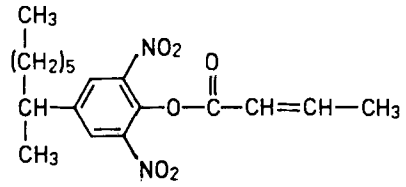
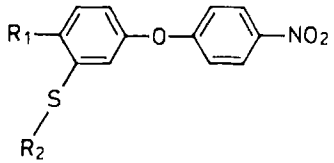
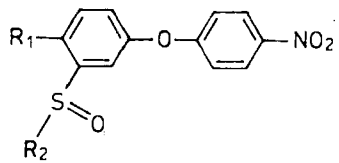


11b

The acute oral LD_{50} of binapacryl for rats is 150–350 mg/kg, that of dinocap 980–1190 mg/kg. Dogs fed for a long period on a diet containing 50 mg/ dinocap suffered no loss of weight.

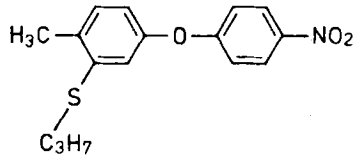
Kato and associates (1978) reported on the acaricidal activity of 4-nitro-diphenyl ethers of the general structures shown below:





The acaricidal activity within this group was found to be mainly dependent on the van der Waals' radius of the substituent R_1 and of the hydrophobicity of the alkyl group R_2.

The most promising member of this class, 4-methyl-3-*n*-propylthiophenyl-4-nitrophenyl ether (NK—592, **12**), was developed as a practical acaricide.

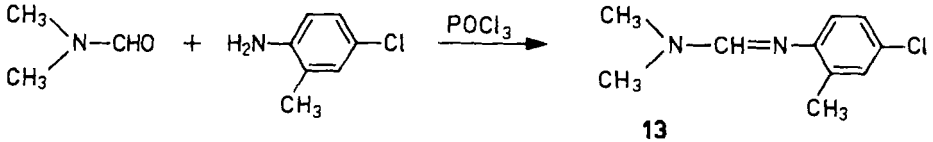


12

2.4 Derivatives containing a C=N or N=N double bond

The acaricidal properties of some structures have been described which have in common that a nitrogen atom is attached by a double bond to a carbon atom or to another nitrogen atom in the molecule.

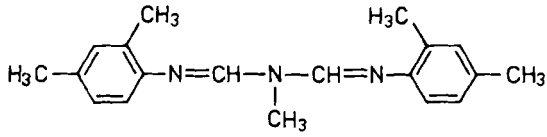
The acaricidal properties of N,N-dimethyl-N'-(4-chloro-2-methylphenyl) formamidine (chlorphenamidine, **13**) have been described by Dittrich (1966). The compound is prepared by the condensation of 4-chloro-2-methylaniline and dimethyl formamide with phosphorus oxychloride (Arndt and Steinhausen, 1963).



13

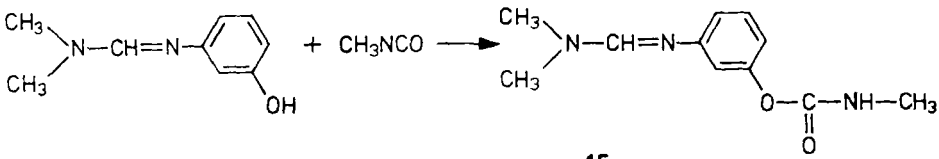
Chlorphenamidine has mainly an ovicidal action, but it acts in all the developmental stages of mites. In plant tissues it can be moderately translocated. Its acute oral LD_{50} for rats is 335 mg/kg. The metabolites of chlorphenamidine include N'-(4-chloro-2-methylphenyl) formamidine, 4'-chloro-*o*-formotoluidine and 4'-chloro-*o*-toluidine (Chang and Knowles, 1977).

1,5-Di-(2,4-dimethylphenyl)-3-methyl-1,3,5-triazapenta-1,4-diene **(14)** (code number BTS 27 419) is rather similar to chlorphenamidine with respect to its characteristic atomic groups. Its toxicological properties are more favourable than those of chlorphenamidine **(13)**, its LD_{50} measured on rats is 400–800 mg/kg.



14

3-Dimethylaminomethyleneiminophenyl N-methylcarbamate (formetanate, **15**) contains both amidine and carbamate groups (Wakerley and Weighton, 1969). The amidine moiety of the molecule is synthesised in the same way as described for chlorphenamidine, and the 3-dimethylaminomethyleneiminophenol obtained is carbamoylated with methyl isocyanate:

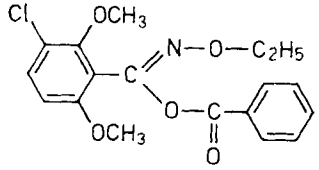


15

The acute oral LD_{50} of formetanate for rats is 24 mg/kg. It is particularly effective against the motile stages of spider mites.

The acaricidal activity of these formamidines is based on a mechanism which is entirely different from that of the chlorinated hydrocarbons, organophosphates and carbamates. Some of them are more toxic to organophosphate-resistant mites than to organophosphate susceptible ones (Dittrich, 1969).

The acaricide O-benzoyl-3-chloro-2,6-dimethoxybenzohydroximate has recently been introduced under the name benzomate **(16)**. It can be prepared according to the general scheme of preparation of O-acylhydroximates, by the reaction of 3-chloro-2,6-dimethoxybenzohydroximate with benzoyl chloride.

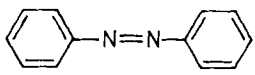


16

The action of benzomate is very specific: it is directed only against mites, and seems to have no harmful effect on useful insects and predators of mites.

The acaricidal effect of the most simple representative of aromatic compounds containing an N=N double bond, azobenzene **(17)**, was first described by Blauvelt in 1945. This compound is prepared by the controlled reduction of nitrobenzene. It exerts its action also in the vapour phase, and therefore it can also be used as a fumigant in glasshouses against eggs and immature stages of mites.

Its oxidised derivative, azoxybenzene (fenazox, **18**), also has acaricidal properties, but it is only active at plant surfaces. Its acute oral LD_{50} for rats is 885 mg/kg.



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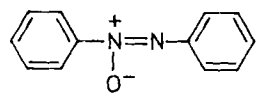
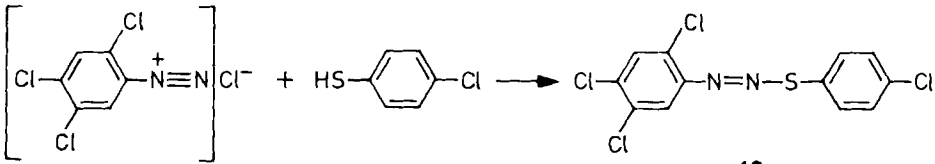


18

2.5 Compounds containing sulfur

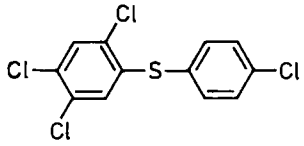
4-Chlorophenyl-2,4,5-trichlorophenyl azosulfide (chlorfensulfide, **19**), developed bv Ishii *et al.* (1961), can be considered as a structural transition from nitrogen-containing compounds to sulfur-containing products. It is obtained by the reaction of 2,4,5-trichlorobenzenediazonium chloride with 4-chlorothiophenol:



19

It is strongly toxic both to eggs and adults; it sterilises adult females. It penetrates leaf tissues rapidly and maintains its activity there for a long period. Its acute toxic LD_{50} for mice is more than 3000 mg/kg.

However, conditions for acaricidal action are aalso satisfied by those derivatives in which the two phenyl groups are linked directly or through the insertion of a methylene group by a bivalent sulfur atom. 2,4,4'5-Tetrachlorodiphenyl sulfide (tetrasul, **20**), 4-chlorobenzyl-4-chlorophenyl sulfide (chlorbenside, **21**) and the 4-fluorophenyl analogue of the latter (fluorobenside, **22**) belong to this type of compound (Meltzer and Dietvoors, 1957; Cranham *et al.*, 1953; Stevenson *et al.*, 1953).



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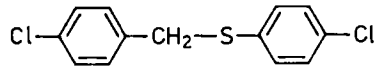

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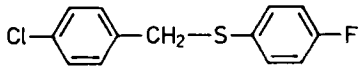


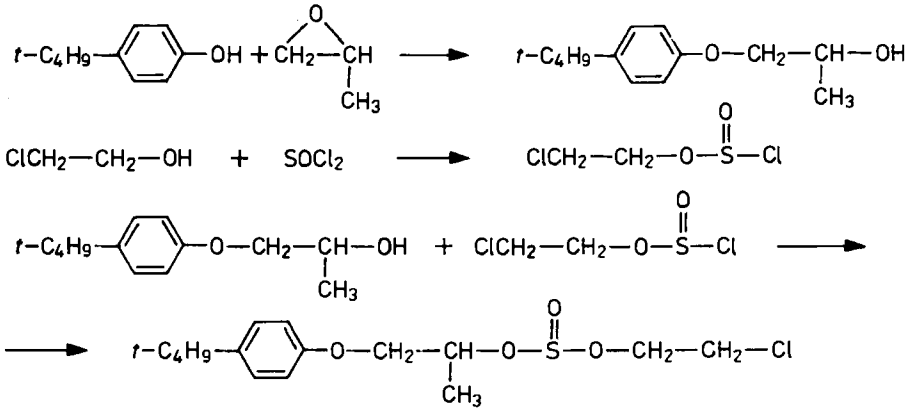
22

Compounds (**20**) and (**21**) are prepared from 4-chlorothiophenol, by reaction with 1,2,4,5-tetrachlorobenzene and 4-chlorobenzyl chloride, respectively.

Both compounds are resistant to hydrolysis, but chlorbenside is susceptible to oxidation, being converted into the sulfoxide, and further to the sulfone.

They are toxic to eggs and larvae of tetranychid mites, and very slightly toxic to mammals. Thus, for example, the acute oral LD_{50} of tetrasul for female rats is 6800 mg/kg.

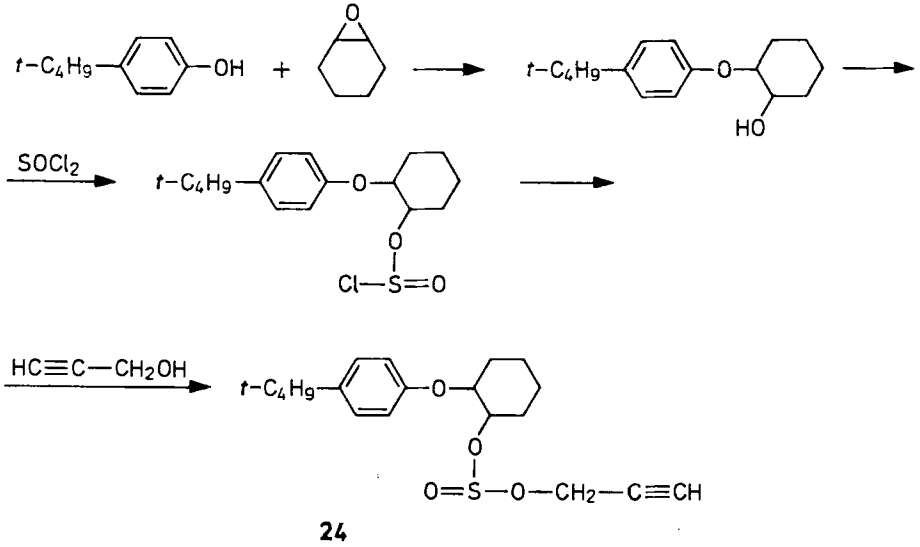
Of the derivatives containing a quadrivalent sulfur atom, the mixed esters of sulfurous acid, e.g. 2-(*p*-*t*-butylphenoxy)isopropyl-2'-chloroethyl sulfite (aramite, **23**), attained practical importance as acaricides. Aramite is prepared according to Scheme 2.1 (Harris and Zukel, 1954; Harris *et al.*, 1948).



23

Scheme 2.1

2-(*p*-*t*-Butylphenoxy)cyclohexyl propargyl sulfite (DO14, Omite®, **24**) is prepared by an analogous route (Scheme 2.2), starting from *p*-*t*-butylphenol and cyclohexene oxide (Covey *et al.*, 1967).



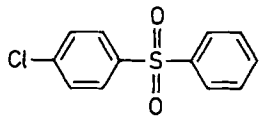
24

Scheme 2.2

The most important group of sulfur containing acaricides are derivatives with a hexavalent sulfur atom: sulfones and sulfonates. Of these, the sulfones were known previously. The history of their development calls to mind the early periods of modern pesticide research, the 1930s, when Paul Müller, looking for compounds with insecticidal action, tested derivatives in which the two *p*-chlorophenyl groups are linked through a central atomic group. 4,4'-Bischlorophenyl sulfone was also among these compounds, which from a historical point of view were the precursors of DDT. Läuger *et al.* (1944) found that when one of the two *p*-chlorine atoms of 4,4'-bischlorophenyl sulfone is omitted, the insecticidal effect is somewhat reduced but, at the same time, 4-chlorodiphenyl sulfone (Sulphenone® **25**) reveals a strong ovicidal action, contrary to the 4,4'-dichloro derivative. 4-Chlorodiphenyl sulfone is prepared on an industrial scale by the reaction of benzenesulfonic acid and chlorobenzene at 200–250°C (Bender and Pitt, 1950).

2,4,5,4'-Tetrachlorophenyl sulfone (tetradifon, **26**) was introduced some years later under the trade name Tedion®. It is prepared by a Friedel–Craft's reaction between 2,4,5-trichlorobenzenesulfonyl chloride and chlorobenzene, or by the oxidation of 2,4,5,4'-tetrachlorodiphenyl sulfide (Meltzer and Huisman, 1954).

The acaricidal properties of these two compounds are roughly similar, but tetradifon is capable of some penetration into the plant and hence it is toxic to larvae and nymphs on the side of leaves opposite to that treated. The acute oral LD_{50} of Sulphenone® for rats is 3650 mg/kg, that of tetradifon more than 14 700 mg/kg.



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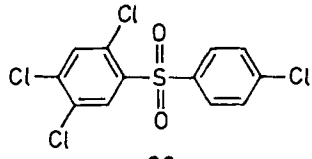
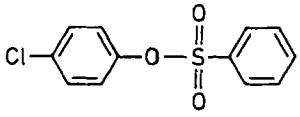


26

Of the sulfonic acid esters, 4-chlorophenyl benzenesulfonate (fenson, **27**), 4-chlorophenyl 4′-chlorobenzenesulfonate (ovex, **28**) and 2,4-dichlorophenyl benzenesulfonate (genite, **29**) found the widest use (Gilbert, 1949; Kenaga and Hummer, 1949; Barnes, 1951; Kirby and Read, 1954). Sulfonic acid esters are prepared by the reaction of the corresponding benzenesulfonyl chloride with the properly substituted chlorophenol. Contrary to sulfones, these compounds have the disadvantage of being hydrolysed by alkali to the corresponding phenol and sulfonic acid.



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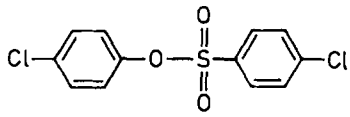

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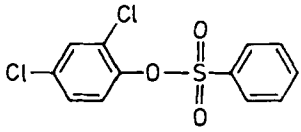
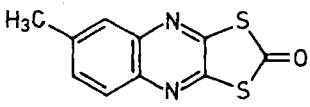


29

They are moderately toxic to mammals, the LD_{50} of all three compounds for rats ranging between 1400 and 2000 mg/kg.

2.6 Heterocyclic compounds

An example of the simultaneous anti-powdery mildew and acaricidal action is the biological effect of 6-methyl-2,3-quinoxalinedithiol cyclic carbonate (oxythioquinox, **30**) and of the related 2,3-quinoxalinediyl cyclic trithiocarbonate (thioquinox, **31**), introduced originally as fungicides against powdery mildew and discussed already under the heading fungicides. These compounds were developed by research workers of the Bayer Co. in the course of their study of the acylated derivatives of 2,3-dimercaptoquinoxaline (Sasse *et al.*, 1958; 1960; Sasse, 1960).



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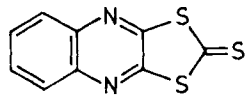


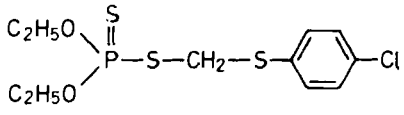
31

They have scarcely any insecticidal effect and exert their action primarily against larvae and eggs of acaridae.

2.7 Organophosphorus compounds

Compounds belonging to the group of organophosphorus compounds differ considerably with respect to their range of action. Many of them have both insecticidal and acaricidal activity, while others have an insecticidal action but are inactive against mites. Some organophosphorus compounds, introduced first as fungicides against powdery mildew, revealed also a strong acaricidal activity. Generally, compounds with systemic properties such as demeton, demeton-methyl, thiodemeton, mevinphos, ethion, omethoate, endothion and others, show both insecticidal and acaricidal activity.

The most important examples of compounds used specifically as acaricides but possessing a weak insecticidal action are S-(4-chlorophenylthiomethyl)-diethyl phosphorothiolothionate (carbophention, **32**) and its 3,5-dichlorphenyl analogue (phenkapton, **33**). These compounds are very similar to each other, but have been developed by two independent research groups (Fancher, 1954; Gätzi and Müller, 1955).



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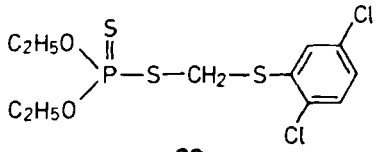

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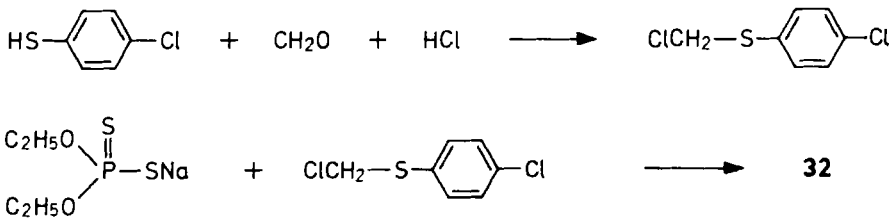
They are prepared by treating the respective thiophenol with formaldehyde and hydrochloric acid, followed by reaction of the substituted chloromethyl phenyl sulfide obtained with sodium diethyl phosphorodithionate:

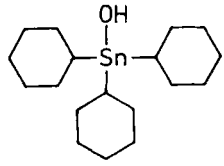


Contrary to most phosphoric acid esters with acaricidal action, neither of the two compounds has systemic properties. Both have a long residual action. The oral LD_{50} of carbophention for rats is 28–100 mg/kg, and that of phenkapton 200–260 mg/kg.

Following the general metabolic pattern of phosphorodithioic acid esters, the P=S group of carbophenthion is converted in plants to a P=O group, resulting in an increased toxicity.

2.8 Organometallic compounds

While triphenyltin hydroxide (fentin hydroxide) in used as a potent fungicide, its saturated analogue, tricyclohexyltin hydroxide **(34)**, is highly active against motile forms of plant-feeding mites (Kenaga, 1966; Allison *et al.*, 1968).

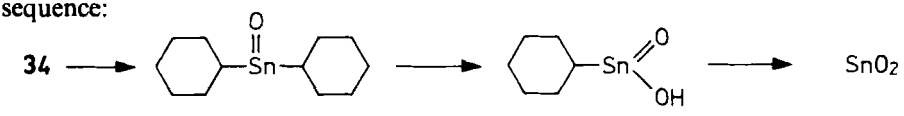


34

Tricyclohexyltin hydroxide can be prepared *via* the Grignard reaction, by reaction of cyclohexyl magnesium halide with stannic chloride.

Its acute oral LD_{50} for rats is 540 mg/kg; the acute dermal LD_{50} for rabbits is more than 2000 mg/kg. The toxicological no-effect level in a two-year test on dogs proved to be 3 mg/kg/day. The eight-day LD_{50} for bobwhite quails is 520 ppm. It is practically nonhazardous to bees.

The decomposition products obtained after sunlamp exposure follow the sequence:



dicyclohexyltin oxide

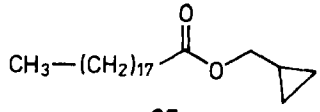
cyclohexyl--stannoic acid

The same mechanism is the probable route of loss from treated apples. The compond disappears with a half-life of two to four weeks, while the total tin has a half-life of four to six weeks. No tendency to accumulate could be observed. The acute oral LD_{50} for rats of dicyclohexyltin oxide is 430, and that of cyclohexyl-stannoic acid 3600 mg/kg.

2.9 Cyclopropane derivatives

Staal and associates (Staal *et al.*, 1975; Henrick *et al.*, 1976) tested a great variety of aliphatic esters containing a cyclopropane moiety as common structural element, such as cyclopropylmethyl carboxylates, cyclopropylmethyl dicarboxylates, alkyl cyclopropanecarboxylates and alkylene biscyclopropanecarboxylates. The most active members of these series were compounds **(35)**, **(36)**, **(37)** and **(38)**.

Hexadecyl cyclopropanecarboxylate (cycloprate, **36**), one of the most active derivatives of all four series, was selected for practical application. It is active against eggs in all stages of embryonic development and the hatching of eggs is prevented. Its activity is accompanied by morphogenetic changes during the late stage of embryonic development.



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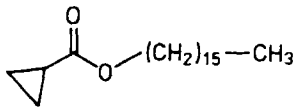

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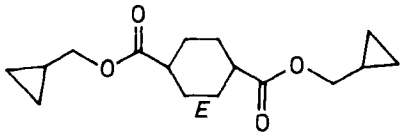

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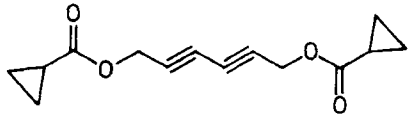
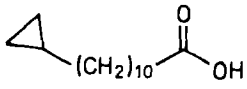


38

Its acute oral toxicity for rats is 12 200 mg/kg. Two thirds of a single oral dose given to rats was found to be excreted within one day. The major metabolites in tissues are 11-cyclopropyl-undecanoic acid **(39)**, 13-cyclopropyl-tridecanoic acid



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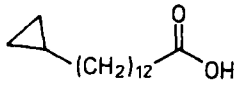

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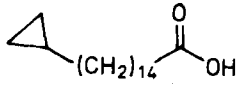

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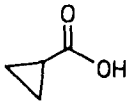

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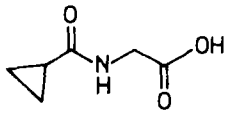
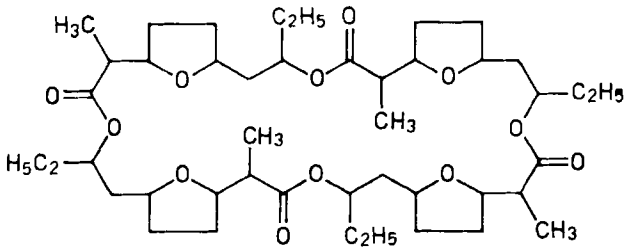


43

(40) and 15-cyclopropyl-pentadecanoic acid **(41)**. The major excretory metabolite in feces was cyclopropanecarboxylic acid **(42)**, in urine N-(cyclopropanecarbonyl) glycine **(43)** (Quistad *et al.*, 1978).

2.10 Antibiotics

During screening studies for antibiotics with pesticidal action, Ando *et al.* (1971a; 1971b) isolated a new antibiotic, tetranactin, from the filter cake of *Streptomyces aureus* Waksman et Henrici, along with two other structurally related substances. All three compounds belong to the class of macrotetrolide antibiotics. Tetranactin consists of four units of homoactic acid **(44)** linked to form a cyclic polyester. Its structure determined by NMR and mass spectrometry proved to be **(45)**.



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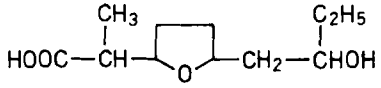
In experiments to verify the structure of tetranactin, alkaline hydrolysis yielded the building element homoactic acid (**44**), while reduction with lithium aluminium hydride gave the diol (**46**).



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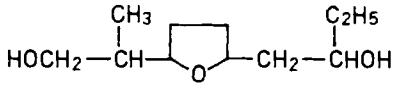

46

2^{16} stereoisomers are possible for the structure of tetranactin. The stereochemical models are as follows (HA = homoactic acid unit):

racemic form

meso form I meso form II

Tetranactin molecules have been shown to have either a two-fold rotational axis (racemic form or meso form I), or a centre of symmetry (meso form II). This is consistent with data of optical rotation, $[\alpha]_D^{23.5} = 0$.

Tetranactin exerts a significant acaricidal effect in a concentration as low as 100 ppm under application conditions. At the same time, it has only a moderate ovicidal effect. To overcome this disadvantage, a search was made for substances showing synergistic action with the antibiotic. Some organophosphorus and carbamate insecticides and sulfonate-type acaricides were shown to synergise the activity of tetranactin against both eggs and adults of mites. The preparation introduced under the trade name Mitecidin-C® is a synergistic mixture of tetranactin and 4-chlorophenyl 4'-chlorobenzenesulfonate (**28**). The preparation of Mitecidin-B® contains 2-*s*-butylphenyl N-methylcarbamate as the synergistic component.

Tetranactin also inhibits the growth of Gram-positive bacteria and some phytopathogenic fungi *in vitro* at low concentrations.

It is relatively stable, and at pH values between 2 and 13 no loss in activity is observed for 5 hours at room temperature, or on exposure to sunshine for several days.

Tetranactin is practically harmless to mammals, its LD_{50} for mice being more than 15 000 mg/kg.

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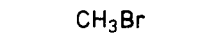
3. Nematocides

Most of the *Nematodae*, forming a group of the *phylum* ringworms *(Nemathelminthes)*, damage mostly the roots of cultivated plants. Injury is manifested in many ways. Free-living root nematodes act as virus vectors and propagate plant viruses. Some nematodes release substances resulting in the formation of root nodules, cysts or other growth anomalies. Others damage the host plants by withdrawing plant nutritions from the leaf tissues or produce enzymes which destroy the cell walls.

One mode of control of nematodes living in the soil is the application of volatile soil fumigants, the vapours of which attain in the air space of the soil a concentration sufficient to kill them. The major part of these substances can be classified among the aliphatic chlorinated hydrocarbons. Their action is aspecific, so that they cannot be used during the active vegetative period because they damage plants. Their most important representatives are bromomethane (**1**), 1,2-dibromoethane (**2**), a mixture of 1,3-dichloropropene (**3**) and 1,2-dichloropropane (**4**), and 1,2-dibromo-3-chloropropane (**5**) (Taylor and McBeth, 1940; Christie, 1945; McBeth, 1954; Raski, 1954).



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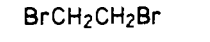

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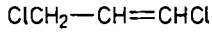

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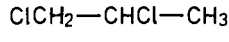


4

5

Of these, 1,2-dibromo-3-chloropropane (**5**) is the most selective against nematodes and, for certain cultures it can be used also in the culturing period.

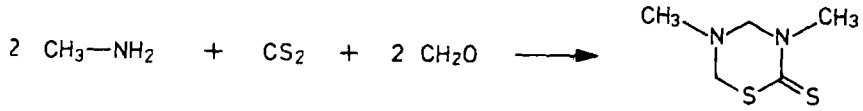
The use of these pesticides is very expensive. The rate of application per unit area is many times that of other pesticides; for example, that of a dichloropropene–dichloropropane mixture is 300–600 l/ha. Their use is therefore profitable mainly in intensive cultures with high-value produce, and is mostly restricted to the protection of vegetables and ornamental plants.

Sodium N-methyldithiocarbamate (metham, **6**) and 3,5-dimethyl-tetrahydro-1,3,5-thiadiazine-2-thione (dazomet, **7**) act also as soil fumigants. The first is

prepared according to the general scheme of preparation of dithiocarbamates, by the reaction of methylamine, carbon disulfide and sodium hydroxide (Dorman and Lindquist 1954).

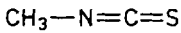
6

Dazomet (**7**) is prepared by a somewhat similar route, *via* the formation of N-methyldithiocarbamate, as a result of the cyclisation of methylamine, carbon disulfide and formaldehyde (Delépine, 1897; Bodendorf, 1930).



7

The action of both compounds is based on the release of methyl isothiocyanate (**8**) during their degradation in the soil.



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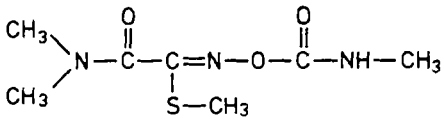
Owing to its strong tendency to addition reactions, methyl isothiocyanate is a biologically potent, aggressive compound. By virtue of this property and its volatility it kills soil insects, soil fungi and weed seeds as well as nematodes, thus acting as a general soil disinfectant.

In addition to nematocides acting in the vapour phase, recently compounds have been introduced which are soluble in water and permeate the capillary system of the soil in the form of their aqueous solutions. A small number of these compounds belong to the group of carbamates, while the larger part belongs to the organophosphorus compounds.

S-Methyl (1-dimethylcarbamoyl)-N-[(methylcarbamoyl)oxy] thioformamidate (oxamil, **9**), which shows some structural relationship to aldicarb used as an insecticide, is the most important representative of the carbamate type nematocides.



9

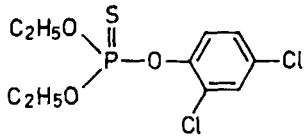
This compound has unique systematic properties and is translocated both upwards and downwards in plants. Applied to the soil surface it has been shown to control soil-born nematodes. In addition, it has an insecticidal effect.

Its excellent pesticidal properties are vitiated by its high toxicity to mammals. Its acute oral LD_{50} for rats is 5.4 mg/kg. In chronic oral toxicity tests the no-effect level for rats was found to be 50 ppm. Atropine sulfate appeared to be an antidote of oxamil, but pyridine-2-aldoxime methiodide (PAM), a well-known antidote to cholinesterase inhibitors, does not appear to be effective in this respect.

O-(2,4-Dichlorophenyl)-O,O-diethyl phosphorothioate (dichlofenthion, **10**) was the first phosphoric acid ester to be introduced as a nematocide. It is applied by spraying and subsequent incorporation into the soil. It has a low solubility and, because of this, its distribution in the soil is slow (Manzelli, 1955; Manzelli and Young, 1957).

O,O-Diethyl-O-[4-(methylsulfonyl)phenyl] phosphorothioate (fensulfothion, **11**), used also as insecticide, exhibits a potent nematocidal action against almost all the phytopathogenic nematodes (Schegk and Schrader, 1958). Its solubility in water is somewhat better than that of dichlofenthion. It is very toxic, its oral LD_{50} for female rats being 2.2 mg/kg, and for male rats 10.5 mg/kg.

The water solubility of O,O-diethyl-O-2-pyrazinyl phosphorothioate (zinophos, **12**) is greater than that of both phosphoric acid esters discussed above. Its 0.1% saturated aqueous solution is readily distributed in the soil. It exerts its action by direct contact with the nematodes at the surface of the plants or in the plant tissues (Motzinger, 1961).



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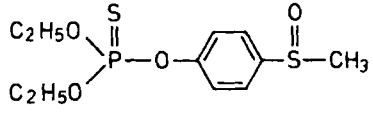

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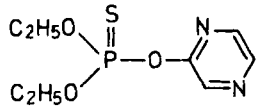
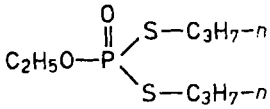


12

While the structures of the organophosphorus nematocides discussed so far are largely similar to the general structural scheme of the derivatives known as insecticides, O-ethyl-S,S-dipropyl phosphorodithioate (prophos, **13**) takes a special place within the group because of its S,S-dithioate structure.

Prophos is prepared by the reaction of ethyl phosphorodichloridate with *n*-propylmercaptan in aqueous sodium hydroxide.



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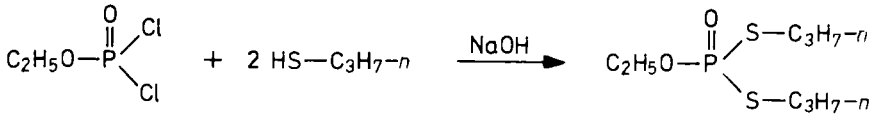
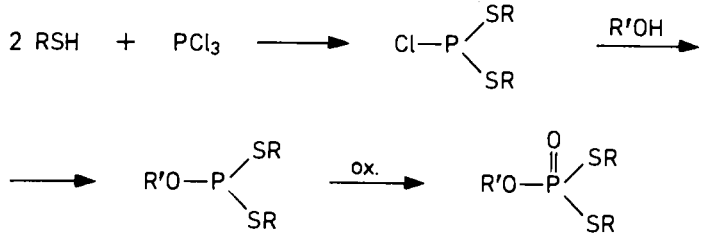


13

Compounds of this type may be prepared also by reaction of the respective mercaptan with phosphorus trichloride, treating the resulting dialkyl phosphorochloridothioite with alcohol and subsequent oxidation with an oxidant such as hydrogen peroxide (Wilson, 1966).

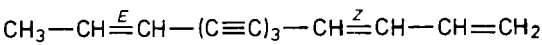


Prophos is a broad-spectrum nematocide and insecticide, and is used mainly for resistant and nonresistant corn rootworm control. It is used as a liquid spray or as formulations containing solid vehicles or extenders. Its half-life in the soil varies between 3 and 12 days depending on the application rate, formulation, type of soil and other factors.

Its acute oral LD_{50} for male rats is 61 mg/kg.

In their search for nematocidal substances in higher plants, Munakata and coworkers (Munakata *et al.*, 1959; Kogiso *et al.*, 1976a; 1976b; Munakata, 1978) isolated two nematocidal polyacetylenes, **(14)** and **(15)** from flowers of *Carthamus tinctorius* and two nematocidal diterpenes having an *ortho*-ester group, odoracin **(16)** and odoratrin **(17)** from the roots of *Daphne odorata*.

The problem of nematode control is far from being solved. Intensive exploitation of the soil and monoculture intensify nematode contamination. In view of the large amounts of chemicals to be used the traditional methods of nematode control are expensive. This necessitates the search for alternative methods and chemicals. The results of the Japanese scientists in connection with plant derived nematocides may represent one of the hopeful new approaches.



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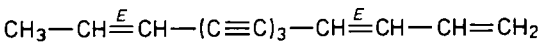

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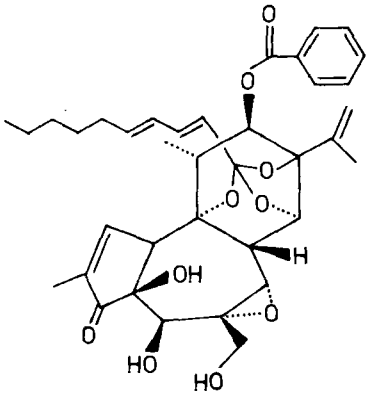

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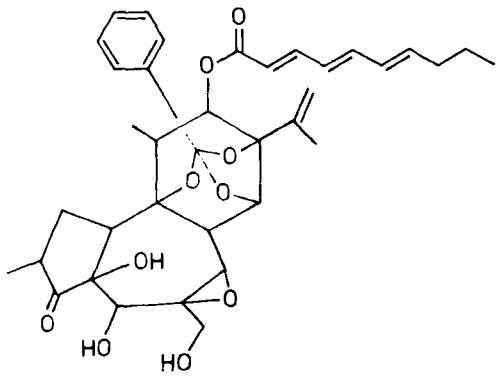

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4. Rodenticides

For many centuries the eradication of rodents has been a grave problem to humanity. In addition to the hygienic aspects, it was important for stock-protection, while exterminating them from crops is one of the tasks of plant protection.

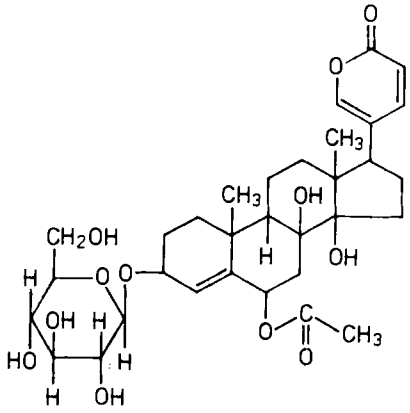
Initially, poisons of vegetable origin and inorganic compounds with toxic properties were used to kill rodents. These active substances were added to ground cereals, or possibly to unground seeds, as the basic substance of the bait. With a few exceptions, these active substances were very strong and general poisons, having a direct toxic action, not only on rodents, but also on useful game, domestic animals, birds and humans. In addition they are dangerous to life *via* the food chain. Selective killing of rodents could only be approached by placing the bait in the appropriate place.

Of the plant poisons, scilliroside, a glucoside of red squill *(Urginea maritima)*, a plant of the family of the Liliaceae, and strychnine, an alkaloid extracted from the seeds of *Strychnos nux vomica* and a number of other species of the family of the Loganiaceae, were initially used for the eradication of rodents. Both are very strong poisons, but while strychnine is a general poison, scilliroside exerts specific action on rats and mice. The acute oral LD_{50} of the latter for rats is 0.4–0.7 mg/kg, while other mammals are not killed by doses up to 16 mg/kg and birds not even by doses as high as 400 mg/kg. Either the dried powder or an extract of red squill was used, mixed with the bait. Scilliroside is a yellow crystalline substance insoluble in water. Its very complex structure **(1)** was elucidated by Stoll *et al.* (1943).

Strychnine **(2)** has a very bitter taste (Woodward *et al.*, 1954). Its oral LD_{50} for rats is 5 mg/kg, but it is a general poison. Its concentration in the bait is 0.25–1%. It may be used only with great caution, by personnel specially trained for the extermination of rodents.

Strychnine enhances stimulus transfer in the spinal marrow resulting in characteristic spasms. It has a characteristic stimulating effect on the respiratory and vascular motor centres, as well as on the cerebral cortex.

Fluoroacetate **(3)**, the sodium salt of monofluoroacetic acid, is also a substance of vegetable origin, reported to poison sheep and cattle repeatedly. It is the toxic substance of a South African plant called "gifblaar" *(Dichapetalum cymosum)* and of the Australian plant *Acacia georginae* (Marais, 1944). The compound is readily soluble in water and is very toxic. Its acute oral LD_{50} for rats is 0.2–2 mg/kg. The compound is converted *via* the citrate cycle into fluorocitrate and this blocks the citrate cycle.



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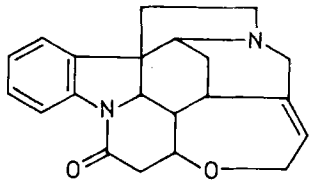

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The amide of fluoroacetate, fluoroacetamide **(4)** is a rodenticide with similar properties (Chapman and Phillips, 1955). Its toxicity to mammals is somewhat lower than that of sodium fluoroacetate, and it is probably safer to handle.

Of the inorganic compounds, not only the compounds of arsenic (As_2O_3, Na_3AsO_3) and phosphorus, but in particular barium carbonate ($BaCO_3$) and thallium sulfate (Tl_2SO_4) were noted for their more specific rodenticidal action. From a hygienic point of view they have the advantage of inducing rodents to search for water, thus they leave their abode and are killed in the open field. Death generally occurs on the second or third day. The concentration of the active substance in the bait is 2–3%, and the minimal lethal dose is 25 mg/kg. Today, these persistent poisons are used only in exceptional cases, under expert supervision, for the extermination of rodents highly resistant to modern rodenticides (Bean and Hudson, 1976).

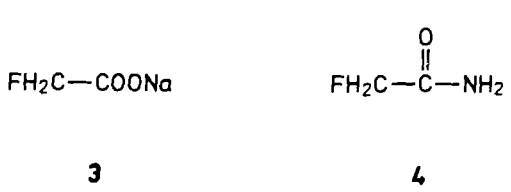
Classic exterminators of field rodents are zinc phosphide (Zn_3P_2) and calcium phosphide (Ca_3P_2), dark grey powders with the smell of rotting fish. These compounds are insoluble in water but, by the action of water, hydrogen phosphide, phosphine (H_3P), is formed, and this exerts the toxic action in the stomachs of rodents (Chefurka *et al.*, 1976).

Fumigants containing potassium nitrate, sulfur, charcoal powder and sawdust should be mentioned. These exterminate field rodents in their burrows by the evolution of carbon monoxide and sulfur dioxide. In a similar way, carbon disulfide kills by this vapour phase effect.

In addition to inorganic rodenticides, active organic substances showing a certain selectivity began to gain ground steadily.

A rodenticide mainly effective against field rodents is crimidine **(5)**, 2-chloro-4-dimethylamino-6-methylpyrimidine, which is prepared by chlorination of the condensation product of acetoacetic ethyl ester and urea, and subsequent reaction of the intermediate formed with dimethyl amine. The inactive isomer of the main product, 4-chloro-2-dimethylamino-6-methylpyrimidine, is formed in an amount

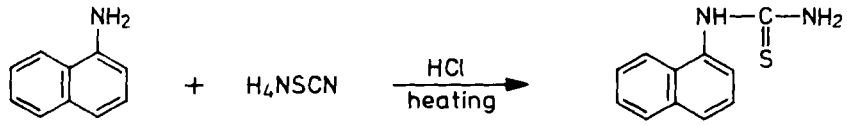
of about 20%. Crimidine is insoluble in water, its oral LD_{50} for rats is 1.2–5 mg/kg. The compound is toxic also to humans and wildlife but, generally, no secondary poisoning occurs, because the active substance rapidly decomposes in the bodies of dead animals (Dubois *et al.*, 1948).



3 4 5

Owing to its selectivity, ANTU (1-napthylthiourea **8**), the most favourable derivative of phenyl thioureas because of its toxic properties and its lack of taste, has been used over a longer period (Richter, 1945). ANTU is prepared by the interaction of α-naphthylamine (**6**) and ammonium thiocyanate (**7**). The acute oral toxic dose is 6–8 mg/kg for rats. More sensitive to the compound than other rodents is the Norway rat *(Rattus norvegicus)*. For humans and useful animals ANTU is relatively nontoxic. By repeated administration of sublethal doses over a longer period animals may tolerate 5–10 times the lethal dose. Thus resistance is rapidly developed. It causes increased permeability of lung capillaries, resulting in pleural effusion and death from drowing pulmonary oedema.

Its usual concentration in the bait is 1–3%.



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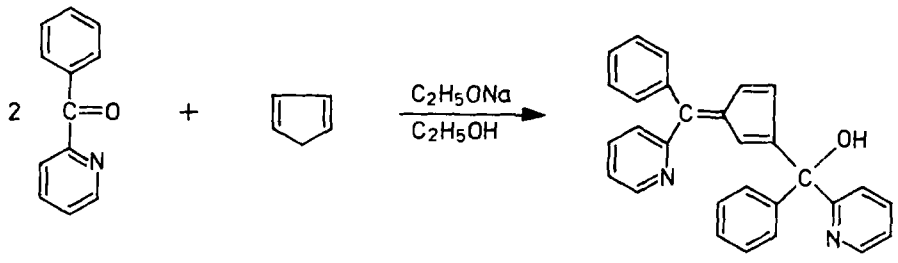
5-(α-Hydroxy-α-2-pyridylbenzyl)-7-(α-pyridylbenzylidene)-bicyclo[2,2,1]hept-5-ene-2,3-dicarboxymide, norbormide (**12**), is a rodenticide of excellent selective action. Its synthesis starts from 2-benzoylpyridine (**9**) and cyclopentadiene (**10**). In a medium of ethyl alcohol and in the presence of sodium ethylate, (**9**) and (**10**) yield a mixture of 40% *cis*- and 60% *trans*-fulvenyl carbinol (**11**). The reaction of this mixture with maleic anhydride gives, by diene synthesis, the stereoisomeric mixture of norbormide (**12**) (Roszkowski *et al.*, 1964, Mohrbacker *et al.*, 1966).

Norbormide is a quick-acting poison. It is particularly effective against Norway rats for which the lethal dose is 11.5 mg/kg. Its toxicity to other rodents is low, and it is only slightly toxic to other animals. It is used mainly when safety is one of the principal requirements during rat extermination.

Phosacetim, O,O-bis(4-chlorophenyl) N-acetimidoyl phosphoramidothioate (**13**), a very selective rodenticide, was found among the cholinesterase-inhibiting phosphoric acid esters. It is toxic mainly to vole, for which the lethal dose is 1.0 mg/kg. It is much less toxic to domestic animals and to beneficial wildlife. The active



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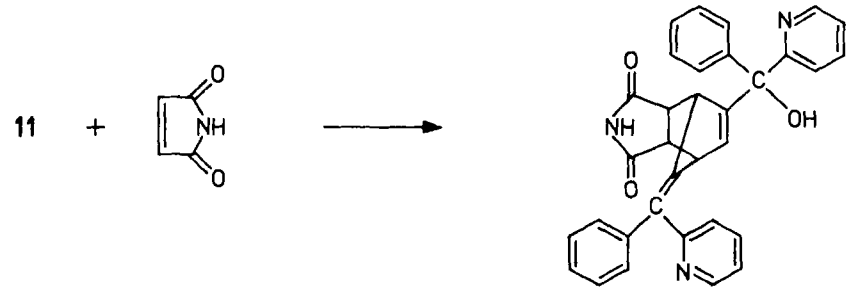

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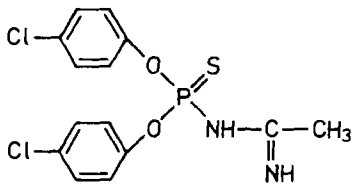
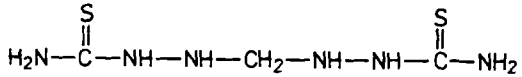
substance is inhibiting cholinesterase *in vitro*, but *in vivo* it is slowly activated. Its use as a rodenticide is based on this property (Dubois *et al.*, 1967).



13

A very quick-acting rodenticide, particularly effective against rats, is 1,1'-methylenebisthiosemicarbazide (**14**). This compound is obtained by the reaction of carbazide with formaldehyde and marketed under the trade name Kayanex®.



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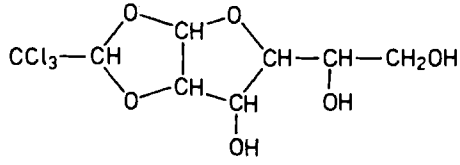
Its acute oral LD_{50} is 25–32 mg/kg for Norway rats. An efficient antidote is vitamin B_6 (Tokumitsu and Oguchi, 1973).

Alphachloralose (**15**), (*R*)-1,2-O-(2,2,2-trichloroethylidene)-α-D-glucofuranose, a narcotic which has been used since a long time against harmful birds, can also be

used against mice (Cornwell and Bull, 1967). In small mammals it slows down the metabolism and lowers the body temperature to a fatal extent. For larger animals, e.g. for rats, it is inefficient. It is rapidly metabolised and hence noncumulative. It is prepared by the reaction of trichloroacetaldehyde and glucose.



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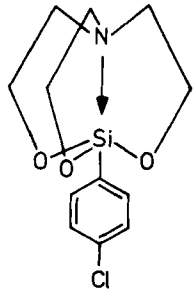
Another single-dose rodenticide is 1-(4-chlorophenyl)silatran (**16**) (Breiter *et al.*, 1970). For Norway rats the acute oral LD_{50} is 1–4 mg/kg. It is rapidly (about 3 days) detoxified by hydrolysis, so there is little hazard of secondary poisoning.



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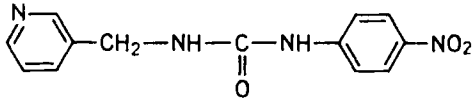
A species selective single-dose rodenticide is pyriminyl, N-3-pyridylmethyl N'-(*p*-nitrophenyl)urea (RH-787, **17**), which is the most effective of a series of compounds of similar composition. It is a very potent broad-spectrum rodenticide. It is toxic mainly to the members of the family *Murianae*, but it is also effective against *Cricetinae* and *Microtinae* spp. (Peardon, 1974, 1978).



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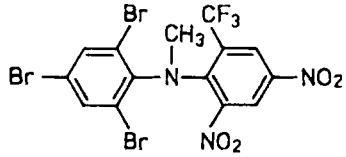
Pyriminyl has a selective action against rodents, its toxicity to domestic and useful animals is minimal, only cats being more sensitive. There is no danger of secondary poisoning. Its LD_{50} for rats is 4.7 mg/kg, for chickens 710 mg/kg, for pigeons 1780 mg/kg and for dogs 500 mg/kg.

It is also very effective against rodents resistant to anticoagulant rodenticides (Gratz, 1973). Its action is relatively slow, but the animal dies without pain 6–8

hours after the uptake of a lethal dose. Development of bait shyness has not been observed (Rowe *et al.*, 1978).

Elucidation of the mode of action of RH-787 is still in progress. The action seems to be effected by the formation of a toxic metabolite, which could be a competitive antagonist of nicotinamide in the synthesis of the coenzyme NAD and its phosphate, NADP. Blocking of methaemoglobin has also been observed, resulting in internal haemorrhage. Other symptoms are paralysis of the hind legs and death after respiratory stress. Its antidote is vitamin PP, nicotinamide (Prevot, 1975).

A rodenticide recently developed is EL-614, 4,6-dinitro-N-methyl-N-(2,4,6-tribromophenyl)-α,α,α-trifluoro-*o*-toluidine (**18**).

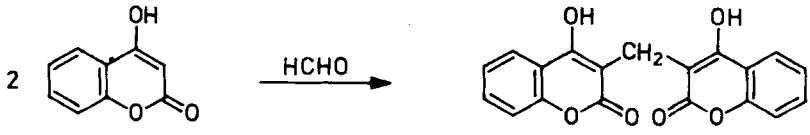


18

It is a specific nonanticoagulant rodenticide, acceptable to rodents without prebaiting. Its acute oral toxicity is 15 mg/kg for rats, and 20 mg/kg for mice. Experiments are still carried out (Dreikorn *et al.*, 1979).

The discovery of rodenticides with an anticoagulant effect opened a new era in the extermination of rodents. In the quantities applied, these active substances are generally nonhazardous to other animals and humans. Their subchronic toxicity is much higher than their acute toxicity. Thus, death occurs only after repeated uptake of small doses, which results in rodent extermination with a safer efficiency even in large areas. Since rodents develop bait shyness to pesticides which are generally of a disagreeable taste, dying occurs rapidly upon acute poisoning, but if the dose is not lethal on the first bite, death does not occur.

The first anticoagulant rodenticide was dicoumarin (**19**). Its anticoagulant effect was first observed on cattle. Coumarin has an odour reminiscent of hay. When mown sweet clover *(Melilotus albe)* becomes mouldy, dicoumarin is formed from coumarin, and cattle fed with such mouldy, sweet clover hay bleed to deat when injured because of reduced blood coagulation (Campbell and Link, 1941; Stahmann *et al.*, 1941). Dicoumarin, 3,3'-methylene-bis(4-hydroxycoumarin), is obtained by the condensation of 2 moles of 4-hydroxycoumarin (**20**) and 1 mole of formaldehyde in aqueous solution.



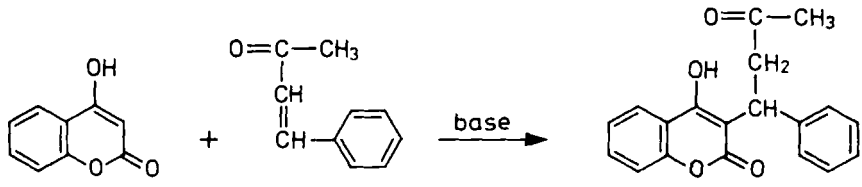
20 **19**

Dicoumarin is a white crystalline substance of slightly bitter taste. Its biological action is twofold. On the one hand, it is an antagonist of vitamin K, reducing the production of prothrombin in liver cells, which results in a decrease of blood coagulability. On the other hand, dicoumarin makes vein walls permeable, so that blood may penetrate the tissues of internal organs. As a result of this double action, animals bleed to death or die from cerebral haemorrhage.

Dicoumarin did not prove to be completely satisfactory for the extermination of rats, since vitamin K either ingested with natural nutrients or produced by the intestinal flora counterbalances the haemorrhagic state: e.g. rats tolerate as much as 2 mg of dicoumarin per day for more than 60 days (Overman *et al.*, 1942).

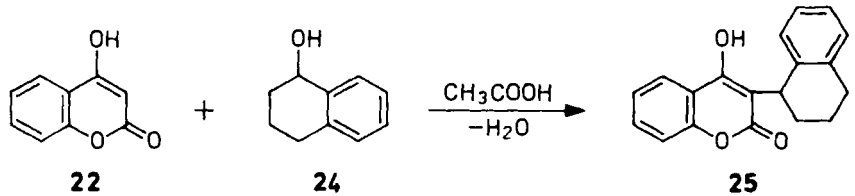
Other derivatives of dicoumarin were also tested but their action was even weaker than that of dicoumarin (Sullivan *et al.*, 1943). At the same time, derivatives of 4-hydroxycoumarin, substituted at the highly reactive position 3, showed considerable anticoagulant activity. The anticoagulant effect of the compound disappeared by substitution of the hydroxyl group in position 4 or by substituents in the benzene ring.

The best known and most widely used anticoagulant rodenticide is 3-(1-phenyl-2-acetylethyl)-4-hydroxycoumarin, (warfarin, **21**). It is synthesised from 4-hydroxycoumarin (**22**) by Michael addition with 1-phenyl-3-oxobutene-1 as the reagent (**23**) (Ikawa *et al.*, 1944).



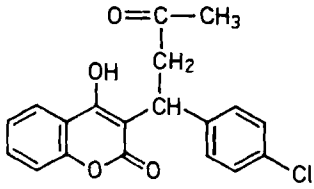
Warfarin is a stable, colourless, odourless and essentially tasteless compound. Owing to its enolic hydroxyl group in position 4, it has an acidic character and forms a water-soluble salt with sodium hydroxide or sodium carbonate. Its acute oral LD_{50} ranges from 58 to 323 mg/kg, depending on the rat species (Oettingen *et al.*, 1975).

Another type of reaction of 4-hydroxycoumarin is condensation with aryl-alkylcarbinols. Thus, condensation of 4-hydroxycoumarin with α-hydroxytetraline (**24**) in acetic acid solution yields 3-(1,2,3,4-tetrahydronaphthyl)-4-hydroxycoumarin (coumatetralyl, **25**) (Hermann and Hombrecher, 1962).



Several other warfarin homologues have been introduced as active substances, such as 3-(2-acetyl-1-*p*-chlorophenylethyl)-4-hydroxycoumarin (coumachlor, **26**), and 3-(2-acetyl-1-furylethyl)-4-hydroxycoumarin (coumafuryl, **27**). Substitution in the aryl radical or lengthening of the side-chain reduces the activity of warfarin homologues. By substitution of the phenyl ring in the side-chain at position 2, activity disappears completely.

The bait concentration of warfarin is 0.005% for Norway rats and 0.025–0.05% for black rats or mice. Coumarin preparations are often combined with sulfaquinoxaline (**28**). This bactericidal substance reduces the bacterial flora producing vitamin K in the intestine. The addition of oil to the bait serves a similar purpose. In this case vitamin K is extracted from the intestine.



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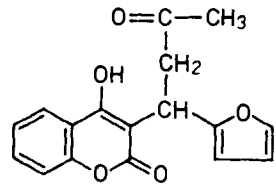

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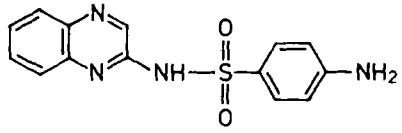
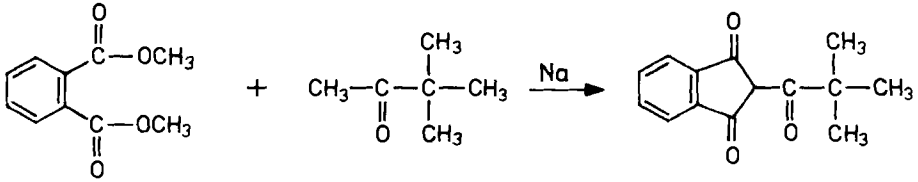


28

Indanedione derivatives, i.e. the derivatives of 2-acyl-1,3-indanedione, are also compounds with anticoagulant properties (Kabat *et al.*, 1944; Shapiro et al., 1960). Their synthesis starts from phthalic acid dimethylester (**29**). In the presence of metallic sodium this compound reacts with methyl-*t*-butyl ketone (pinacolon, **30**) to produce 2-pivaloylindane-1,3-dione (pindone, **31**).



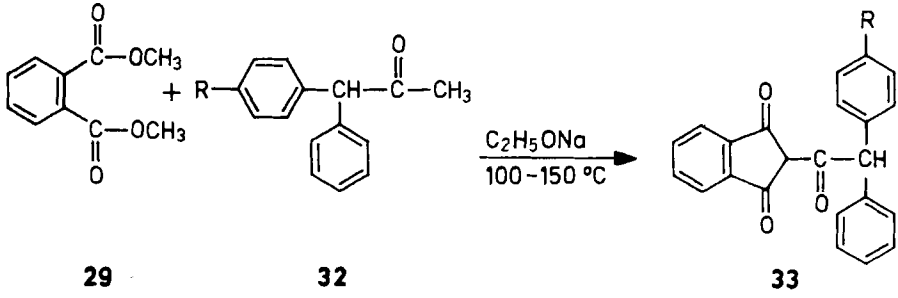
29 **30** **31**

Substances with particularly favourable properties can be obtained by the condensation of phthalic acid dimethylester with 1,1-diphenyl acetone or 1-(4-chlorophenyl)-1-phenyl acetone (**32**).

Diphacinone, 2-diphenylacetylindane-1,3-dione, and chlorophacinone, 2-(2-*p*-chlorophenyl-2-phenylacetyl)indane-1,3-dione (**33**) are compounds with a similar

action as warfarin, but their acute toxicity is higher. Chlorophacinone has a selective action on *Citellus* spp. Their bait concentration is 0.025%.

The effect of anticoagulant rodenticides can be recognised at an early stage in humans and domestic animals and can be counteracted by the administration of vitamin K.



29 32 33

R=H diphacinone
R=Cl chlorophacinone

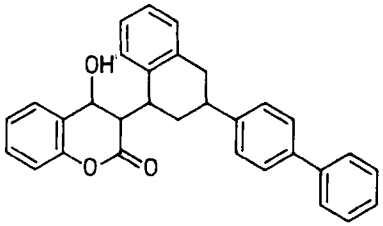
The wide application of anticoagulant rodenticides for more than 20 years has gradually increased the genetic resistance of rodents to these active substances. Warfarin resistance and cross-resistance to similar anticoagulants predominate in certain territories to such an extent that it impedes the practical use of these active substances (Gratz, 1973).

The rodenticidal efficacy of warfarin increases with admixture of calciferol in many anticoagulant-resistant rodent species. The mixture is semi-acute in action. 1–2 feeds are sufficient to cause death. This advantage, combined with excellent acceptability, is responsible for its success in the control of mice (Lund, 1974).

As a result of intensive research, derivatives of 4-hydroxycoumarin were found, which proved to be particularly efficient against rodents and resistant to anticoagulant rodenticides. Difenacoum (**34**) is a chronic rodenticide, which acts as a typical indirect blood anticoagulant similar to warfarin. However, it is effective against rats and mice, which are resistant to warfarin and other anticoagulant rodenticides, and is more toxic than warfarin to susceptible strains of these rodents. The chemical composition of difenacoum is 3-(3-*p*-biphenyl-1,2,3,4-tetrahydronaphth-1-yl)-4-hydroxycoumarin. Its acute oral LD_{50} is 1.8 mg/kg for Norway rats (Hadler *et al.*, 1975a,b).

An even more important derivative is 3-[3-(4'-bromobiphenyl-4-yl)-1,2,3,4-tetrahydronaphth-1-yl]-4-hydroxycoumarin (brodifacoum, **35**). This anticoagulant of exceptional potency is capable of control resistant rodents as well as several noncommensal species. Contrary to first generation anticoagulants, a bait concentration of only 50 mg/kg brodifacoum is adequate to give control even in a single feeding for most species. As with other anticoagulants, vitamin K_1 is an effective antidote. In contrast with other acute rodenticides, symptoms are delayed and no bait shyness is observed (Dubock and Kaukeinen, 1978). Its effectiveness

against Norway rats, roof rats and house mice is greater than that of any other compound ever tested (Kaukeinen, 1979, 1981, Apperson *et al.*, 1981) A most promising rodenticide is bromadiolone **(36)**, 3-[3-(4'-bromo-1,1'-biphenyl-4-yl)-3-hydroxy-1-phenylpropyl]-4-hydroxycoumarin. The compound was found to be a very potent and highly palatable anticoagulant, capable of achieving 100% mortality in Norway rats with one day feeding at a bait concentration of only 0.005% (Grand, 1976). Its acute oral LD_{50} for rats is 1.1 mg/kg. Thus even with a highly toxic active ingredient, the low concentration of this material in bait provides proper safety margins. However, special precaution must be taken around poultry because they are more sensitive to bromadiolone than to warfarin or to chlorophacinone (Marsh, 1977).



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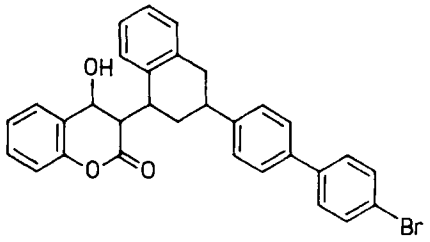

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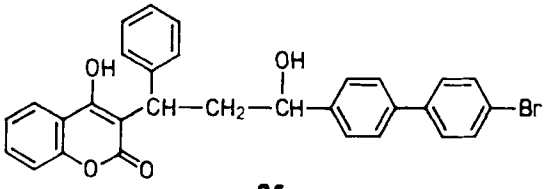

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5. Fungicides

5.1 Inorganic fungicides

5.1.1 Metal salts

The fungitoxic properties of various metal salts were first investigated by Wütrich (1892), and later by Wöber (1920). On the basis of papers published to 1950, Horsfall (1956) established the following order of fungitoxicity for metals: Ag > Hg > Cu > Cd > Ni > Pb > Co > Zn > Fe > Ca.

The compounds of copper and mercury attained importance in practical agriculture, while the salts of other metals were mostly the subjects of scientific research. Thus, for example, Farkas and Király (1960) found nickel(II)hexammine chloride to be effective against the black smut and red smut of wheat. The compound also kills the rust colonies when applied after infection, thus having a curative effect as well as increasing the yield.

According to the investigations of Fattinger (1950), the fungicidal action of copper is enhanced by cadmium, cobalt, nickel and zinc compounds in *Alternaria tenuis* and *Trichothecium roseum* cultures. Zinc sulfate ($ZnSO_4 \cdot 7H_2O$) was tried in place of copper sulfate; its effect however was inferior to that of the copper compound. Nevertheless, it is still used against rosette disease a physiological disease caused by zinc deficiency.

The use of copper compounds was first mentioned in the literature by Schulthuss (1761), who recommended treating seeds with a 1.5% aqueous copper sulfate solution for the protection of wheat against bunt. Fundamental research on seed treatment with copper compounds is linked with the name of Prévost (1807), the initiator of the extensive use of copper compounds, mainly for seed treatment, but later also for foliage spraying. Although the importance of copper compounds has decreased considerably since the discovery of fungicidal mercury compounds and, later, organic fungicides with systemic action, coppercontaining preparations in agriculture (Bordeaux mixture, copper oxychloride, copper combinations, etc.) are indispensable even today, being used primarily against late blight of tomato and potato, brown rot of citrus fruits and black pod of cacao.

Copper compounds are protective fungicides with a broad range of action and long residual activity. In the treatment of seeds they have proved most effective against bunt. They do not, however, give adequate protection against *Fusarium* diseases or covered smut and leaf stripe of barley. Their range of action as foliage fungicides includes mainly *Peronospora*, *Phytophthora* and *Cercospora*.

The first investigations elucidating the mode of action of copper sulfate and of copper salts in general were carried out by Bodnár and Terényi (1925, 1930) and Bodnár *et al.* (1927), who showed that during seed treatment the copper from the copper salt solution is adsorbed by the spores of *Tilletia* fungi, inhibiting

sporulation. The spores remained viable, however, and sporulated on a culture medium after the leaching of the adsorbed copper with dilute acid. On the other hand, complete inhibition of sporulation could be attained with copper(II)-tetrammine sulfate. They concluded from this that the copper(II)tetrammine ion penetrates the spore cell.

Bodnár and Terényi found that the anion concentration did not change during the experiment, while the pH value of the seed-dressing solution decreased; that is to say, the hydrogen ion concentration increased, and the concentration of the Cu(II) ions decreased correspondingly. Thus, the process taking place during treatment of the seeds is essentially one of ion-exchange.

Later investigations by Terényi (1931) showed that a potent seed dressing is formed when dilute, 0.2% copper sulfate solution reacts with 0.09% potassium mercury(II) chloride, inactive itself. He presumed that a complex compound is formed by the interaction of the two compounds which, like copper(II)tetrammine sulfate, was able to penetrate the fungal cell membrane.

The fungicidal effect of copper compounds can be attributed to the complex-forming reactions of the copper(II) ions that penetrate the cell with the thiol or amino groups of the fungus, resulting in nonspecific inhibition of enzymes and denaturation of proteins of the fungus (Somers, 1961).

Two factors are essential to the fungicidal action:

(a) the presence of soluble copper(II) ions and

(b) the penetration of the copper(II) compound into the cell.

Water-soluble copper compounds can also exert phytotoxic effects, hence the preference for some water-insoluble copper compounds. In the latter case the conditions of the fungitoxicity are realised partly by the successive solubilising effect of environmental factors, partly through concentrating in fungal spores of the small quantity solubilised. Somers (1963) used radioactive copper compounds to prove that copper can collect fungal spores to even one hundred times the original concentration of the solution, depending on the environment. In the formation of water-soluble copper(II) ions from basic copper compounds, carbon dioxide in the atmosphere or in rain water, possibly ammonium salts, excrements of fungal spores and even secretions of plant leaves play a role (Arman and Wain, 1963).

McCallan and Wilcoxon (1936) were the first to report that fungal spores can solubilise copper. In the bathing medium of *Neurospora sitophilus* spores they detected malic acid and certain amine acids which were able to dissolve copper even from dry deposits of Bordeaux mixture. In this case, complex compounds of the copper(II) ions are formed and, as shown already by the investigations of Bodnár and Terényi (1930), the fungicidal action of copper(II) complexes proved to be superior to that of copper(II) ions. Horsfall *et al.* (1937) made similar observations. This phenomenon can be explained by the much higher lipoid solubility of copper(II) complexes (Horsfall, 1957; Durkee, 1958) which allows them to penetrate the cell more easily. They dissociate in the cell, and copper(II) ions are liberated. Thus, complex-forming compounds seem to aid the transport of the

fungitoxic copper(II) ion to the site of action (El-Samadisy and Matolcsy, 1975). Unlike the other copper compounds applied, copper(I) oxide must first be oxidised.

Recently, the fungitoxic action of copper(II) ions has also been explained in terms of the inhibition of specific processes. Thus, it is thought possible that copper has an inhibiting effect on the pyruvate dehydrogenase system (Kaars Sijpesteijn, 1970), or on lipoic acid dehydrogenase (Wren and Massey, 1966; Casola *et al.*, 1966). This is important, because more authors have recently reported the development of resistance to copper compounds (Reddy and Apparao, 1970). When systematically sprayed with copper-containing fungicides, *Gloeosporium ampelophagum*, which causes anthranose in vine, developed over the course of time a 5 to 8-fold copper tolerance. Resistance has also been demonstrated *in vitro* by these authors.

The difference between the fungitoxic and the phytotoxic concentrations of copper is small; from the beginning, therefore, attention has been paid to the phytotoxicity of copper. Seed treatment with copper sulfate, generally rather effective against smut, often damages considerably the germinating ability of wheat, depending on the species, degree of ripeness and cracking of the seeds.

Water-soluble copper compounds are in any case unsuitable as foliage sprays, due to their strong scorching effect. The phytotoxity of water-insoluble copper compounds is weaker, and is to be expected when more soluble copper compounds are formed than needed. Phytotoxicity is caused by the copper(II) ions penetrating the plant cells. Fortunately, the translocation of copper(II) ions is moderate in plants, so that only local damage occurs and the whole plant is not killed.

Copper uptake and injury of the plant depend on many factors, mainly on the sensitivity of the plant to copper. Field-grown plants (potato, tomato, sugar beet, hop, etc.) are generally less sensitive, while fruit trees (peach, certain kinds of apple trees) and some of the shrubs do not tolerate preparations containing copper at all. The cuticle thickness of the leaf and fruit largely determines the extent of injury. Dulgerov (1968) found that copper sulfate will penetrate the leaves and fruit of apple to a depth of 200–300 microns, but will penetrate damaged fruit to a depth of 7000 microns. The mode and time of application of copper-containing preparations, as well as climatic conditions, affect the degree of injury. The phytotoxic property of copper compounds was previously utilised for weed control, and copper sulfate was used at one time as a selective herbicide for the control of annual weeds in cereals. Its algicidal action has been known for a long time, and it has even been used for the control of slugs.

Gudkova (1969) investigated the effect of copper-containing preparations on carbohydrate metabolism in potato leaves and tubers. In the leaves the quantity of monosaccharides did not change immediately after treatment, but increased after ten days. This increase continued during the whole period of development. Simultaneously, the quantity of disaccharides decreased. In the tubers, the quantity of soluble carbohydrates was considerably higher that in the controls. On the other hand, the starch content was sharply reduced.

Copper compounds are not hazardous to mammals. Large quantities in the body, however, can cause fatal gastroenteritis, for example. The acute oral LD_{50} of copper sulfate (the compound most generally used) for rats is 300 mg/kg. Rud *et al.* (1969) reported in detail the effect of small quantities (1.7 mg copper/kg) of copper-containing fungicides (copper sulfate, Bordeaux mixture, copper oxychloride) in a 70-day feeding test. The experimental animals showed certain changes in amino acid metabolism and 11-hydroxysteroid and ascorbic acid contect in the liver, but no essential changes were observed.

Most of the copper spray that gets into the soil is bound by the soil, so that it does not reach the secondary roots which, in any case, can take up only very small quantities of copper.

Bordeaux mixture in the soil at a concentration of $5 \cdot 10^{-5}$% stimulates the microbial degradation of original and added organic matter (Azad *et al.*, 1971). The effect of copper oxychloride on soil bacteria has been studied by Gil Diaz-Ordonez *et al.* (1970).

In the present-day application of copper-containing preparations, the aim is to utilise as much of the long residual life as is possible. Thus, they are recommended, for example, for the protection of vine against late *Peronospora* infection. However, it must be remembered that the residual copper content of must occasionally stimulates considerably the formation of hydrogen sulfide during fermentation (Eschenbruch and Kleynhans, 1974).

In the nineteenth century, the copper compound used in the largest amounts was copper sulfate ($CuSO_4 \cdot 5H_2O$). Owing to its high phytotoxicity it was used initially as a seed treatment for the control of bunt of wheat and as a selective herbicide for the control of annual weeds of cereals. It gained widespread use in agriculture, when, after several years of experimentation, Millardet (1885), a professor at Bordeaux University, published his finding that copper sulfate neutralised with milk of lime can also be used as a foliage spray, and that it gives excellent protection against *Plasmopara viticola*, the fungus causing a dangerous disease in vine.

The formation of Bordeaux mixture, i.e., the mechanism of the reaction of copper sulfate with calcium hydroxide, has been studied by several researchers. The simple neutralisation reaction initially assumed,

$$CuSO_4 + Ca(OH)_2 \rightarrow Cu(OH)_2 + CaSO_4$$

was rejected when it was established that when only 0.75 equivalents of calcium hydroxide are added to the copper sulfate solution, all of the copper is precipitated. The precipitate is tribasic copper sulfate of the composition $CuSO_4 \cdot 3Cu(OH)_2$ (Pickering, 1907; Wöber, 1919). However, experience has shown that for the preparation of an efficient Bordeaux mixture, even an equivalent quantity of hydroxide is insufficient, and calcium hydroxide must be added in excess. Gypsum of large mass and fine distribution, formed in this case as a by-product, adsorbs and stabilises the copper hydroxide (Martin, 1932; Martin *et al.*, 1942). The empirical formula of this precipitate is $Cu_4Ca_nSO_4(OH)_{6+2n}$. On the basis of X-ray

investigations Magdoff *et al.* (1958), demonstrated the existence of complex salts of different compositions, depending on the ratio of the two compounds:

$$CuCa_2SO_4(OH)_4 \cdot H_2O,\ Cu_2Ca_2SO_4(OH)_6 \cdot 3H_2O,\ Cu_4Ca_4SO_4(OH)_{14} \cdot 3H_2O,$$
$$Cu_5Ca_2SO_4(OH)_{12} \cdot H_2O.$$

When adequately and freshly prepared Bordeaux mixture is sprayed within a short time of preparation it has a high tenacity both on the leaves, and on the bark of trees. It cannot resist prolonged, heavy rain, however, so various substances which enhance its adhering power have been recommended as additives, such as calcium lignosulfate, sucrose, molasses, coconut milk, and, more recently nonionic surfactants (e.g. Triton X-100).

Bordeaux mixture, in spite of having solved several problems in plant protection at the end of the nineteenth century and at the beginning of the twentieth, has many disadvantageous properties. Its action is not uniform, but depends on the copper–calcium ratio and on the mode of preparation. Since it is corrosive it cannot be stored in iron or steel containers. Moreover it is incompatible with other pesticides, it scorches the more sensitive plants, and its preparation is elaborate. Thus its use is restricted. Finally, it must be used immediately after its preparation because it crystallises on standing, converting into calcium cuprite, so that its fungicidal action is considerably reduced (Burchfield and Schechtman, 1955).

To avoid the difficulties of preparation, several dry preparations have been put on the market, from which a spray can be simply prepared with water. A stable product of high activity that is less phytotoxic and is resistant to weather is formed by dehydrating the 10% aqueous suspension of copper sulfate and calcium hydroxide with a stream of hot air at 80–175°C (Hess *et al.*, 1968).

Copper(II) sulfate monohydrate ($CuSO_4 \cdot H_2O$) is used as a dust or as a component of dry Bordeaux mixture.

Copper(II) oxychloride came into use at the beginning of the century, and due to its very easy handling, economical preparation and relatively low price, is today the most widely used copper-containing fungicide. This compound, $3Cu(OH)_2 \cdot CuCl_2 \cdot H_2O$, is a green or bluish-green powder insoluble in water, and is prepared by the oxidation of copper(I) chloride solutions with air. It is generally used as a wettable powder, sometimes as pasty or liquid preparations. It is compatible with almost all pesticides. In some modern formulations it has been combined with copper strearate or oil (Toman *et al.*, 1967; Screenivasan, 1968).

The composition and action of basic copper(II) carbonate depend on its mode of preparation. This salt of composition, $Cu(OH)_2 \cdot CuCO_3$, is known in mineralogy as malachite. It is a green substance, practically insoluble in water. It dissolves in ammonium hydroxide, and was previously used for the treatment of vine against downy mildew (Gastine, 1889). Later, it was used for treating seeds, either alone or in combination with other (arsenic) compounds. It has found wide use, particularly in the USA. The blue compound of composition $2CuCO_3 \cdot Cu(OH)_2$, known by the name azurite, has a poorer fungicidal action.

The active substance of Burgundy mixture is also basic copper(II) carbonate. Owing to difficulties in the preparation of Bordeaux mixture, Masson (1887) recommended the use of soda instead of lime. The use of Burgundy mixture increased after the World War I. Its tenacity, however, is inferior to that of Bordeaux mixture and its phytotoxic effect greater.

The components of the so-called Cheshunt compound are copper sulfate and ammonium carbonate (Bewley, 1921). The aqueous solution contains copper(II)ammonium sulfate, forming basic sulfate after application. It has been used for seed treatment.

Copper(I) oxide (Cu_2O) is a reddish crystalline powder, practically insoluble in water. Its protectiveness against bunt depends on weather and other conditions, so it has not been widely used. It is not phytotoxic, so it was also used for a time as a spray against *Phytophtora* and *Peronospora* spp. Its acute oral LD_{50} for rats is 470 mg/kg (Horsfall, 1932).

Dust for seed treatment containing the active substances copper(I) and copper(II) arsenite has been used with good effect against bunt of wheat.

Copper(II)tetrammine sulfate ($Cu(NH_3)_4SO_4$) can be prepared from copper sulfate and ammonium hydroxide. A freshly prepared solution gave the best protection against bunt of wheat, but an excess of ammonium hydroxide considerably reduced its germinating power (Audoynaud, 1885).

In addition to those listed above, the use of other copper compounds as fungicides (copper nitrate, copper hydrazine sulfate, copper silicates, copper zeolites, etc.) has been recommended but without lasting success. In addition to inorganic copper compounds, several organic compounds of copper have been investigated, but only a few had an acceptable fungitoxic effect. These are discussed in the chapter on organic fungicides.

5.1.2 Sulfur and its inorganic compounds

The biocidal effect of sulfur has been known since antiquity. Homer tells how Odysseus disinfected his house by burning sulfur. Its agricultural application is linked with the name of Forsyth (1802), who recommended the use of sulfur against diseases of fruit trees caused by powdery mildew fungi. Its large-scale use began at the beginning of the twentieth century, and because it is cheap and not hazardous to the environment, it is still the fungicide used in the largest quantity.

Elemental sulfur is a protective fungicide with contact action. Its range of action involves primarily powdery mildew fungi, but it has a fungicidal effect also on fungi that cause scab. Sulfur has the favourable side effect of being an acaricide (Goodwin and Martin, 1928, 1929). It is due largely to this fact that in orchards and vineyards treated with sulfur, damage caused by mites was not considerable until the sixties. It can be used for most crops, with the exception of a few plants, to which it is phytotoxic, particularly above 30°C and in dry weather.

The mode of action of elemental sulfur has been investigated in great detail since it came into use. The first theories were based on the physical properties of sulfur.

Electricity generated upon contact of sulfur with the plant (Mangini, 1871) and the sun-ray collecting lens effect (Mach, 1879) were the first attempts to explain the fungitoxic effect of sulfur. Subsequently, attempts were made to clarify the role of the water-soluble compounds of sulfur, and in this period only Sempio (1932) was a proponent of the direct effect of sulfur.

Elemental sulfur is a hydrophobic substance, practically insoluble in water. It was formerly thought that sulfur could not permeate the fungal cells, but needed first be converted into a water-soluble form. Two possibilities were given: oxidation or reduction.

In air, sulfur is oxidised by the action of heat, light, oxygen and atmospheric humidity, and it was thought that the sulfur dioxide (Mach and Portele, 1884) or sulfur trioxide (Marcille, 1911) thus formed was the toxic agent. Young (1922) was of the opinion that acid compounds, primarily pentathionic acid ($H_2S_5O_6$), present in an aqueous suspension of sulfur, were the carriers of biocidal activity. However, these theories were soon disproved by the observation that the fungitoxic effect of these acid sulfur compounds is actually a pH effect, their salts not being fungitoxic (Parker-Rhodes, 1942; Wilcoxon and McCallan, 1930).

The reduction theory was developed simultaneously with the oxidation theory. Hydrogen sulfide is formed by yeast cells and leaf surfaces that are treated with sulfur (Polacci, 1875). Hydrogen sulfide is soluble in water. Its aqueous solution can permeate the cells, and it is thus toxic to fungi (McCallan and Wilcoxon, 1931; Horsfall, 1945). On the other hand, Eyre and Salmon (1916) found that hydrogen sulfide is not toxic to powdery mildews, against which elemental sulfur had mainly been used. Finally, Miller *et al.* (1953), using a modern radiotracer technique, showed that, depending on the fungus, colloidal sulfur is between 5 and 50 times more toxic to fungal spores than an equivalent quantity of hydrogen sulfide. Thus, hydrogen sulfide formed from elemental sulfur cannot be responsible for the fungitoxicity of sulfur.

The fungicidal effect of sulfur is thus a direct effect. The permeation of the hydrophobic sulfur into the fungal cells has been explained in several ways. In view of the fact that oxygen readily permeates the cell membrane and sulfur is next to oxygen in the periodic table, Horsfall (1956) logically assumed that the cell membrane could be permeable also to sulfur, although perhaps to a lesser extent. According to another theory, the permeation of lipophilic sulfur is increased by the lipoid matter in the spore membrane, and the different lipoid contents of the various fungus species affect their sensitivity to sulfur. This concept is supported also by the range of action of sulfur. Miller *et al.* (1953) showed that *Monilinia fructicola* is 62 times as sensitive to sulfur as *Stemphylium sarcinaeforme*, while the latter is rather more sensitive to water-soluble fungicides. Sulfur is very efficient against drought-resistent fungi, such as powdery mildew and rusts, with, presumably, a higher fat content, while it is not toxic to so-called water-born fungi such as *Peronospora* and *Botrytis* spp.

Several theories were also propounded on the action of sulfur within the fungal cell. Initially, enzymatic processes were suggested, in which sulfur reacts with

compounds in fungi containing —SH groups. Investigations showed that glutathione, present in all living organisms can reduce sulfur into hydrogen sulfide *in vitro* and *in vivo*. However, later works indicated the involvement of enzymatic processes, too, (McCallan and Wilcoxon, 1931), showing that SH-containing compounds such as glutathione and cysteine are only cofactors in the reduction of elemental sulfur (Ahlström *et al.*, 1944). The enzyme is a dehydrogenase in nature. Owens (1960) found that elemental sulfur interferes in acetate-citrate metabolism and inactivates the enzymes involved by the formation of free radicals. According to Ishimoto *et al.* (1957), sulfur reacts directly with cytochrome C_3 and is reduced to hydrogen sulfide. Martin (1957) found that sulfur inhibits the action of iron-containing enzymes such as catalase, peroxidase, cytochrome oxidase and cytochrome reductase. Tweedy and Turner (1966) proposed a scheme for the reduction of elemental sulfur by the cytochrome system. They found that sulfur interferes with nearly all metabolic pathways, and the metabolic condition of *conidia* of *Monilinia fructicola* appears to be catabolic rather than anabolic while reducing sulfur. DNA and RNA synthesis almost ceases, and the amounts of lipids, free fatty acids and amino acids decrease. Carbon dioxide formation is increased four-fold and oxygen uptake two-fold by the action of sulfur (Tweedy, 1969). Indeed, the fungicidal action of sulfur cannot be explained by a single scheme, because several chemical and biochemical processes participate.

The activity of the different allotropic forms of sulfur has also been investigated with respect to permeation. Feichtmeir (1949) demonstrated that amorphous sulfur is about three times as active as crystalline sulfur of comparable particle size.

Particle size plays an important role in the fungitoxicity of sulfur. It can be generally stated that the smaller the sulfur particles the higher the fungitoxicity (Wilcoxon and McCallan, 1931).

A particle size below 1 micron, however, proved to be disadvantageous for practical purposes. These small particles oxidise rapidly, and phytotoxicity increases while the duration of action decreases. In addition to particle size, adherence to plant surfaces and to the fungi also plays a role in the field efficiency of sulfur.

Elemental sulfur is used in three kinds of formulation in agricultural practice. In the beginning, it was used as a dust in plant protection. Sulfur ground to a particle size of 2–8 microns is most suitable for the preparation of sulfur-containing dusts, its rough particles providing good adherence. To prevent coagulation and to increase the adhering power of the particles, mineral products, such as kaolin, bentonite, talc, or slacked lime powder, are used for dilution. The content of elemental sulfur in dusts generally varies between 50 and 90%.

Today elemental sulfur is generally used in the form of wettable powders in agriculture. These preparations contain finely ground sulfur with surfactants and auxiliary substances providing good floatability and adhering power. Sulfur being a hydrophobic substance, surfactants (wetting agents) must be added to render the elemental sulfur particles capable of suspension in water. Good floatability (stable suspension) depends mainly on the particle size. Suspensions stable over a long

period can be obtained only from sulfur with a particle size of about 1 micron. This is achieved by grinding the sulfur in colloidal mills (particle size 0.25–1.5 microns), or by chemical decomposition, in which hydrogen sulfide reacts with sulfur dioxide producing finely divided sulfur of particle size 0.01–0.1 micron. Sulfur containing wettable powders generally contain 70–80% elemental sulfur. The great advantage of these formulations is that a spray can be directly prepared from them with water, and, if needed, they are compatible with other substances (fungicides, insecticides). Recently, paste formulations have also been introduced.

In closed systems (greenhouses), elemental sulfur has also been used as a fumigant, vaporised over hot water conduits, or in hot air or with dry steam (Bergmann, 1852; Barker and Wallace, 1922).

In continously wet, hot weather elemental sulfur may cause injury, particularly to certain sulfur-sensitive plants. Phytotoxicity is manifested by a small or large reduction in photosynthesis and respiration, in the scorching of leaves and, in severe cases, in retarded foliage growth (Hoffman, 1933, 1934, 1936). Turell (1950) attributes phytotoxicity to a decrease in critical temperature and to the absorption of sun rays (lens effect). In lemon cultures, damage due to sulfur which would otherwise occur only at higher temperatures has been observed at lower temperatures. However, the true reason for its phytotoxicity is most probably the fact that sulfur penetrates the plant tissues and, as a hydrogen acceptor, detrimentally influences metabolic processes.

Polysulfide derivatives are also effective fungicides. These compounds are prepared from alkali or alkaline earth-metal sulfides by the addition of further sulfur. When acidified, polysulfides rapidly decompose, and the polysulfide-sulfur is liberated as elemental sulfur. Applied to plants, polysulfides form a coat of elemental sulfur on the surface of the plant, the thickness of this coat depending on the polysulfide-sulfur content of the spray. The fungitoxicity of polysulfides is greater than that of elemental sulfur (Foreman, 1910). Indeed, Martin and Salmon, (1932) concluded from their observations that, even in the case of elemental sulfur polysulfide-sulfur is the carrier of fungicidal action. Alkali promotes the fungicidal action of polysulfides (Goodwin and Salmon, 1927; Goodwin *et al.*, 1930).

Lime sulfur is the polysulfide that has been used since the earliest time. Its composition is $CaS \cdot S_x$, but it is not a homogeneous compound. The main components are calcium pentasulfide and tetrasulfide, but it also contains calcium thiosulfate and calcium sulfite. Originally lime sulfur was home made; today it is also manufactured industrially from a suspension of sulfur and calcium hydroxide, under pressure and in the absence of air. Upon concentration, lime sulfur rapidly decomposes with the formation of hydrogen sulfide. It is therefore marketed in the form of an aqueous solution of a density not less than 1.28. Its disadvantages are its very high corrosiveness and the high water content of the preparation, which increase transportation costs. Lime sulfur can be stabilised by the addition of sugar. A dry product, containing 70% $CaS \cdot S_x$ and 5% sulfur, has also been introduced under the name Dry Lime Sulfur.

Another disadvantage of lime sulfur is its incompatibility with several other pesticides due to its high reactivity. The introduction of modern sulfur-containing and synthetic organic fungicides has pushed the use of lime sulfur into the background.

Lime sulfur is a protective fungicide, mainly against powdery mildews, but it also has a thinning effect on red spider mite populations.

Barium polysulfide ($BaS \cdot S_x$) can easily be mixed with cold water. Its solid preparation contains BaS and elemental sulfur. Barium compounds are strong poisons; relevant precautionary measures must be observed, when they are handled.

Polysulfides, particularly lime sulfur, are more phytotoxic than elemental sulfur. Since they are alkaline they may attack the cell membrane of the plant and permeate the cells. Although this alkaline action is balanced by the acid sulfur compounds formed (H_2S, SO_2, $H_2S_5O_6$), these acid compounds are also aggressive and may penetrate the cells of the plant (Terényi, 1931; Berry, 1938). Injury by lime sulfur is manifested as scorching, the tips and edges of young leaves becoming brown and necrotic spots forming along the thicker veins of older leaves. Injury occurs mainly in the drying period of the spray. The addition of ferrous sulfate has been recommended to reduce the phytotoxicity of lime sulfur. Ferrous sulfate binds monosulfide-sulfur as an insoluble compound and precipitates polysulfide-sulfur as finely divided elemental sulfur.

Elemental sulfur does not cause problems from the point of view of environmental protection. It is not toxic to humans or animals, although it may cause some eye or skin irritation in sensitive humans. Sulfur entering the soil is oxidised to sulfuric acid by *Thyobacillus thyooxidans* (Foltzer, 1979).

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5.2 Elementorganic compounds

5.2.1 Mercury compounds with fungicidal properties

Mercury compounds, long used in medicine for their excellent bactericidal properties, have also been used against phytopathogenous fungi. Hiltner (1915) found mercuric chloride ($HgCl_2$) efficient against *Fusarium nivale*. The use of Hg_2Cl_2 was also tried, but this compound is efficient only after its oxidation to mercury(II) chloride. The inorganic compounds of mercury are little used in plant protection, because they are phytotoxic at efficient concentrations and inhibit germination when applied as seed-dressings. Moreover, they are highly toxic to warm-blooded organisms.

The organic compounds of mercury, however, proved to be excellent fungicides, and since the beginning of this century have been from the practical viewpoint, one of the most important preparations in the control of phytopathogenous fungi. Schrauth and Schoeller (1910) established that the microbiocidal activity of organic mercury compounds is much greater than that of inorganic mercury salts. Actually they were used only for seed-dressing, but were later also used as leaf fungicides. Their importance has now decreased considerably, mainly for reasons of environmental protection, and great efforts are being made to replace these active substances with compounds of similar efficiency but less harmful side-effects. Still, due to their excellent fungicidal properties, they remain indispensable for the dressing of seeds, provided that adequate safety measures are observed.

The general formula of organic mercury compounds is:

$$R—Hg—X,$$

where R is a hydrocarbon or substituted hydrocarbon and X is a dissociable atomic group originating from an inorganic or organic compound (e.g., acids, phenols,

amines, and thiols). Symmetric R_2Hg compounds have practically no fungicidal or bactericidal properties.

Organic mercury compounds are discussed in three main groups, according to the and volatility of which depend on the nature of the R and X radicals. The hydroxy compounds are usually fairly soluble in water. Volatility is important in the biological efficiency of organic mercury compounds, which can be easily reduced. The sensitivity to reducing agents differs among the single compounds, but each derivative can be reduced in two steps to elemental mercury.

Organic mercury compounds are discussed in three main groups, according to the nature of the hydrocarbon or substituted hydrocarbon radical.

Alkylmercury compounds

Organic mercury compounds containing an alkyl group with a low carbon atom number are classed in this group. The fungicidal effect of the derivatives decreases with increasing carbon atom number (Gassner, 1951), so that, in practice, only methyl- and ethylmercury compounds are important.

Several methods of preparation have been developed, among them the following:

(a) Alkyl halogenide or alkyl sulfate, reacts with mercury or sodium amalgam, yielding alkylmercury compounds. The reaction is catalysed by light. The dialkylmercury derivative formed can be converted with organic or inorganic mercury salts to the corresponding alkylmercury salts:

$$R_2Hg + HgX_2 \rightarrow 2RHgX$$

(Sneed and Maynard, 1922; Maynard, 1932).

(b) Alkylmercury compounds can be prepared by the reaction of mercury salts and metallorganic compounds. Owing to the rather cumbersome and costly preparation of dialkylmercury compounds, the industrial manufacture of alkylmercury compounds began only in the 1930s. Alkylmercury derivatives can be obtained from alkylmagnesium bromide in an ethereal medium with mercury bromide by the Grignard reaction (Slotta and Jacobi, 1929):

$$RMgBr + HgBr_2 \rightarrow RHgBr + MgBr_2$$

Using anhydrous tetrahydrofurane as solvent, the chloride derivatives, slightly soluble in ether, can also be prepared directly (Coates, 1960). Alkylation can also be undertaken with tetraethyl lead compounds (Whelen, 1959).

(c) According to Razuvaev *et al.* (1954), the mercury salts of organic acids can be decomposed to alkylmercury salts with hydrogen peroxide as follows:

$$Hg(OOCCH_3)_2 \rightarrow CH_3HgOOCCH_3 + CO_2$$

The presence of peracetic acid facilitates this reaction (Kloes *et al.*, 1963).

Alkylmercury chlorides are crystalline compounds, slightly soluble in water. Their melting point is relatively high, but they are highly volatile and toxic substances, and must be handled with extreme care. Their halogen content can be

separated with potassium or sodium hydroxide, and thus converting to the hydroxy compounds:

$$RHgCl + KOH \rightarrow RHgOH + KCl$$

Alkylmercury hydroxides proper can be used as fungicides, but as intermediate products can be converted with the corresponding acid to various alkylmercury derivatives.

Of the alkylmercury compounds, ethylmercury chloride (CH_3CH_2HgCl) has found the most widespread application. Owing to its excellent fungicidal properties it is used almost world-wide as a seed dressing. It is a white, crystalline compound, slightly soluble in water (1.5 mg/l). Its vapour tension is high, 0.1 Pa at 20°C, which further increases the danger of using this highly toxic active substance. Its acute oral LD_{50} in rats is 30 mg/kg. The methyl derivative is not used because its volatility is almost 30 times that of ethylmercury chloride.

Owing to its lower volatility, ethylmercury phosphate—$(C_2H_5Hg)_3PO_4$—is less hazardous than ethylmercury chloride. The compound is a white, crystalline substance, readily soluble in water; it is therefore mainly used as the active substance in wet seed dressings.

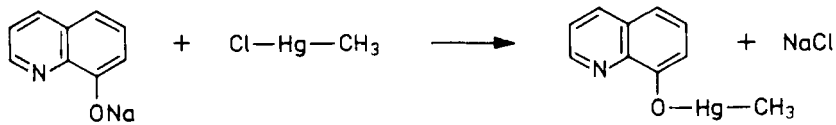
Methylmercury dicyandiamide or N-cyano-N'-(methylmercury)guanidine (**1**) is the active substance of Panogen® dressing. It is less volatile than methylmercury cyanide. It is sprayed on the seeds in an organic solvent solution. Part of the active substance evaporates together with the solvent, reaching the parts of the seeds not directly sprayed in the vapour phase, penetrating into the seed coat and the spores. Because of this and its high toxicity (acute oral $LD_{50} = 45$ mg/kg for rats), it can be used only in an air-tight dresser (Swennson, 1952).

The active substance is easily obtained from methylmercury hydroxide reacted with dicyandiamide:

$$CH_3HgOH + H_2NC(=NH)NHCN \xrightarrow[-H_2O]{} CH_3HgNHC(=NH)NHCN$$

1

Methylmercury 8-hydroxyquinolate (**2**) can be prepared from the sodium salt of 8-hidroxyquinoline, which itself has fungicide properties, and from methylmercury chloride (acute oral $LD_{50} = 72$ mg/kg for rats). It is recommended primarily for the dressing of cereal seeds, but is not widely used.



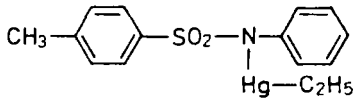
2

The seed-dressing effect of methylmercury sulfate (**3**) was first investigated by Melnikov and Rokitskaya (1937), and subsequently found widespread

$$(CH_3Hg)_2SO_4$$
3

application in Western Europe. It is readily soluble in water and is therefore very efficient both in solution and in the vapour phase. It is used primarily for the control of the fungal pests of cereals, beets, potatoes and bulbs.

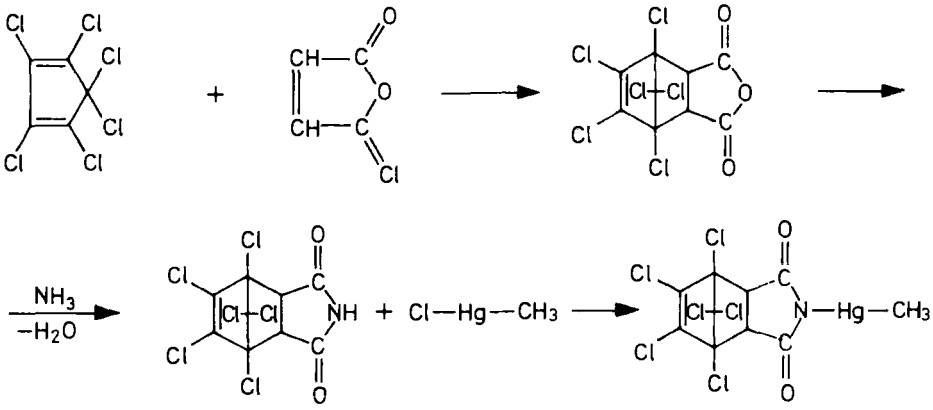
The N-(ethylmercury)-*p*-toluene-sulfonanilide (**4**) active substance is insoluble in water and has low volatility. It is used widely as a seed-dressing mainly in the USA.



4

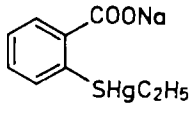
Of the alkylmercury compounds, N-alkylmercury-3,4,5,6,7,7-hexachloro-3,6-*endo*-methano-1,2,3,6-tetrahydrophthalimide derivatives can be used as foliage fungicides as well as seed-dressings (Kleiman, 1952). They are fungicides with eradicative and protective activity, particularly against powdery mildews and *Venturia* spp. The methyl (MEMMI, **5**) and ethyl derivatives are known. These compounds are readily soluble in water and are not volatile.

Their synthesis begins with hexachlorocyclopentadiene reacted with maleic acid. The adduct obtained is treated with ammonia, and the resulting imide is mixed in a solvent with methyl- or ethylmercury chloride:

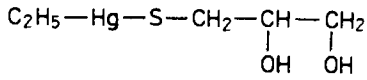


5

Of the alkylmercury compounds, ethylmercury thiosalicylate (**6**) and ethylmercury 2,3-dihydroxypropylmercaptide (**7**) should also be mentioned. These active substances are also used in practice, mainly in agriculture in the USA.



6



7

Alkoxyalkylmercury compounds

Organic mercury compounds in this group have been known since 1913 (Schoeller *et al.*, 1913). They are prepared by introducing ethylene gas into a slurry of mercury acetate in methanol:

$$CH_3OH + CH_2 = CH_2 + Hg(OOCCH_3)_2 \rightarrow CH_3OC_2H_4HgOOCCH_3 + CH_3COOH$$

Methoxyethylmercury acetate **(8)** is readily soluble in water and can be used by itself as a seed dressing, but is generally used as an intermediate product in the preparation of other active substances in this group.

From the aqueous solution of methoxyethylmercury acetate, methoxyethylmercury chloride **(9)**, a white, crystalline substance slightly soluble in water, is precipitated with sodium chloride:

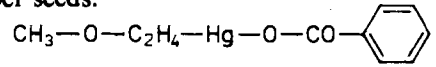
$$\underset{\mathbf{8}}{CH_3OC_2H_4HgOOCCH_3} + NaCl \rightarrow \underset{\mathbf{9}}{CH_3OC_2H_4HgCl} + CH_3COONa$$

Its water solubility is 5%; it is therefore used mainly as the active substance of wet seed treatment. The compound has a characteristic, unpleasant odour. Its fungicide spectrum is very wide, and it can be used as a dressing for the seeds of almost every cultivated plant. The compound is relatively stable in neutral and mildly alkaline media. In acid media it decomposes by ethylene evolution into mercury(II) chloride (Chatt, 1951). The peroral LD_{50} for rats is 50 mg/kg. In the formulation of the active substance, sodium hydrogen carbonate and sodium carbonate are added to promote dissolution, while a water soluble dye is added to mark the toxicity of the compound.

Methoxyethylmercury silicate **(10)** is almost insoluble in water. The oral toxicity for rats is $LD_{50} = 75$ mg/kg. Both its chemical and biological properties are similar to those of methoxyethylmercury chloride. It is used by itself or combined with other fungicides (e. g. hexachlorobenzene) for the seed treatment of cereals, maize, beet and legumes. It is prepared from an aqueous solution of methoxyethylmercury acetate with sodium silicate:

$$3CH_3OC_2H_4HgOOCCH_3 + Na_3HSiO_4 \rightarrow \underset{\mathbf{10}}{(CH_3OC_2H_4Hg)_3HSiO_4} + 3CH_3COONa$$

Nitzany (1966) described the most recent addition to this group, the active substance methoxyethylmercury benzoate **(11)**, and recommends it for the treatment of cucumber seeds.



11

Arylmercury compounds

The group of aromatic mercury compounds contains valuable active substances which can be used for seed treatment and as leaf fungicides, particularly against the fungal diseases of rice. Phenylmercury acetate, phenylmercury chloride and N-phenylmercury-*p*-toluenesulfonanilide have been used since 1953 in rice cultures, predominantly against rice blast caused by *Piricularia orysae*. These compounds are also very efficient against stem rot caused by *Helminthosporium sigmoideum*, and even against the fungus *Cochliobolus miyabeanus*.

Ishiyama (1969) found that the biological efficiency of phenylmercury compounds depends on the following order of activity of the R radical: phenyl > *o*- and *p*-tolyl > ethyl-, methoxyethyl-, dimethylphenyl > naphthyl.

The basic compound of this group is phenylmercury acetate **(12)**, one of the earnest known organic mercury compounds. Many processes have been developed for its preparation. Phenylmercury derivatives can be obtained from benzene reacted with mercury acetate at about 100°C. The reaction temperature can be reduced with catalysts, for example boron trifluoride (Dimroth, 1926; Kobe and Lueth, 1942).

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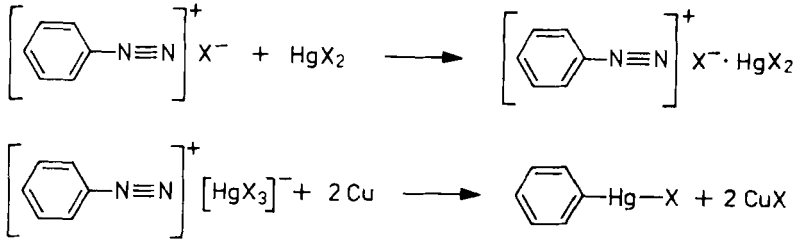
A very good yield of phenylmercury halogenides can be obtained by Nesmejanov synthesis (1929). Diazotised aniline is reacted with mercury(II) halogenides, and the double salt obtained is reduced with copper (Reutov, 1960):



The reaction proceeds in aqueous medium at 0°C, preferably with copper(I) chloride as catalyst.

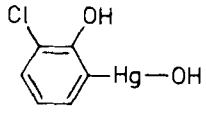
Phenylmercury acetate is a white crystalline compound, its solubility in water is 4.3 g/l, and its acute oral LD_{50} is 17–20 mg/kg for rats. It also has a dermal toxicity.

Phenylmercury acetate is excellent for seed treatment and, in addition, is an eradicant leaf fungicide against apple scab (prebloom period) and against the fungal diseases of rice (Frohberger, 1969).

Phenylmercury chloride (C_6H_5HgCl) can be precipitated from the aqueous solution of phenylmercury acetate by the addition of sodium chloride. The active substance can be also prepared directly from aniline by Nesmejanov synthesis. Being only slightly soluble in water, it is less phytotoxic than the acetate. It is used

for seed treatment and can also be used for foliage application, primarily against apple scab fungi. Acute oral LD_{50} = 40 mg/kg for rats.

The first organic mercury compound, 3-chloro-2-hydroxyphenylmercury hydroxide **(13)**, also belonging to this group of organic mercury compounds, is already of historical interest (Grewe, 1965a):



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The active substance is a white powder with a phenol-like odour, very slightly soluble in water. It is of moved efficiency against blight and other seed-borne fungal diseases, and does not inhibit the germination of cereals, even in long-term treatment. Moreover, it has been found efficient against various soil fungi and bacteria, for example, against cane gall of fruit trees and club root of cabbage. It has been marketed world-wide under name Uspulum (Riehm, 1913 and 1914).

Action of mercury compounds

The biological action of mercury compounds is characterised by their interaction with the thiol groups in the organism (Ulfvarson, 1969). Living organisms contain a great number of sulfhydryl compounds of vital importance; therefore no selective toxic process in the toxic effect of mercury compounds has been established. That fungi only rarely develop resistance to mercury compounds during long-term application can be explained by the general toxic properties of these compounds. According to Akiba and Ishii (1952), the thiol groups in certain bacteria which became resistant to mercury compounds were more numerous groups than those in nonresistant strains.

It is generally accepted that the basis of the biological activity of mercury compounds is their reaction with the thiol groups, but the biological action is rather more complicated. Frank (1955) showed that mercury compounds can influence the effect of enzymes which do not contain thiol groups. Mercury also reacts with the phosphoryl groups of the cell membranes (Bassow *et al.*, 1961) and with the amino and carboxyl groups of the enzymes (Lipscomb *et al.*, 1968). Webb (1966) lists more than 40 enzymes inhibited by mercury compounds.

There is also a difference between the modes of action of inorganic and organic mercury compounds. In general, the Hg^{2+} ion is a more efficient enzyme inhibitor than organic mercury compounds, but the latter are more potent fungicides because, owing to their lipoid solubility, they penetrate the fungal cells more rapidly. Therefore, in organic mercury compounds of type RHgX the nature of R will primarily determine the efficiency of the compound. According to Gassner (1951), the toxic effect decreases with increasing molecular weight of the R group; methylmercury salts are therefore the most efficient.

Of the organic mercury compounds, aryl mercury compounds have a different action and, because of their low phytotoxicity and loco-systemic effect, they can also be applied as foliage fungicides. The behaviour of phenylmercury compounds is different at the surface of the leaves and after their absorption, and in the latter case, their action differs further, depending on the fungus species (Ishiyama, 1969). This phenomenon was investigated mainly in conjunction with fungus species causing diseases in rice cultures. It has been established that only one hour after spraying, phenylmercury acetate, which is readily soluble in water, already inhibits the germination of spores only scarcely, and in the case of *Cochliobolus miyabeanus* its effect completely ceases after absorption. Phenylmercury chloride, slightly soluble in water, inhibits infection by fungi for 1–2 days, and loses its effect only after this period. At the same time, active substances absorbed have a protective effect against the growth of certain fungus micelia on unsprayed leaves or leaves developing after treatment. The absorption and translocation of phenylmercury compounds have already been verified by radioactive methods (Ross and Stewart, 1962; Okamoto and Saito, 1953).

It has been established in experiments investigating this phenomenon that phenylmercury compounds are degraded after their absorption and that the protective effect is actually indirect. By the action of these compounds, the quantity of amino acids (glutamic acid, alanine, etc.) decreases in the sap of the rice leaves, which increases the resistance of rice against rice blast.

Plants absorb mercury compounds accumulated in the soil by a different process. Methylmercury compounds are strongly absorbed and concentrated in various parts of the plant (Bache *et al.*, 1973; Lee, 1974).

The sensitivity of plants to mercury compounds are different. In general, the fungitoxic concentration does not harm the seeds and bulbs of the plants; the therapeutic index of mercury compounds for seed treatment is therefore satisfactory. Potato seed is an exception because it is susceptible to many species. However, only aryl mercury compounds are suitable for foliage application, and these only in the case of certain plants or in certain stages of development. Thus, phenylmercury acetate or chloride are not phytotoxic to apple trees in the prebloom period. Arylmercury compounds are not phytotoxic to the rice plant at all. Phytotoxicity is mainly caused primarily by mercury vapours formed on the reduction of mercury compounds (Hitchcock and Zimmermann, 1957). According to Lee *et al.* (1973), mercury compounds inhibit the biochemical reactions of the electron transport of photosynthesis, depending on the pH value and on the concentration.

Since the 1950s the role of mercury and its inorganic and organic compounds in environmental pollution has been the subject of intensive world-wide investigation (Wood, 1971, 1972; Vallee and Ulmer, 1972; Saha, 1972; Melnikov, 1974; Carter *et. al.*, 1979). Attention has been focused on the increasing number of cases of environmental pollution by mercury compounds. In Sweden, a mass extermination of birds was observed, and in Japan and in the U. S. A. human beings were affected by mercury poisoning (Kurland *et al.*, 1960). In the region of Minamata bay,

hundreds of persons became ill with the so-called Minamata disease, with symptoms of paralysis and irreversible or fatal neurological disorders. In 1965, a similar incident occurred along the Agano river. Up to 1972, more than 400 people had become ill, and 70 of these had died. Investigations proved that these outbreaks were undoubtedly caused by mercury and its compounds.

Mercury compounds can penetrate an organism through the skin by absorption, through the mouth and by respiration. The toxicological properties of these compounds in warm-blooded organisms differ in several aspects. Generally, there is no difference of order between the acute oral LD_{50} values. However, in the mode of uptake the quality of the R group is important because it determines the sorption properties of the compounds and, thereby, the distribution of the compounds in the organism, their metabolism and excretion (Lundgren *et. al.*, 1967). Alkylmercury compounds are the most harmful, behaving differently from the inorganic and other organic mercury compounds (Tejning, 1971). Their high volatility increases toxicity, but the most important factor is their slow metabolic rate in warm-blooded organism (Gage, 1964), which allows them to accumulate in organisms subject to the continuous consumption of very small quantities of this compound (Wright *et al.*, 1973a; 1973b). Toxic effects are manifested by characteristic neurotoxic symptoms: fatigue, headache, incoordination, tremor, auditory disturbances, sensitivity and other mental disturbances. Experiments showed that a mercury concentration of more than 8 mg/kg in brain tissue cannot safely be tolerated.

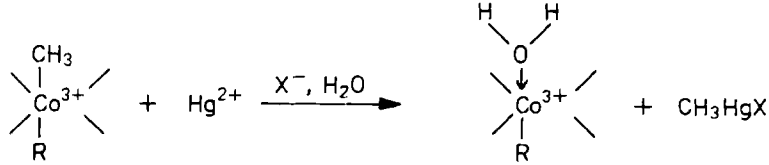
Methylmercury nitrate introduced through the mouth into the stomach appears in the bloodstream only 15 minutes after absorption, and attains its highest concentration after six hours. Of the absorbed quantity, 34% was excreted in 49 days in the feces and only 3% in the urine. The biological half-life of methylmercury compounds is about 70 days. As to the site of accumulation, half of the methylmercury compounds accumulate in the liver and 10% in the brain (Alberg *et al.*, 1969). Moreover, it has been established that the concentration of methylmercury in the red blood cells is ten times that in the blood plasma.

On the other hand, methoxyalkyl- and phenylmercury compounds are less stable, decomposing into mercury(II) salts and leaving the organism rapidly. A considerably larger amount, about one-third of the total quantity of mercury is excreted in urine, which also indicates a different metabolism. Miller *et al.*, (1960) found that metalmercury could not be detected in any of the organs of the experimental animals only a relatively short time after feeding with phenylmercury acetate.

The different behaviour of methylmercury compounds was partly accounted for by Westöö (1967), who found that the homogenates of liver are able to methylate inorganic mercury, and the discovery by Wood *et al.* (1968) that methylmercury salts are formed from inorganic mercury salts in bacteria. The finding that, independent of the source of the mercury, the most stable and at the same time the most toxic mercury compounds can be synthesised in the biosphere and can accumulate permanently in living organisms, was conclusive for limiting the use of mercury compounds and their total exclusion from agriculture.

Jensen and Jernelov (1969) proved that inorganic mercury is converted into methylmercury compounds by several anaerobic microorganisms in lake and river sludges. According to Beckert *et al.* (1974), under agricultural conditions the same process proceeds in the soil highly volatile methylmercury compounds are formed, and mercury circulation between atmosphere and soil is much quicker than has been assumed. Several research workers investigated this process, aiming to find the mechanism of methylation. Wood *et al.* (1968), using methanogenic bacteria in their experiments, ascribed the methylating role to methylcobalamine, which is an analogue of vitamin B-12 (methylcobalt-5,6-dimethylbenzimidazolyl-cobamide) and a well-known methyl donor of biological systems. With this compound, methylation can also be carried out by the pure chemical method under mild reducing conditions. According to Hill *et al.* (1970), this nonenzymatic reaction proceeds by the electrophilic attack by Hg^{2+} on methylcobalamine, rupturing the Co—C sigma bond. Law *et al.* (1971), and later De Simone *et al.* (1973), demonstrated that the CH_3 ion can actually be transferred to mercury. However, the nonenzymatic reaction occurs only in the presence of Hg^{2+}. The reduction of Hg^{2+} to Hg_2^{2+} or to Hg^0 results in the inhibition of catalysis.

The nonenzymatic process is described by Wood (1971) as follows:



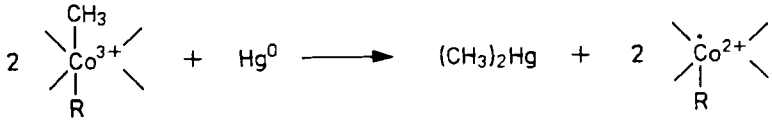
R = 5,6-dimethylbenzimidazole

According to Imura *et al.* (1971), dimethylmercury and methylmercury chloride are formed in the reaction in varying proportions, depending on the molar ratio of the reacting substances and on the reaction time. If the reaction mixture contains an equimolecular quantity of mercury(II) chloride or less, dimethylmercury is formed and converted into the monomethyl derivative by the addition of further amounts of mercury(I) chloride in a slightly acid medium.

$$2CH_3[Co] + HgCl_2 \rightarrow (CH_3)_2Hg$$

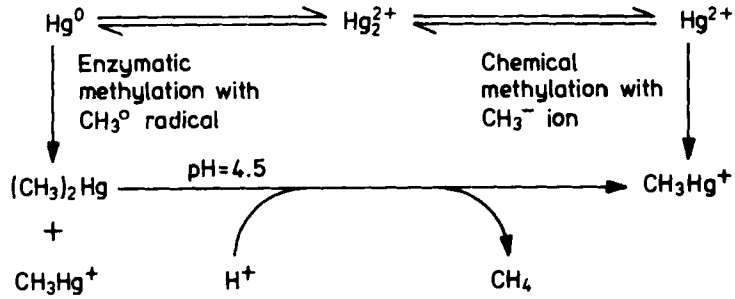
$$(CH_3)_2Hg + HgCl_2 \rightarrow 2CH_3HgCl$$

Each microorganism containing methylcobalamine ($CH_3[Co]$) is able to synthesise methylmercury compounds. Methylcobalamine is a known co-enzyme of both anaerobic and aerobic bacteria, thus being always present in the sludges of lakes and rivers in quantities dependent on the microorganism population. The higher the methylcobalamine concentration of the sediment, the higher is the rate of methylation of mercury. According to Wood (1971) the enzymatic reaction proceeds as follows:

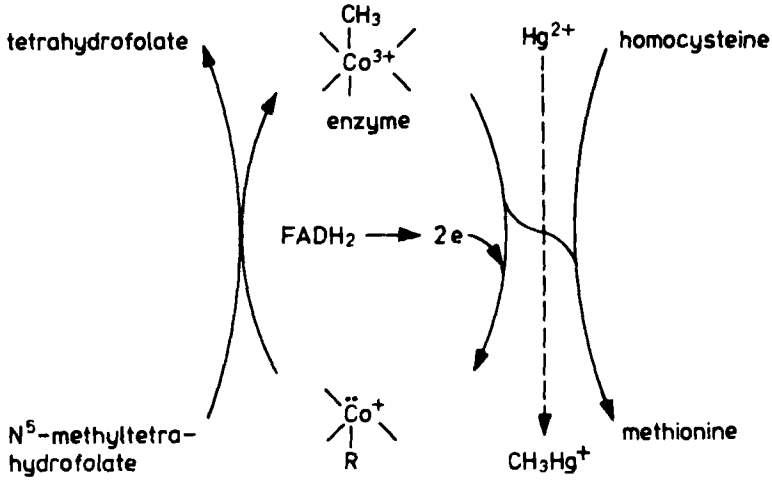


Under anaerobic conditions, Hg^{2+} is reduced to elemental mercury. The proportion of methlymercury compounds formed depends on the elemental mercury content of the sediments.

Wood (1971) proposes the following summary scheme for the methylation of mercury:



Methylcobalamine can be isolated from warm-blooded organisms as well as from microorganism, i. e., from calf liver and human blood plasma (Lindstrand, 1964). A study of methylation in the liver of warm-blooded organisms showed similar results. However, with S-adenosylmethionine, another known methyl donor of biological systems, the methylation of mercury does not take place. Similar results were obtained with N^5-methyltetrahydrofolate. These methyl donors give only carbonium ions (CH_3^+), with which no dimethylmercury can be formed, whereas methylcobalamine, which is bound in the N^5-methyltetrahydrofolate homocystein transmetylase enzyme, can, with ATP and H_2, give both carbanions (CH_3^-) and methyl radicals (CH_3°), with which methylmercury derivatives can be synthesised from inorganic mercury salts and elemental mercury (Brodie *et al.*, 1971). On the other hand, methylcobalamine can be regenerated by the other methyl donor. Brodie *et al.* (1970) proposed the following mechanism for the methylation of mercury in the liver (Wood, 1971):

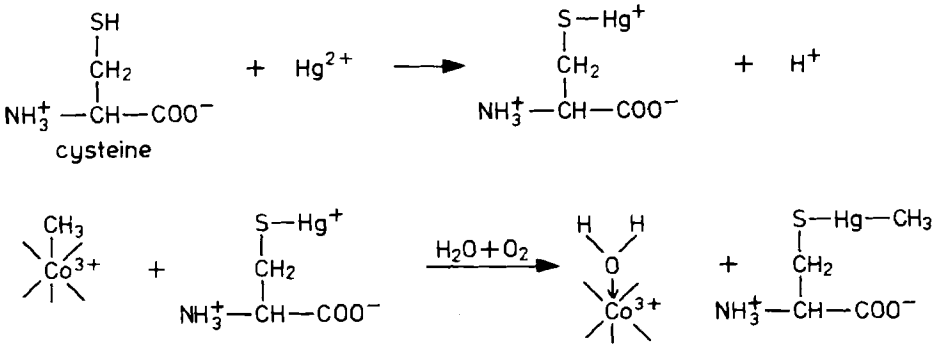


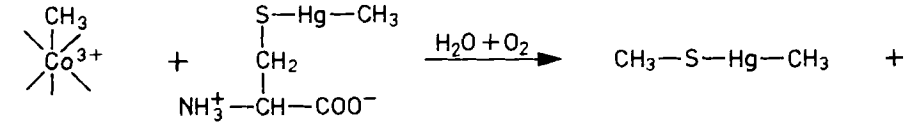
Landner (1971), in his investigations on *Neurospora crassa*, connects the methylation of mercury with the biosynthesis of methyl ions.

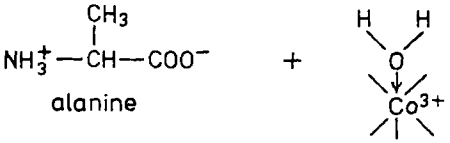
Finally, in whatever form mercury is introduced into the environment, it is converted into methylmercury compounds in both microorganism and warm-blooded organisms. Inorganic mercury salts and elemental mercury are methylated directly, while arylmercury and methoxyalkylmercury compounds are first reduced to mercury metal and subsequently methylated. Several bacteria, primarily *Pseudomonas* species, can absorb mercury compounds from the environment, reduce them and evaporate mercury metal (Suzuki *et al.*, 1968; Tonomura and Kanzaki, 1969).

Methylmercury compounds, already in concentrations as low as 0.1 μg/kg, decrease in sea diatoms *(Nitzschia delicatissima)* and during freshwater phytoplankton photosynthesis and growth (Harris *et al.*, 1970). Methylmercury continuously formed is ingested by fish. The mercury content of fish varies, depending on the species, weight and age of fish, on the degree of water contamination and on the kind of mercury compound. Pike may concentrate Hg up to 3000-fold. It has been established 85–90% of the mercury content of fish is methylmercury, which is excreted very slowly, having a biological half-life of several years. The immediate cause of the mass extermination of birds in Sweden was methylmercury, as methylmercury dicyandiamide is widely used in Sweden for seed treatment. The mercury level was very high in the birds killed, but also in many Swedish agricultural products, particularly in eggs (Borg *et al.*, 1966). Therefore, seed-dressings containing methlymercury compounds were prohibited in Sweden in 1966. Since then mercury content has decreased in birds and in eggs (Johnels, 1969).

The orginal cause of the, "Minamata disease" was the emptying into Minamata bay of the mercury catalyst from the nearly petrochemical plant. This waste product was converted into methylmercury compounds by the microorganisms growing in the sludge of the bay, and was ingested by the human organism *via* the consumption of seafood (Lofröth, 1969). The CH_3HgSCH_3 compound has been isolated from the shellfish of the bay (Fujiki, 1963). Wood (1971) proposed the following scheme for the formation of methylmercury thiomethyl:







A complex is formed with Hg^{2+} and cysteine. This complex is methylated by methylcobalamin in the presence of methionine in two steps, to yield methylmercury thiomethyl. Vonk and Kaars Sispesteijn (1973, 1974) found that in certain fungi the toxicity of mercury(II) chloride is greatly increased by methionine. According to these authors, this is due to the synthesis of CH_3SHg— or $(CH_3S)_2Hg$ compounds. Synthetic methylthiomercury compounds are actually more toxic because their stronger lyophilic character enables easier penetration of the cell membrane.

The mercury content of the oceans, which may be almost exclusively of natural origin, is a separate problem. According to Kishore and Guinn (1971) the increase in mercury contamination of the oceans since 1878 has been negligible, but at the same time the mercury content of fish in landlocked seas increased considerably in certain cases. Thus, for example, in fish of the Baltic Sea a remarkably high mercury content has been registered along the Swedish coast. This may be explained by the large amounts of mercury-containing fungicides used in Swedish forestry. It is not yet certain whether fish can synthesise methylmercury, but it is known that marine algae can accumulate up to one hundred times the mercury concentration of water, thereby providing a constant source of mercury for the fish food chain. Methylmercury compounds accumulated in human organisms at the end of the food chain are mainly excreted in the feces, and during the sewerage process are reconverted into volatile dimethylmercury by anaerobic bacteria.

Thus, mercury circulates rapidly in the ecosystem, and mercury compounds penetrating the soil reach humans and other warm-blooded organism *via* the food chain much more quickly than had been previously assumed. The danger to life caused by the very toxic methylmercury compounds has increased considerably.

Owing to the environmental dangers of mercury, its use in pesticides has been limited. In Japan, organic mercury compounds used in fungicides in rice culture were replaced by phosphoric acid esters in 1968. However, the quantity of mercury used in agriculture is responsible for only a small part of the mercury polluting the environment, and the overall problem of environmental pollution by mercury is not yet solved.

5.2.2 Organic tin compounds

Metal ions are generally toxic. However, while the toxicity of most of the element organic compounds (Hg-, As-compounds) is only modified and in some ways occasionally even decreased by the organic atom group, tin is biologically considerably more active in its organic compounds than in its inorganic, ionic form. Its biological activity increases, in general, with an increase in the number of the carbon–tin bonds. The study of organic tin compounds with fungicidal action has a history of about three decades. Van der Kerk and coworkers (1954, 1962, 1975) were the first to investigate the biological activity of these compounds. They found that certain organic tin compounds, particularly triorganotin compounds are excellent fungicidal active substances in practice. The general formula of these compounds is:

$$R_3SnX$$

where R is an identical or different alkyl or aryl group, and X is a halogen, hydroxy, carboxylate, oxygen or sulfur (the latter two substituted with another $—SnR_3$ group).

The fungitoxic action of compounds containing three organic (R) groups depends primarily on the nature of R. In the aliphatic series, toxicity is at the maximum with the tripropyl and tributyl derivatives, while in the case of aromatic compounds triphenyl tin compounds are most effective. Substitution in the phenyl radical usually reduces the toxic effect. The effect of X on biological activity is minimal, so the toxicity of the compounds is presumably due to the trialkyltin ion, or to undissociated R_3SnOH, which is easily formed by hydrolysis according to the following reaction:

$$R_3SnCl + HOH \rightarrow R_3SnOH + HCl$$

The main method of preparation of triorganotin compounds is by the reaction of tetraorganotin compounds with an inorganic salt of tetravalent tin. The reaction is most rapid with tin tetrachloride:

$$3R_4Sn + SnCl_4 \rightarrow 4R_3SnCl$$

Chlorides are intermediate products because the chlorine atom can be exchanged for several nucleophilic radicals. First, with alkali, the hydroxy compound:

$$R_3SnCl + KOH \rightarrow R_3SnOH + KCl$$

is obtained, and then, with acid, the appropriate derivative can be prepared.

The earliest general method for the preparation of tetraorganotin compounds is by the reaction of sodium tin with organic halogenides (Löwig, 1852):

$$4SnNa + 4RX \rightarrow 4NaX + 3Sn + R_4Sn$$

This method is not practical on an industrial scale, because three-quarters of the tin remains unconverted and in a form difficult to recover. The Grignard process, in

which a yield of 50–90% of the various organic tin compounds can be generally obtained, is industrially viable (Pope and Peachey, 1903):

$$SnX_4 + 4RMgX \rightarrow R_4Sn + 4MgX_2$$

In spite of the excellent yields this process is extremely labour-consuming and dangerous especially in large scale. It is used mainly for the preparation of phenyltin compounds. The alkylaluminium treatment is also an industrial process:

$$3SnX_4 + 4R_3Al \rightarrow 3R_4Sn + 4AlX_3$$

particularly where there is a production of alkylaluminium too. For the preparation of some derivatives it can adopt the Wurtz-reaction (Van der Kerk and Luijten, 1954)

$$4RX + SnX_4 + 8Na \rightarrow 8NaX + R_4Sn$$

The reaction proceeds with higher yield and under more simple conditions if the R_2SnX_2 compound is used as the original substance and one part of the tetraalkyltin compound is reacted with SnX_4 and recycled:

$$R_2SnX_2 + 2RX + 4Na \rightarrow R_4Sn + 4NaX$$
$$R_4Sn + SnX_4 \rightarrow 2R_2SnX_2$$

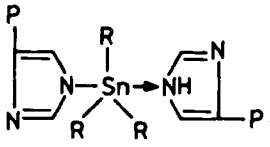
Organic tin compounds are contact fungicides. Their range of action is similar to that of copper compounds, but they are considerably more potent. However, their use for plant protection is limited by their phytotoxicity to more sensitive plants, and by their strong and lasting toxic action on warm-blooded organisms. Recent research has been concerned mainly with the reduction of both of these harmful effects.

Fungicide active substances, widely used for plant protection, belong to the triaryltin group. In these compounds, phytotoxicity depends on the anionic part. Chlorides and sulfates are strongly phytotoxic, due to the inorganic acids formed by hydrolysis. Most plants can tolerate the hydroxy and acetate derivatives (Hatzios and Penner, 1978). The most useful compounds considering phytotoxicity are triphenyltin sulfide $(C_6H_5)_3Sn—S—Sn(C_6H_5)_3$ and tripheniltin disulfide $(C_6H_5)_3Sn—S—S—Sn(C_6H_5)_3$, but these compounds have only a limited fungicidal action.

The general biological action of organic tin compounds is the inhibition of oxidative phosphorylation in the mitochondria, that is, the blocking of the incorporation of phosphoric acid into adenosine diphosphate in resulting in adenosine triphosphate of high energy content (Stockdale *et al.*, 1970).

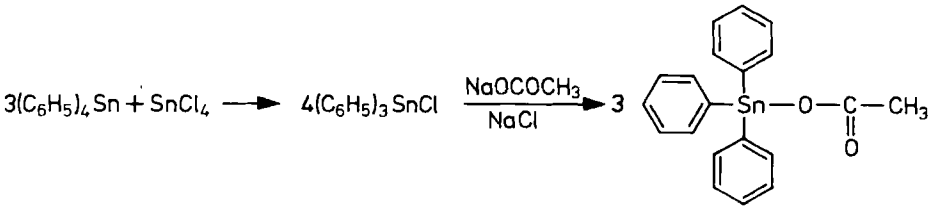
Aldridge and Cremer (1958) made a distinction between the biological action of diethyl- and triethyltin compounds, according to which diethyltin compounds also inhibit the functioning of alpha-keto acid oxidase. According to Rose (1971), the toxic and phytotoxic action of triorganotin compounds can be explained by the

specific activity by which these compounds are able to form compounds of coordination number 5 with proteins (P) containing 2 histidine rings:



Because of the properties mentioned, only two active substances of this group, triphenyltin acetate, and triphenyltin hydroxide formed from it by hydrolysis, are widely used for chemical plant protection at present. Concerning the mode of action, there is actually only one active substance, but the acetate is more useful for practical application.

Triphenyltin acetate (fentin acetate, **14**) is prepared according to the following scheme:



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This active substance, appearing as white, odourless crystals, was developed by Van der Kerk and Luijten (1954, 1956). It hydrolyses rapidly in aqueous medium to form triphenyltin hydroxide. Although of the organotin compounds it is the one best tolerated by plants, it is used mainly for the protection of field crops (sugar beet, potato). In certain cases, it causes phytotoxic damage, even in potatoes. This phytotoxicity can be reduced by combination with maneb, and a synergistic effect has even been detected between the two active substances (Härtel, 1964). The combination is marketed under the name Brestan®.

Fentin acetate is more effective against *Cercospora beticola* of sugar beet than any other fungicide. Moreover, it influences favourably the chlorophyll formation (Holz and Lange, 1962) and sugar formation in sugar beet (Härtel, 1964). It is used for the control of *Phytophtora infestans* of potato, against *Septoria* sp. on celery and against *Colletotrichum* on bean and pea.

Triphenyltin acetate has a relatively low persistency. Triphenyltin hydroxide, formed in the presence of water, is converted by light, ultraviolet light in particular by successive desarylation, into inorganic tin compounds. The diphenyl derivative is scarcely toxic, while the monophenyl compound is unstable (Kroeller, 1960). In the soil, about 25% of fentin acetate is broken down by microorganisms after 9 weeks but metabolites could not be identified (Suess and Eben 1973; Barnes *et al.*, 1973). It is moderately toxic to warm-blooded organisms, acute oral LD_{50} for rats

being 135 mg/kg. It does not accumulate in the organism, as proved with rats and guinea pigs and by a two-year feeding experiment on dogs. It has been shown by radiochemical methods that on oral application the active substance is excreted from the animal organism after 6–8 weeks. In experiments with guinea pigs a daily dosage of 5–20 mg/kg of fentin acetate reduced the number of leucocytes and lymphocytes in the blood. This phenomenon can be useful in testing for possible poison. No cases of poisonous effects on human beings have yet been reported (Klimmer, 1968). No carcinogenic effect has so far been observed in connection with organic tin compounds (Klimmer, 1964).

Metabolism of alkyltin compounds in liver microsomal monooxygenase systems and in mammals leads to the following sequence of detannylation (carbon–tin cleavage) reaction:

$$R_4Sn \rightarrow R_3SnX \rightarrow R_2SnX_2 \rightarrow RSnX_3 \rightarrow SnX_4$$

(X = anion) (Blair, 1975).

The first step of this detannylation reaction sequence yields derivatives of increased toxicity and potency as inhibitors to mitochondrial respiration, whereas each subsequent step reduces the potency and alters the type of biological activity (Thayer, 1974). In the microsomal monooxygenase metabolism of trialkyltin acetate, carbon hydroxylation is the major biological oxidation reaction (Fish *et al.*, 1976), whereas triphenyltin acetate is quite resistant to monooxygenase attack even though it undergoes detannylation in rats (Kimmel *et al.*, 1977).

According to Polster and Halacka (1972), triphenyltin compounds are very toxic to aquatic snails, small fish and zooplankton; the concentration of these compounds in water must therefore not exceed 3 μg/l. It is harmless to bees.

The range of action of triphenyltin hydroxide (fentin hydroxide, **15**)

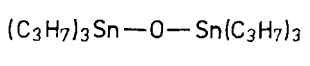
$$(C_6H_5)_3SnOH$$

15

is identical with that of triphenyltin acetate. Acute oral LD_{50} for rats is 511 mg/kg.

Of the organotin compounds in trial experiments, tripropyltin derivatives should be mentioned. These have been tested mainly for the prevention of pathogenous fungi *(Piricularia, Corticum)* and the bacterial diseases *(Xanthomonas orysae)* of rice, and were found effective. Tripropyltin oxide **(16)** was found to be most effective, its phytotoxicity being reduced by formulation with lime. Even so, application in fruit orchards is not recommended in the growing season. With certain tripropyl compounds, insecticidal and insect-repellent actions were observed as side-effects.

Of the butyltin derivatives the active substances dibutyltin disalicylate **(17)** and bis (tri-*n*-butyltin) oxide **(18)** are effective against potato blight, but have only about one-tenth the effect of triphenyltin compounds (McIntosh, 1970).



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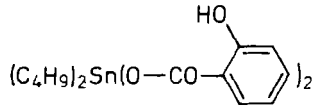

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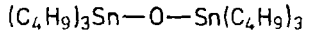


18

5.2.3 Fungitoxic arsenic compounds

Because of their phytotoxic and strongly toxic properties for humans, arsenic compounds are increasingly being replaced by other fungicidal compounds. Of the inorganic compounds of arsenic, the fungicidal properties of lead arsenate ($PbHAsO_4$) (see insecticides) in the prevention of apple scab have been recognised by Waite (1910), and the combination of lead arsenate with lime sulfur has been widely used as an insecticide–fungicide in fruit cultivation. Its effect was attributed to the high water-solubility of the calcium thioarsenate formed. Whetzel *et al.* (1929) have also reported the fungitoxic action of calcium arsenate against *Alternaria* spp.

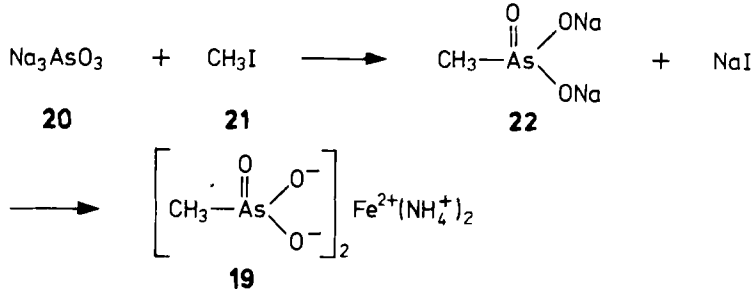
Considerably greater importance has been attached to the organic compounds of arsenic, which are active fungicides even at very low concentrations and also have a curative effect. In general, their fungicidal activity is lower than that of organic mercury compounds, and they also have some disadvantages from the viewpoint of environmental protection. Therefore, preparations with organic arsenic compounds as the active substance have not been widely applied in Europe. However, in the USA and particularly in Japan (rice cultures) they have been used in large quantities in the past for the prevention of various fungal diseases. Today, their use is prohibited in many countries.

The fungicidal action of organic arsenic compounds has been discussed extensively in the literature, but the exact mechanism has not yet been determined (Bodnár *et al.*, 1935; Adams and Howard, 1963; Webb, 1966; Kaars Sijpesteijn *et al.*, 1969). It has been established that the compounds of trivalent arsenic have a considerably higher activity against fungi than the derivatives of pentavalent arsenic. Trivalent arsenic compounds strongly inhibit the activity of enzymes oxidising alpha ketonic acids. It has been also proved that arsenic compounds react in the animal organism with the sulfhydryl groups of the dithiol derivatives of alpha lipoid acid, which are co-factors in the oxidation processes of alpha ketonic acids. Presumably this is the basis of the fungicidal and bactericidal effect of organic arsenic compounds.

In general, the acute toxicity of organic arsenic compounds is moderate, but at the end of their decomposition mechanism they are broken down into very toxic inorganic arsenic compounds in the soil, in plants and in warm-blooded organisms

(Fumimoto and Nakamura, 1971). Enriched in the soil, these metabolites can also be absorbed by the plants. In addition, the carcinogenic effect (lung and liver cancer) of arsenic compounds has recently been reported (Anonym, 1975).

Of the more important organic arsenic compounds, the iron–ammonium salt of metylarsonic acid **(19)**, should be mentioned. It is miscible in water and stable in alkaline medium, but is decomposed by acids (acute oral $LD_{50} = 1000$ mg/kg). It is prepared by reacting sodium arsenite **(20)** with methyl iodide **(21)**, and converting the disodium salt obtained **(22)** into iron–ammonium salt (Quick and Adams, 1922).



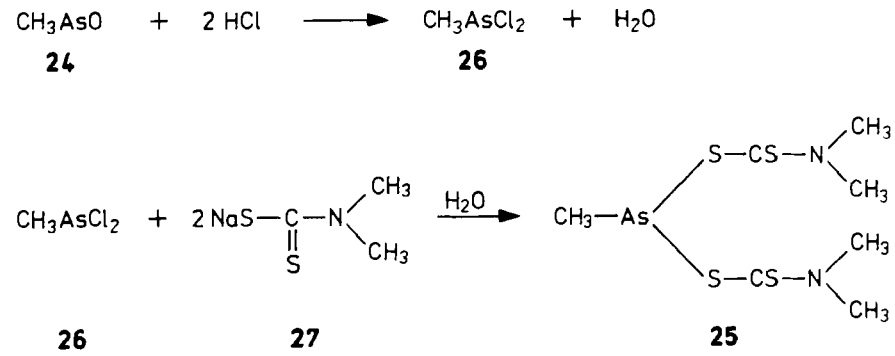
20 **21** **22** **19**

Its most important application is in the prevention of *Hypochnus sasakii* fungi in rice crops. Methylarsenic sulfide **(23)** has been used as a seed dressing since 1931. According to Frohberger and Urbschat (1958), it is effective for the control of *Rhizoctonia solani*, surpassing even seed protectants containing mercury (Rhizoctol). Methylarsenic sulfide is used in combination with benquinox active substance for seed and soil treatment in the protection of cotton crops. It is a white or pale yellow compound with a slight odour of carbon disulfide and is insoluble in water. It is prepared by the reaction of methylarsine oxide **(24)** with hydrogen sulfide in aqueous medium.

$$\underset{\mathbf{24}}{CH_3AsO} + H_2S \rightarrow \underset{\mathbf{23}}{CH_3AsS}$$

Methylarsinediyl bis(dimethyldithiocarbamate) **(25)** is a white crystalline compound, insoluble in water (Urbschat *et al.*, 1949). It is used in fruit orchards against *Venturia inaequalis* and *Venturia pirina* and in rice and coffee plantations for the prevention of diseases caused by *Hypochnus sasakii*. It has the unique property of deepening intensely the red and yellow colour of apples (Grewe, 1965b). It is phytotoxic in concentrations (0.1–0.2%) and effective against apple scab, and is therefore used for this purpose in combination with TMTD and ziram (Urbacid®, Tuzet®). In the action of the active substance the dimethyldithiocarbamate group naturally plays an important part along with arsenic.

Its perparation begins with methylarsine oxide **(24)**, which is converted with Its perparation begins with methylarsine oxide **(24)**, which is converted with hydrochloric acid into methylarsine dichloride **(26)**, this substance then being reacted with the sodium salt of dimethyldithiocarbamoic acid **(27)** (Schlör, 1970). (Acute oral $LD_{50} = 175$ mg/kg).



5.2.4 Organic phosphorus compounds

The important microbiological action of organic phosphorus compounds was discovered more than 40 years ago (Jerchel, 1943), but detailed studies of their fungicidal and bactericidal properties were not made until the 1960s. Today, the number of organic phosphorus compounds of various structures for which a more or less strong fungicidal action has been established is already more than one hundred. Of these derivatives relatively few active substances have been actually applied as fungicides, however, primarily because most of the compounds are strongly phytotoxic, and also because organic phosphorus compounds with fungicidal properties are generally very selective against fungus species. Several summary works have been published on the subject (Melnikov, 1967; Tolkmith and Mussel, 1967, 1974; Melnikov and Grapov, 1968; Scheinpflug and Jung, 1968; Nádasy 1969; Melnikov, 1969; Grapov and Melnikov, 1973).

Data on the mode of action of organic phosphorus compounds with fungicidal properties are still scarce (Myers *et al.*, 1957). The main difficulty in this field is that the action of these compounds on microorganisms is very selective, so that the mode of action is also presumably specific. Therefore, no general theory can be formulated, as can, for example, for the mode of action of organic phosphorus compounds with insecticidal properties, which is generally considered to be unequivocal.

On comparing the phosphate derivatives with the thio-, generally poly-thiophosphate derivatives, it may be concluded that the effect of derivatives also containing sulfur is always much higher. A possible mode of the fungicidal action is connected with the disturbance of the redox processes of the fungal cells. Moreover, it is assumed that sulfur-containing derivatives also attach the nucleic acids at the site of the phosphate radicals and interfere with their normal functions.

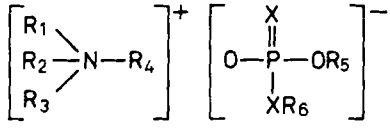
It has also been observed that the fungicidal property of organic phosphorus compounds increases with their tendency to form metal chelate compounds. This phenomenon is particularly characteristic of derivates containing amido groups, which may form chelate compounds with the microelements needed for normal

functioning of the enzyme system of fungi. It is also possible that certain organic phosphorus compounds influence fungal metabolism by direct phosphorylation, and thereby disturb the normal vital functions of the cells. In this respect there is a similarity with the action of dithiocarbamates.

In terms of environmental protection, organic phosphorus compounds with fungicidal action are of great importance because, after the present statutory waiting time, their degradation products are mostly compounds biologically inactive in relation to warm-blooded organisms, so that there is no danger of environmental contamination. Moreover, certain active substances being produced and applied already on a large scale particularly in Japan, have replaced those fungicides, such as organic arsenic and mercury compounds used to protect rice, which present problems for environmental protection.

The general synthesis of organic phosphorus compounds is discussed in detail in the section dealing with insecticidal compounds.

One group of fungicidal organic phosphorus compounds worthy of mention are quaternary ammonium salts of the general formula **(28)**, which have very notable bactericidal and fungicidal properties (Melnikov *et al.*, 1962).



28

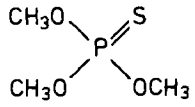
$R_1, R_2, R_3, R_4, R_5, R_6$ = alkyl or aryl radicals,
X = O or S

Due to their high phytotoxicity, no active substance of possible use in plant protection could be developed from this group, but they hold promise for medicine and animal husbandry, being nontoxic to warm-blooded organisms.

Many trivalent phosphorus compounds, trialkyl phosphites and trialkyl phosphorotrithioite exhibit fungicidal properties, mainly because of their considerable reducing effect and high reactivity (Nishizawa *et al.*, 1959). These compounds are also very phytotoxic, and are therefore used mainly as defoliants, for example, merphos and tributyl phosphorotrithioite.

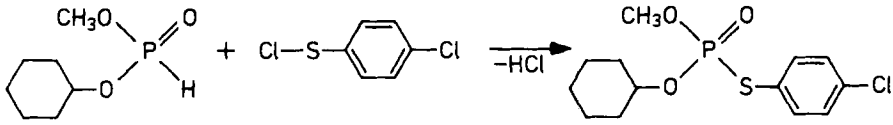
In general, the group of alkyl phosphates comprises only derivatives with very low fungicidal action; in derivatives of thiophosphoric acid, however, fungicidal properties considerably increase. The simplest thiophosphate, O,O,O-trimethyl phosphorothioate **(29)** and some of its homologues are very effective against plant diseases caused by *Pythium* sp. They exhibit high selectivity, and proved completely ineffective against other soil fungi, for example, *Rhizoctonia* sp., *Fusarium* sp. and *Verticillium* sp.

Active substances of the thiophosphate group have been used for a relatively long period. The active substance O-methyl-O-cyclohexyl-S-(4-chlorophenyl) phos-



29

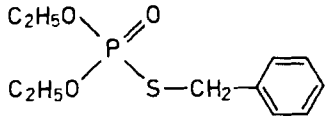
phorothioate (**30**) was developed by the Farbenfabriken Bayer in 1965 (Scheinpflug *et al.*, 1963). In concentrations of 5–100 mg/kg it protects rice against *Piricularia orysae*, and also has a curative effect. It is prepared by reacting methylcyclohexyl phosphite with 4-chlorobenzene sulfenyl chloride:



30

It also has the advantage of being effective against two rice cicada species (*Nephotettix concticeps* and *Delphacodes steriatella*). It is marketed under the trade name Cerezin® (LD_{50} = 160 mg/kg acute oral for rats).

The active substance S-benzyl-O,O-diethyl phosphorothioate (**31**) (EBP, trade name Kitazin®) is very effective in the protection of rice against *Piricularia orysae* and *Hypochnus sasakii* fungi (Kado *et al.*, 1964).



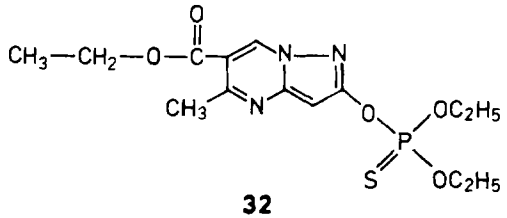
31

The active substance is relatively soluble in water (500 mg/l) and has a systemic action. It is readily absorbed by the root system and rapidly translocated in the transpiration stream to the site of pathogenic infection. Four days following infection it has a curative effect. During this time the compound kills the *Piricularia orysae* fungi (Maeda *et al.*, 1970). Acute oral LD_{50} = 600 mg/kg for rats. It reduces the growth of micelia and spore formation (Kado and Yoshinaga, 1969; Kakiki *et al.*, 1969).

On investigating the relationship between the action and structure of the compounds, Kado (1969) established that S-benzyl-O,O-dialkyl derivatives are more effective than the respective O-benzyl-phosphate, phosphorothioate and phosphorodithioate derivatives. The O,O-diisopropyl derivative is more stable than the diethyl derivative and at the same time less toxic to warm-blooded organism (Yamamoto *et al.*, 1973). Recently, 15000 tons of the diisopropyl derivative (IBP), marketed under the name Kitazin P®, has been used in Japan for prevention of rice blast (Searle *et al.*, 1973).

Kakiki *et al.*, (1969) reported that EBP inhibited the incorporation of glucosamine-1-^{14}C into the cell wall of *Piricularia orysae*. This suggested that a mode of action of this compound might be the inhibition of chitin biosynthesis. According to the experiments of Akatsuka *et al.* (1977) and of Kodama *et al.* (1979) the specific inhibition of conversion from phosphatidylethanolamine to phosphatidylcholin by the transmethylation of S-adenosylmethionine might be one of the modes of action of IBP.

An organophosphorus compound of quite a novel type, which proved to have a general curative effect against powdery mildew and *Piricularia orysae* was developed by Mildenberger and Scherer (1966). The active substance is O-6-ethoxycarbonyl-5-methylpyrazolo[1,5-a]pyrimidin-2-yl-O,O-diethyl phosphorothioate, (pyrazophos, **32**).



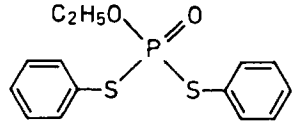
32

The active substance gives very good preventive protection against powdery mildew fungi and is able to arrest fungal development up to the 5th day following infection. It has a systemic effect, the plant rapidly absorbing the active substance through both leaves and stem, from where it is translocated acropetally. Absorption through the roots is considerably slower, however, and pyrazophos is unsuitable for seed treatment or as a soil fungicide (Herbold, 1972; Zilka and Stingel, 1975). It is nonphytotoxic and moderately toxic to warm-blooded organisms (LD_{50} = 140 mg/kg acute oral for rats). As a phosphoric ester, it has also some insecticidal, acaricidal and nematicidal effects (Smith, 1969).

The preparation Afugan® EC of Hoechst AG can be used for the protection of cereals, grapes, fruits, vegetables and ornamental plants, having a wide range of action against powdery mildew fungi. De Waard (1974) showed that the fungitoxic agent is the metabolite 6-ethoxycarbonyl-5-methylphyrazolo[1,5-a]pyrimidine, which inhibits certain dehydrogenases.

In the group of phosphorothioates, an increase in the number of sulfur atoms linked to the phosphorus atom increases the fungicidal effect of the aliphatic esters (Hacskaylo and Stewart, 1962). Thus, simple trialkyl phosphorodithioates are more efficient than trialkyl phosphorothioates, and the fungicidal activity of phosphorotrithioates and tetrathioates is even more potent (Mandelbaum *et al.*, 1967). In the trialkyl phosphoropolythioates, the trimethyl derivatives have the highest activity, the effect decreasing with the increasing number of carbon atoms in the alkyl group. Unfortunately, in many cases the phytotoxicity of the compounds also increases with the increasing number of sulfur atoms, limiting the application of these compounds.

The aromatic esters of dithio- and trithiophosphoric acids are better tolerated by plants. O-Ethyl-S,S-diphenyl phosphorodithioate (edifenphos, 33), is very effective against *Piricularia orysae* and even against *Pellicularia sasakii.*



33

It is marketed under the name Hinosan®. In addition to its protective action, it kills fungi in the leaf tissues, even several days after infection, and prevents their propagation. It is moderately toxic to warm-blooded organisms, acute oral LD_{50} being for rats 340 mg/kg (Scheinpflug and Jung, 1968; Chen *et al.*, 1972). It is very well tolerated by rice and is also effective against many fungal parasites (*Cochliobolus miyabeanus, Hormodendrum* sp.).

Edifenphos may affect, on the one hand, the permeability of the cell membrane, and, on the other hand inhibit chitin synthesis (De Waard, 1972). Its metabolism in rice plants has been investigated on radiolabelled ^{35}S and ^{32}P edifenphos active substances. The primary step of metabolism of the active substance in the micelium of *Piricularia orysae* fungus is the hydrolysis of one of the P—S bonds. This is followed by the hydrolysis of the other P—S bond or of the ethylester bond, and phosphoric acid is finally formed (Uesugi and Tomizawa, 1971). Harvested rice has been extracted with water and organic solvents. In the aqueous phase, mainly O-ethyl-S-phenyl thiophosphoric acid, S,S-diphenyl dithiophosphoric acid and S-phenyl thiophosphoric acid have been detected, while the organic solvent phase contained edifenphos, O,O-diethyl-S-phenyl phosphorothioate, S,S,S-triphenyl phosphorotrithioate and diphenyl sulfide. A similar metabolism was found in warm-blooded organisms. Edifenphos hydrolyses less than the other organophosphorus compounds (Takase and Ken BiTan, 1973; Ueyama *et al.*, 1973).

Newer data suggest that the primary antifungal action of edifenphos is due to interference of phosphatidylcholine biosynthesis by the transmethylation reaction of S-adenosyl-L-methionine. Therefore, the mode of action of edifenphos has a strong resemblance to that of IBP (Kitantin P®) (Kodama *et al.*, 1980).

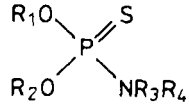
Edifenphos was degraded in flooded soil samples more rapidly than in nonflooded soil at 50% water holding capacity. *A Pseudomonas* strain utilised edifenphos as the sole carbon source. Soil sterilisation retarded degradation of edifenphos (Rajaram and Sethunathan, 1976).

The fungicidal effect of organophosphorus compounds is further increased on their passing from esters to ester amides (Melnikov, 1967; Tolkmith and Mussel, 1974; Melnikov and Grapov, 1968).

It was found for ester amides, represented by the general formula **(34),** that

— substitution of the alkyl radical by an aryl radical increases the fungicidal effect;

— of the substituents of the aryl radical, halogens reduce, while alkyl substituents increase, the fungitoxic action;



34

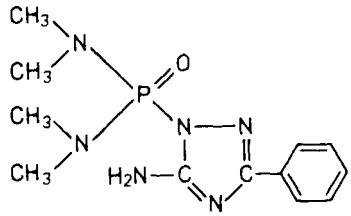
R_1, R_2, R_3, R_4 = alkyl or aryl radicals

— the fungicidal action is stronger when the aryl radical is linked through oxygen to the phosphorus atom and not through sulfur, because, on hydrolysis, phenol with fungicidal action is formed.

The size and structure of the compounds of the amide group are also important from the viewpoint of fungicidal action. If the nitrogen atom is incorporated into an aromatic group, fungicidal activity generally decreases. However, when the aromatic ring also contains a thiocyano group, fungicidal action is considerably increased, as, unfortunately, phytotoxicity.

Mandelbaum *et al.*, (1970) found that the substitution of one of the methoxy groups in dimethoate for a dimethylamino group gives a considerable fungicidal effect to the compound. Thus, compared to dichlone, O-methyl-S-(methyl-carbamoylmethyl)dimethylamido phosphorodithioat inhibited the micelium growth of *Botrytis cinerea* and *Fusarium moniliforme* 42.8% and 28.4% more, respectively.

The first organic phosphoric compound with fungicidal properties to be marketed, triamiphos **(35)**, is also an amide.



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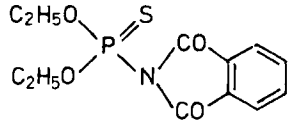
Triamiphos, 5-amino-3-phenyl-1H-1,2,4-triazol-1-yl-N,N,N',N'-tetramethyl-phosphonic diamide, marketed as Wepsyn®, has been used primarily in floriculture (roses) and apple orchards for the control of powdery mildew (Koopmans, 1960). In addition to its prophylactic use, it is absorbed by the plants and has a curative effect. According to Magendans and Dekker (1966), triamiphos primarily inhibits the formation of haustoria, but it also reduces spore formation. It also has insecticidal properties, mainly against aphids. Today, triamiphos has been replaced by other pesticides because it is expensive to produce and is very toxic to warm-blooded organisms, its acute oral LD_{50} being 20 mg/kg for rats.

The phosphorylated derivatives of 3-amino-1,2,4-triazoles have been studied extensively by Van der Bos *et al.* (1960). It was established during this research that

the carrier of fungitoxic action is the bis(dimethylamido) phosphoryl group, but the compound must contain an alkyl radical (with at most 11 carbon atoms) or a phenyl radical in position 3. Halogenated hydrocarbon radicals reduce the effect, and thiophosphorylated derivatives similarly have lower fungitoxicity.

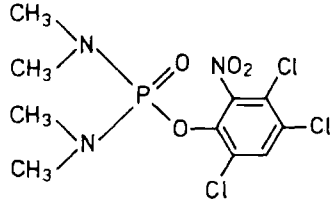
Tolkmith (1966) developed the active substance O,O-diethyl phthalimidophosphonothioate (ditalimfos **36**), which is a very effective fungicide against powdery mildew in apple and cherry orchards, cucumbers and roses, and is also effective against apple scab *(Venturia inaequalis)* and diseases caused by *Monilia fructicola*, etc. (Huisman, 1972; Huisman and Peskett, 1973). In addition to its protective effect ditalimfos also has a curative action, and is virtually nontoxic to warm-blooded organisms.



36

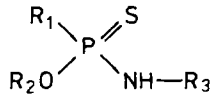
Tolkmith *et al.* (1967) also made a detailed investigation of the related compounds and found that the fungicidal activity of the derivatives is increased when the thiono sulfur is replaced by oxygen, or when a methylene group, an oxygen or a sulfur atom is introduced between the P and N atoms. Substituents in the phthalimido group reduce the fungicidal action.

Also in this group O-(2-nitro-3,4,6-trichlorophenyl)-N,N,N′,N′-tetramethylphosphonic diamid (**37**) developed by Demecko and Konecny (1970), is very effective against powdery mildew of cucumber and barley. It also has an acaricidal effect.



37

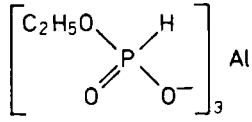
Several compounds with fungicidal properties have also been found among the derivatives of phosphonic, thio- and dithiophosphonic acids. Compounds of general formula (**38**) have the highest activity.



38

R_1, R_2, R_3 = aryl or alkyl radicals

The newest active substance developed by the Rhône-Poulenc (Horrière, 1977) is ethyl hydrogen phosphonate aluminium-salt **(39)**. Its common name is fosetyl. This fungicide is truly systemic with protectant and curative properties, primarily active against *Phycomycetes* fungi (Bertrand *et al.*, 1977; Williams *et al.*, 1977). It has been widely tested on temperate and tropical crops (Beach, 1979) and has successfully controlled many important *Phytophthora* spp and downy mildew. Mixtures with

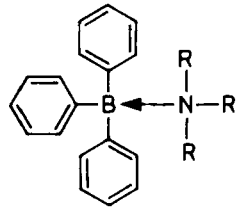


39

protectant fungicides (folpet, mancozeb) are being developed for use on vines (Chalandon *et al.*, 1979). Studies on efficacy, crop safety, toxicology and residues indicate that this fungicide represents an important advance in the control of *Phycomycete* disease. There may also be a role for this fungicide as prophylactic orchard spray before harvest (Bompeix *et al.*, 1979).

5.2.5 Organic boron compounds

The fungicidal effect of organic boron compounds is under investigation. An active substance worth mentioning is triphenyl boron which forms coordination compounds with nitrogen bases (ammonia, triethylamine, pyridine, etc.) **(40)**. It is effective against soil fungi (*Pythium* spp., *Rhizoctonia* spp.) (Birnbaum and Anderson, 1964).



40

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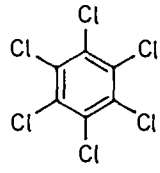
5.3 Benzene derivatives

5.3.1 Polychlorobenzenes, chloronitrobenzenes

The chlorinated and nitrated derivatives of aromatic hydrocarbons, primarily of benzene are used for the prevention of fungal infections from the soil by seed or soil treatment. Their action in the soil is enhanced by their medium volatility.

The fungicidal activity of the chlorinated benzene derivatives become stronger as the number of chlorine atoms increases. Hexachlorobenzene (HCB, **1**), is the most efficient. A good yield can be produced by the catalytic chlorination of benzene or its chlorinated derivatives at higher temperatures in the liquid or vapour phase. It was found effective in the control of bunt of wheat *(Tilletia tritici)*, but this protective action depends on the purity of the substance (at least 90%) and its quantity. This active substance (HCB) must be used in relatively high quantities, alone, or in combination with other fungicides in mixed seed protectants. It is used as a soil fungicide for the control of dwarf bunt (Yersin *et al.*, 1946). Hexachlorobenzene has a medium toxicity for humans, but it may cause hypertrophy of the liver if absorbed by the organism over a long period. In people with sensitive skin it may cause a slight skin irritation. The maximum permissible concentration of hexachlorobenzene in air is 0.9 mg/m^3.

The active substance quintozene 2,3,4,5,6-pentachloro-1-nitrobenzene (PCNB, **2**), contains also a nitro group. It is formed by the chlorination of nitrobenzene at 60–70°C in chlorosulfonic acid in the presence of an iodine catalyst. Pentachloronitrobenzene is stable in acid solution, but hydrolyses into pentachlorophenol and nitrite in alkaline solution, indicating that the nitro group is more reactive than the halogen atoms. Quintozene reacts through the nitro group with cell constituents: this is supported by its metabolism in plants into pentachloroaniline (**3**) and pentachlorobenzene mercapturic acid, N-acetyl-S-(2,3,4,5,6-pentachlorophenyl)-L-cysteine (**4**) (Gorbach and Wagner, 1967).



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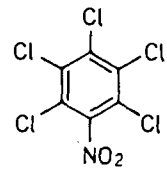
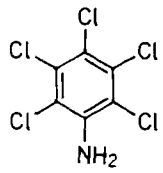


2

Quintozene has a selective action. It prevents the growth of mycelia in *Rhizoctonia solani*, even at low concentrations, while even larger quantities have almost no effect on the species *Pythium* and *Fusarium* (Barnes and Zerkel, 1961). This selective action is ascribed to the fact that the sensitive fungal species have considerable chitin in their cell walls, while *Pythium*, for example, is practically chitin-free (Macris and Georgopoulos, 1969). These authors also found that the cellular membrane of *Neurospora crassa* treated with quintozene contained 28–29% less hexosamine than the control. Quintozene seems to inhibit chitin synthesis. Moreover, the amount absorbed by the fungi — that is, the equilibrium between the absorption rate and the detoxification of the active substance — is also important in the selectivity (Nakanishi and Oku, 1970). In seed treatment it is effective against the seedling pests of vegetables, and in field crops against the snow mould of rye, while as soil fungicide it is used against *Rhizoctonia* infection of potatoes and the seedling diseases of cotton.

In the moist soil, quintozene is metabolised relatively rapidly into pentachloroaniline **(3)** and methylthiopentachlorobenzene **(5)** by microorganisms (Nakanishi and Oku, 1969). Pentachloroaniline is stable in both wet and dry soils, but has a more restricted spectrum of action than quintozene. It is active only against *Rhizoctonia solani*, and protects against the fungal infection for a long period, although not so effectively as quintozene (Ko and Farley, 1969). Neither quintozene nor its metabolites migrate in the soil. The predominant part of the active substance applied on and worked into the soil is found to a depth of 40 cm (Leistra and Smelt, 1974).

Reductive dechlorination proceeds by the action of light, but splitting of the NO_2 group may also occur. Under natural conditions, however, little if any degradation is caused by sunlight (Crosby and Hamadmad, 1971).



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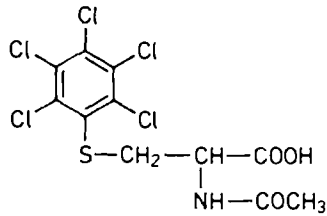
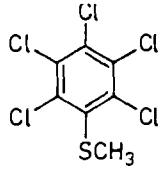


4

Quintozene is virtually nontoxic, acute oral LD_{50} being greater than 12 000 mg/kg, but it may cause slight irritation to the skin in sensitive humans. Its chronic toxicity is low (Borzelleca *et al.*, 1971), but according to some investigations, it may cause tumour in mice (Searle, 1966; Innes *et al.*, 1969). It has been assumed that potential carcinogenic polychloroazobenzenes (**6**) may be formed in the soil from pentachloronitrobenzene or its metabolite, pentachloroaniline (Weisburger and Weisburger, 1966). According to Buser and Bosshardt (1975), no significant quantities of polychloroazobenzene were formed in soils treated with pentachloronitrobenzene. On the other hand, Clarke (1971) reports a mutagenic effect.

An active substance effective against *Fusarium* spp. is tetrachoronitrobenzene, of whose three possible isomers 2,3,5,6-tetrachloronitrobenzene (tecnazen, **7**) has proved most efficient.



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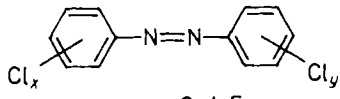
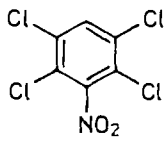


$x \neq y = 3, 4, 5$

6



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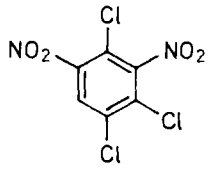
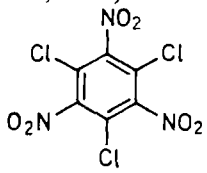


8

It is synthesised by the nitration of 1,2,4,5-tetrachlorobenzene. It was used initially for the protection of stored potato tubers and to inhibit their sprouting. Because of its volatility, it was later used as an aerosol against *Botrytis* spp. in greenhouses. However, it may be phytotoxic under extreme temperature conditions, or in treatment carried out in direct sunlight (Brown, 1947).

A product containing chloronitrobenzenes of various compositions is formed by the nitration of the isomer mixture of trichlorobenzene. These active substances are used as soil fungicides, either individually or in mixtures on various crops, in particular against *Rhizoctonia* and pathogenous fungi causing seedling diseases. Their action is selective. 3,5-dinitro-1,2,4-trichlorobenzene (**8**) is effective against *Plasmadiophora brassicae*, while 1,3,5-trichloro-2,4,6-trinitrobenzene (**9**) attacks *Cladosporium fulvum*. However, because of its great instability the latter is no longer used. Another substance, 4,6-dinitro-1,2,3-trichlorobenzene (**10**), has also been used (Richardson, 1968).



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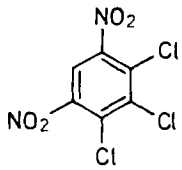


10

In general, chlorinated nitrobenzenes reduce the growth rate of fungi and spore formation, but they do not inhibit the germination of spores. The effect of halogenated dinitro- or trinitrobenzenes is more similar to that of halogenated mononitrobenzenes than to that of dinitroalkylphenols.

The development of resistance to chlorinated and nitrated benzene derivatives has been studied by several researchers (Priest and Wood, 1961; Georgopoulos and Zaracovitis, 1967). *Botrytis allii* strains in cultures under laboratory conditions could be resistant to tetrachloronitrobenzenes, dicloran and 2,3,5,6-tetrachloronitroaniline (Priest and Wood, 1961). Resistance was not important under field conditions (Kuiper, 1965; Skorda, 1977).

The term "aromatic hydrocarbon group" was suggested in 1967 for fungitoxic aromatic hydrocarbons which permit the development of resistant sectors by fungal colonies exposed to them (Georgopoulos and Zaracovitis, 1967). These fungicides were grouped together on the basis of a positive cross-resistance relationship; fungal strains selected by one were more or less resistant to all other members of the group. Compounds which were included in the aromatic hydrocarbon group were the chlorinated nitrobenzenes, dicloran, biphenyl and biphenyl derivatives, naphthalene and acenaphthene. Cross-resistance tests in subsequent years led to the addition of hexachlorobenzene (Kuiper, 1967) and the specific fungicide chloroneb (Tillman and Sisler, 1973).

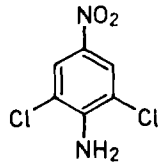
Several aromatic hydrocarbon fungicides were subsequently shown to increase sectoring (somatic recombination) in diploid colonies of *Aspergillus nidulans*. This ability to interfere in some way with the mitotic division provided a second criterion for the classification of a fungicide with the aromatic hydrocarbon group (Georgopoulos *et al.*, 1967).

Chlorinated nitrobenzenes or their metabolites are fairly stable compounds and, in spite of the fact that they are only slightly toxic to warm-blooded organisms, their intensive use in the prevention of fungal infection of the soil causes grave problems for the environmental protection. In quintozene and tecnazene the impurities of the technical product (pentachlorobenzene and hexachlorobenzene, and their metabolites; pentachloroaniline and methylthiopentachlorobenzene) are persistent in the soil and may cause contamination for 2–3 years (Beck and Hansen, 1974).

Chlorinated nitrobenzenes are rapidly excreted from warm-blooded organisms, particularly in the urine. In general, the nitro group is reduced, then acylated, the metabolite then being excreted from the organism in glucuronide or sulfate form (Bray *et al.*, 1953; Betts *et al.*, 1955).

The active substance 2,6-dichloro-4-nitroaniline also containing an amino group **(11)**, is known as dicloran. It has been marketed under the trade name Botran, indicating that this active substance is important primarily for its excellent effect against *Botrytis* spp. (Clark *et al.*, 1960). It is a fungicide of relatively low activity, but its high chemical stability and volatility enhances its action in the soil and makes it suitable for thermal fumigation of greenhouses. To a lesser degree, dicloran is effective for the control of diseases caused by *Monilia* and *Rhizopus* spp. Dicloran is absorbed by the roots of several plants (Groves and Chough, 1970), and the active

substance is incorporated into the cell constituents of the plants. It is produced from chlorobenzene by nitration, reaction with ammonia and subsequent chlorination. The compound is not sensitive to heat, light, hydrolysis and oxidation. According to Weber and Ogawa (1965), its biological action consists in the specific inhibition of protein synthesis. This is shown by the unaffected glucose metabolism in the cells treated and by the insignificant protein degradation. It inhibits the growth of mycelia but not the germination of spores (Ogawa *et al.*, 1963). The compound is not generally phytotoxic, but young lettuce seedlings are sensitive to it. It is not toxic to warm-blooded organisms. In rats it is rapidly metabolised and excreted in the urine, as is 2,6-dichlorohydroxyaniline sulfate. In plants it is metabolised into polar compounds, and in the soil it is rapidly broken down by bacteria.



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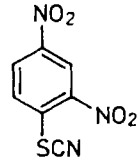


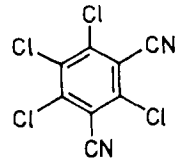
12

The first organic compound to replace copper-containing fungicides was 2,4-dinitrophenylthiocyanate **(12)**, DNRB or dinitrorhodanebenzene (Summers and Black, 1968), a yellow compound, insoluble in water. It is now less important owing to increasing use of new active substances. It is effective mainly against apple and pear scab, but has also been used successfully against downy mildew of vine. In the late-summer spraying of apple trees, a favourable side-effect observed was the heightened colour of the fruit. More susceptible apple species showed phytotoxic symptoms, particularly under extreme temperature conditions (Josepovits, 1961).

Its toxicity to warm-blooded organisms is low, but it may cause allergic dermatitis in susceptible humans. This effect is due to the 2,4-dinitrochlorobenzene impurity contained in the technical product (Bordás, 1964).

Chlorthalonil, 2,4,5,6-tetrachloro-isophthalonitrile **(13)**, is a fungicide with a wide range of action similar to ethylene bisdithiocarbamates, and is effective against *Phytophthora* and rust fungi (Turner *et al.*, 1964).

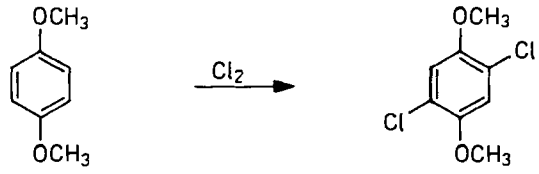
Chlorthalonil is chemically stable in both acid and alkaline media. It has a low sensitivity to light (Loeffler, 1978) and therefore has long-lasting action as a foliage fungicide. Its phytotoxicity is low. Its fungicidal action is presumably caused by the high reactivity of the chlorine atoms, whereby the compound reacts immediately with the thiol enzymes of the fungi (Vincent and Sisler, 1968; Tillman *et al.*, 1973; Szalkowski and Stallard, 1977).



13

It has also a wide range of algicidal action (Goulding, 1971). It is most effective against blue-green algae, which cause the greatest problems in water purification. In the concentrations used (max. 0.01 ppm) it is not dangerous to fish.

A fungicidal active substance of this group, also having moderate systemic effect, is chloroneb, 1,4-dichloro-2,5-dimethoxybenzene **(14)**. It is synthesised by the chlorination of *p*-dimethoxybenzene **(15)** (Plazek, 1930; Alvarez, 1968).



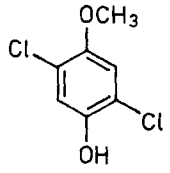
15 **14**

The active substance is absorbed from the soil through the roots, and is concentrated mainly in the roots and the lower parts of the plants, where it is most needed for the prevention of infection by soil fungi. Only a small quantity of chloroneb is translocated into the upper parts of the plant in its original form, but the fungicidal concentration is nevertheless established (Fielding and Rhodes, 1967; Kirk *et al.*, 1969). It is therefore a very efficient fungicide for the treatment of soil and seeds, being particularly effective against *Rhizoctonia* spp. and moderately effective against *Pythium* spp., although it is largely ineffective against *Fusarium* spp. It is used for the protection of cotton, beans and soybeans. Choroneb with thiuram provides a synergistic mixture against *Pythium ultimum*, (Richardson, 1973). Chloroneb seems to inhibit DNA synthesis: this is supported by the experiments of Hock and Sisler (1969a), which showed that at a concentration of 39 μM, chloroneb inhibits over 85% of the incorporation of radioactive thymidine into the DNA fraction of intact fungal cells. Chloroneb has less effect on RNA and protein synthesis (Tillman and Sisler, 1973). Lyr and Werner (1982) found that chloroneb is bound to the mitochondrial membrane in sensitive organisms, and a good correlation exists between binding capacity, damage to mitochondrial structure and function and growth inhibitory effects.

Chloroneb is demethylised in the plants and is metabolised to the same active 2,5-dichloro-4-methoxyphenol **(16)** (Pease, 1967; Hock and Sisler, 1969b; Werner *et al.*, 1978). Rhodes *et al.*, 1971) also detected the metabolites 2,5-dichloroquinone **(17)** and 2,5-dichlorohydroquinone **(18)** in small quantities which are less active. According to Thorn (1973), 2,5-dichloro-4-methoxyphenol, formed in the plant *Phaseolus vulgaris*, is metabolised into β-D-glucoside and accumulates in the hypocotyl and the cotyledon. The half-life of chloroneb in the soil is 3–6 months, and it has virtually no mobility (Rhodes *et al.*, 1970). Under moist soil conditions it is rapidly decomposed by microorganisms. Chloroneb is almost nontoxic, and does not cause chronic changes (Hodge *et al.*, 1949).

In animal organisms, too, chloroneb is degraded into 2,5-dichloro-4-methoxyphenol and is excreted in the urine in free form or as glucuronide or sulfate

conjugate (Gutenmann and Lisk, 1969; Rhodes and Peàse, 1971). Chloroneb or its metabolite could not be detected even in traces in the milk of lactating cows on a dosage in the diet of 2–5 mg/kg/day.



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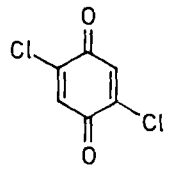

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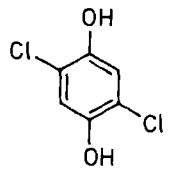


18

5.3.2 Phenol derivatives

Phenol and its derivatives are disinfectants which have long been used in the treatment of human diseases. In addition to their antiseptic and bactericidal action, they are also very good fungicides. Their use for agricultural plant protection is limited, however, because of their strong phytotoxicity. Their application in agriculture is thus restricted to soil treatment.

They are also used extensively for the protection of timber and in industrial manufacturing processes for the control of mould (paper and leather industries, etc.)

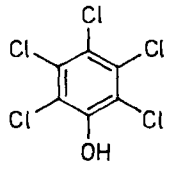
The fungitoxicity of phenol generally increases by halogen, nitro or alkyl substitution. Polyphenols are less toxic than phenol itself. The fungitoxicity of phenol also depends on the position of the OH group; when this is hindered by vicinal *ortho* substitutions (e.g. in 2,6-dialkylphenols) the fungitoxic action is very weak.

Phenols are pseudo-acids. Because the OH group is ionised, their water-soluble sodium salts can be prepared. They can also be esterified with organic acids. The binding of the phenolic OH group, by esterification for example, considerably reduces fungitoxicity. If, however, the enzymes of the fungi are able to liberate the phenolic OH group within the fungal organism (e.g. from esters of low carbon atom number) fungitoxicity remains unchanged. This phenomenon may be a factor in selective action.

The most efficient chlorinated phenol derivative is pentachlorophenol (**19**). It is manufactured by the catalytic chlorination of phenol and forms a colourless, crystalline product. Owing to its phytotoxicity it is normally used as a herbicide in plant protection, although it is also extensively employed in the protection of timber, paper and leather from fungal rots. At concentrations as low as 10^{-7} to 10^{-6} M it is a very effective uncoupler of oxidative phosphorylation *in vitro*, that is, it prevents the incorporation of inorganic phosphorus into ATP without influencing electron transport. The cells thus continue to respire, but soon exhaust the energy reserves necessary for growth. Munakata and Kuwahara (1969) observed that an aqueous solution of the sodium salt of pentachlorophenol is degraded by sunlight. Of the degradation products, 2,4,5,6-tetrachlororesorcinol

(20) and chloroanilic acid (21) have been identified, and various benzoquinones containing two or more rings have been isolated. The fungitoxicity of these latter metabolites is greater and their phytotoxicity less than those of pentachlorophenol.

The acute oral LD_{50} of pentachlorophenol is 210 mg/kg for rats. In aqueous solutions stronger than 1% it causes severe skin irritation. It may also be inhaled or absorbed through the skin, but it has no chronic toxic effect because it is rapidly excreted or metabolised. It is toxic to fish, certain species being sensitive to a concentration as low as 0.2 mg/l (Bevenue and Beckman, 1967).



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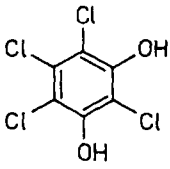

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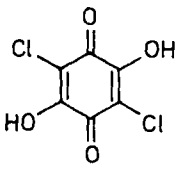
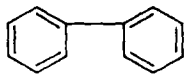


21

Diphenyl (22) is formed by the pyrolytic dehydrogenation of benzene. It is a highly volatile compound readily absorbed by the skin of fruits, thereby giving protection from diseases by the inhibition of fungal spore germination at the surface and of the hyphal growth in existing mycelia, and by preventing the development of new spores (Ramsey *et al.*, 1944). It is effective against many fungus species, especially against those infecting citrus fruits, such as *Penicilium italicum*, *P. digitatum*, *Diplodia matalensis*, *Botrytis cinerea* and *Phomopsis citri* (Wallnoefer and Rehm, 1968). Harding (1959) observed resistant *P. italicum* strains on longer exposure. Georgopoulos *et al.*, (1967) found, in conjunction with the mode of action of diphenyl, that the active substance does not damage the membrane when acting to prevent germination of *Fusarium solani conidia*, but they observed a considerable stimulation of potassium uptake by fungi sensitive to diphenyl, indicating a possible effect at the site of transport of the potassium on the fungal membrane.

Its acute oral LD_{50} is 3280 mg/kg for rats. It is dangerous to human beings at vapour concentrations greater than 0.005 mg/l.



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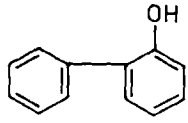


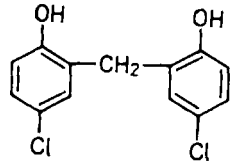
23

Diphenyl is hydroxylated in the organism of rats, and forms up to 30% 4-hydoxydiphenyl, 5,3% 4,4'-dihydroxydiphenyl, 3% 3,4-dihydroxydiphenyl, 18.4% 4-hydroxydiphenyl glucuronide and 1.3% diphenylmercapturic acid. Diphenyl in the original form has also been isolated from urine (West *et al.*, 1956). In rabbits, 64% of 1 g diphenyl administered per os was excreted in the urine after 4

days as free 4-hydroxydiphenyl or its sulfate, or as glucuronide (Block and Cornish, 1959). The compound 2-phenylphenol **(23)** is prepared by the reaction of chlorobenzene with sodium hydroxide. Its sodium salt is less fungitoxic, but is easier to handle because of its higher water-solubility. Development of resistance to the sodium salt has been observed, and since the resistant strains also tolerate diphenyl, this indicates that the mode of action of this active substance is connected with the diphenyl structure and not the phenolic OH group (Harding, 1962). But diphenyl is also presumably hydroxylated in the fungal cells, as is usual in initial steps of the oxidative degradation of aromatic compounds by microorganisms (Rogoff and Wender, 1962).

These active substances are used in the impregnation of packing materials (paper, wooden boxes, etc.) against mould, particularly of citrus fruits, during storage transport. The possible scalding of citrus fruits can be reduced by the addition of hexamine (acute oral $LD_{50} = 2480$). It has no chronic toxicity, but may cause skin irritation in susceptible persons. Rabbits excreted it in the urine as glucuronide. Sulfate of glucuronide could also be detected in rats. Its metabolite formed in the largest quantity is 2,5-dihydroxydiphenyl (Ernst, 1965).

Dichlorophen **(24)**, 4,4'-dichloro-2,2'-methylenediphenol is synthesised by the condensation of 4-chlorophenol and aqueous formaldehyde in methanol with sulfuric acid.



24

These diphenols have been studied by Marsh *et al.* (1949), who established that the biologically active bis-phenols are those in which the phenolic OH groups are in the *ortho* position in relation to the bridge connecting the two rings. Compounds containing more than two OH groups are less active. Substitution by halogens increases the fungitoxic effect, but more than two chlorine atoms again decreases the activity. Halogen substitution exerts the maximum effect when in the *para* position in relation to the OH group. The type of bridge connecting the two phenol rings has, in general, little influence on the fungitoxicity of diphenols (Marsh and Butler, 1946; Marsh *et al.*, 1949). Dichlorophen, which has both fungicidal and bactericidal properties, is the most effective. Its main field of application is the prevention of rot in cotton and textile materials caused by mould fungi. Acute peroral LD_{50} for dogs is 2000 mg/kg.

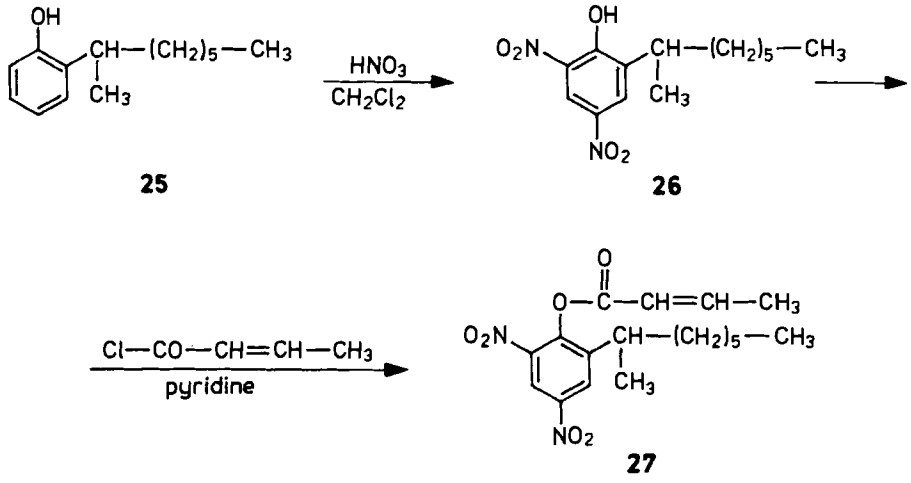
5.3.3 Dinitroalkyl phenols

The fungitoxic effect of phenols can be increased by the introduction of nitro groups. Even the introduction of a single nitro group strengthens the antifungal action, but dinitrophenols have been applied most widely as fungicides. Dinitro-

phenols proper cannot be applied as foliage fungicides because they are highly phytotoxic. When, however, the molecule is alkylated or the acidity of the phenolic OH group is reduced by esterification, the phytotoxicity of the compounds is considerably decreased, and they can then be used as foliage fungicides. With this transformation of the molecule the fungicidal action increases. Moreover, toxicity to warm-blooded organisms decreases. However, these active substances need a longer waiting time than usual due to their long-term action, so they cannot be considered promising considering environmental protection. The fungitoxicity of dinitrophenols depends mainly on the penetration of the molecule into the cell, which is a function of the lipid solubility of the molecule. Only compounds having suitable hydrophilic–hydrophobic partition coefficients become satisfactory fungicides (Kirby and Frick, 1958).

The mode of action of dinitrophenols is that free dinitroalkylphenols liberated in the organism inhibit oxidative phosphorylation. In this group of compounds the biological action is connected with the biochemical reducibility of the nitro group and, in this respect, species-specific differences can be observed between different organisms (Josepovits, 1966).

For the last 30 years one of the most important fungicides against powdery mildew has been Karathane®, the active substance of which is dinocap, 2,4-dinitro-6-(1-methyl-*n*-heptyl)phenyl crotonate (**27**). Synthesis begins with the nitration of isooctylphenol (**25**) in a medium containing methylene chloride. The dinitroisooctylphenol (**26**) obtained is then reacted in pyridine with crotonyl chloride (Reichner *et al.*, 1962).



25 **26** **27**

The dark brown liquid formed is immiscible in water.

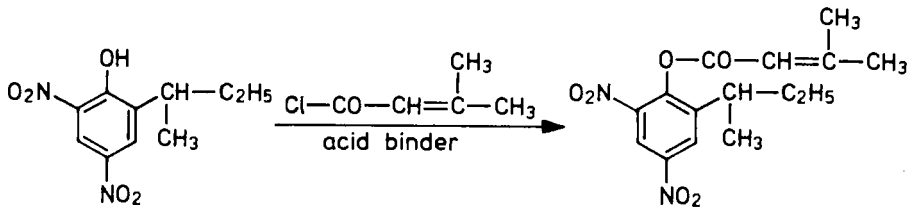
Dinocap is effective only against powdery mildew fungi. In contrast to the sulfur preparations, it exerts a fungicidal action at low temperatures (5–10°C), making possible the prevention of fungi growth even in early spring (Perrot *et al.*, 1958). It

also has a weak curative effect. It is used primarily in orchards, vine cultures and vegetables, and for the protection of ornamental plants.

The technical products is not a uniform compound. Intensive investigations showed it to be actually a mixture of 6 isomeric compounds. According to Kirby *et al.* (1964 and 1966), 2,4-dinitro-6-isooctylphenyl crotonate is the carrier of acaricidic and phytotoxic activity, while 2,6-dinitro-4-isooctylphenyl crotonate is the most effective component against powdery mildew (Pianka and Sweet, 1968). Both derivatives may have 3 isomers, depending on the nature of the isooctyl chain: 1-methylheptyl, 1-ethylhexyl and 1-propylpentyl isomers (Clifford *et al.*, 1965; Byrde *et al.*, 1966; Fieldgate and Woodcock, 1968).

It is moderately toxic to warm-blooded organisms, its acute oral LD_{50} being 980 mg/kg for rats. The chronic toxicity of dinocap is also low. Dogs fed a diet containing 50 mg/kg/day for one year suffered no loss in weight.

Binapacryl **(29)** is a compound with an action weaker than that of dinocap, and was initially also used as an acaricide. Its structural basis is dinoseb **(28)**, which is an active substance with herbicidal properties. Binapacryl is formed by the esterification of dinoseb with 3-methylcrotonic acid chloride, its chemical composition being 4,6-dinitro-2-*sec*-butylphenyl-3-methyl crotonate.



28 **29**

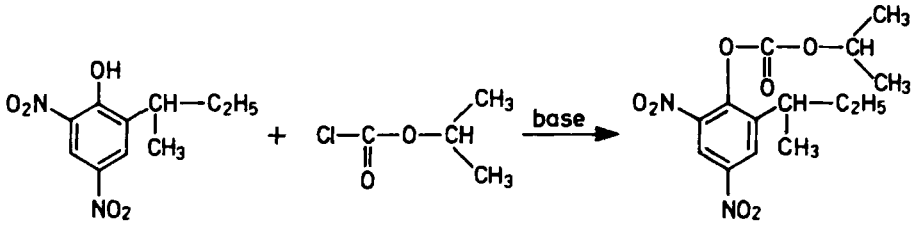
It hydrolyses on prolonged contact with water and is slowly decomposed by the action of sunlight. It is nonphytotoxic, only some scorching of young tomato plants, grapes and certain species of roses being observed. It is used against powdery mildew in orchards.

Reichner *et al.* (1962) have investigated the role of the esterification component in dinitrobutylphenol. They establised that the biocidal effect of such compounds generally decreases with increasing molecular weight of the acid component. It increases, on the other hand, beginning with the saturated aliphatic carboxylic acids through the unsaturated acids, up to the cycloaliphatic acids, decreasing again with the aromatic acids. Chlorine substitution in aliphatic acids, nitro or alkyl group substitution in aromatic acids reduces or cancels the effect almost without exception.

Products esterified with unsaturated aliphatic carboxylic acids are less phytotoxic when they contain a branched chain than when they contain a straight chain of identical molecular weigth. The phytotoxicity of the compound decreases with increasing chain length of the unsaturated acid. The ester formed with

3-methylcrotonic acid is very suitable, due partly to the double bond and partly to the branched chain. Because of this structure binapacryl has good acaricidal and fungicidal action and reduced phytotoxicity, that is, it is well tolerated by plants. It is not harmful to bees and is of moderate toxicity to warm-blooded organisms, acute oral LD_{50} being 161 mg/kg for rats. It is however, harmful to fish (Emmel and Czech, 1960).

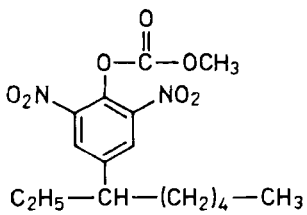
Dinoseb is also the basic compound of dinobuton **(30)**. On condensing the alkali salt of dinoseb with isopropyl chloroformiate **(31)**, a yellow crystalline product, 2-*sec*-butyl-4,6-dinitrophenyl isopropyl carbonate is obtained (Pianka and Smith, 1965), which is almost insoluble in water.



28 **31** **30**

Dinobuton is a contact acaricide and fungicide, effective against *Tetranychus telarius* and powdery mildew fungi and used mainly on tomatoes. It is phytotoxic to some species of roses and chrysanthemums. It decomposes rapidly in the soil.

Dinocton is the isomeric mixture of 2,4-dinitro-6-octylphenyl methyl carbonate and 2,6-dinitro-4-octylphenyl methyl carbonate, in which the octyl group may be present in the form of 3 isomers, as for dinocap. In general, two active substances are present, one being dinocton-4, which is a mixture of mainly 2,6-dinitro-4-(1-ethylhexyl)phenyl methyl carbonate **(32)** and 2,6-dinitro-4-(1-propylpentyl)phenyl methyl carbonate **(33)**, with an acute oral LD_{50} value of 460 mg/kg and a fungicidal effect primarily against powdery mildews. The other active substance, dinocton-6, consists essentially of 4,6-dinitro-2-(1-ethylhexyl)phenyl methyl carbonate **(34)** and 2,4-dinitro-6 (1-propylpentyl)phenyl methyl carbonate **(35)**. This active substance has an acaricidic effect, but it can also be used as a fungicide (acute oral $LD_{50} = 1250$ mg/kg for rats).



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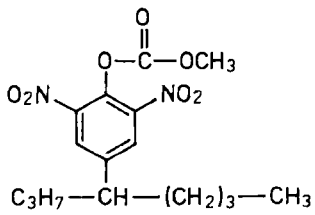

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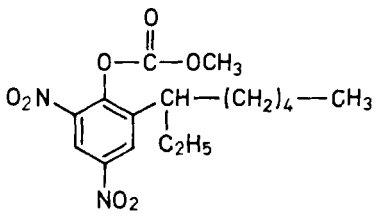

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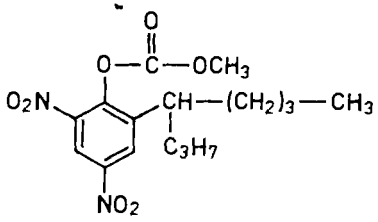
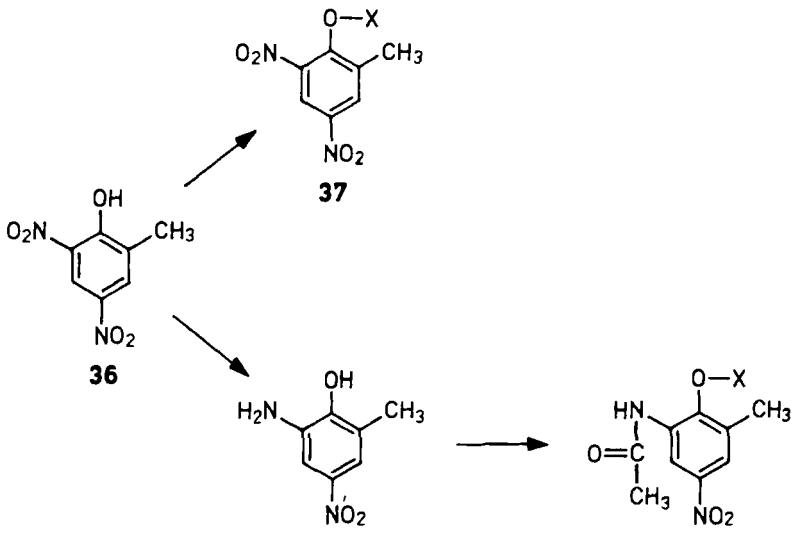


35

In the organism, aromatic nitro compounds are enzymatically reduced to amino compounds, while nitroso and hydroxyamino compounds are also formed as intermediate products. In compounds containing several nitro groups, usually only one nitro group is reduced. In dinitroalkylphenols the nitro group in the *ortho* position with respect to the OH group is primarily affected *in vivo*, and 2-amino-4-nitro compounds are formed. In isolated organs *in vitro*, the formation of 4-amino-2-nitro compounds has also been observed. Both isomers are less toxic than the 2,4-dinitro compounds. The original dinitrophenol is excreted by rats as glucuronide in the urine (Ernst and Baer, 1964).

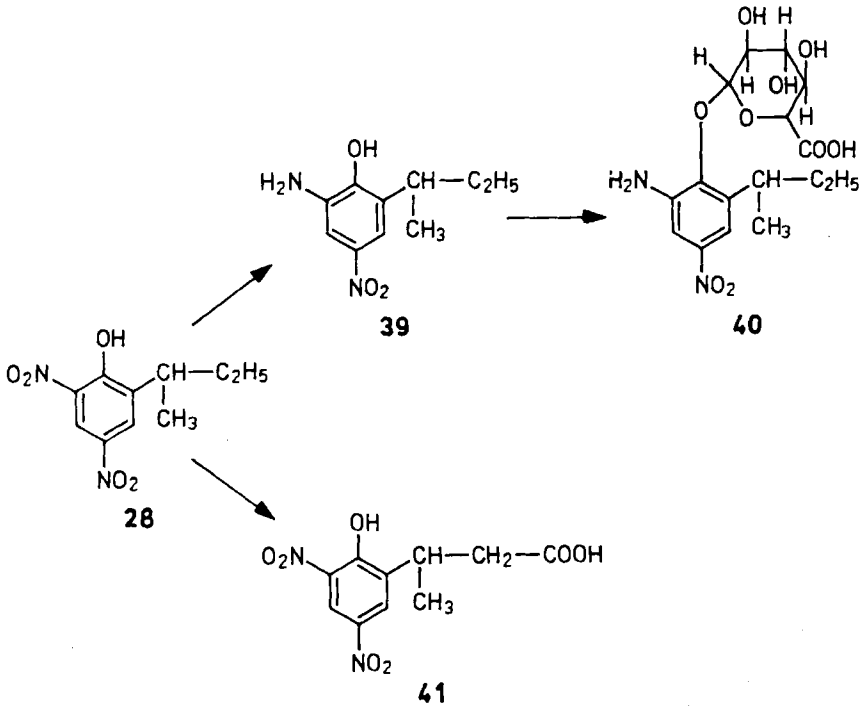
Dinitroorthocresol (DNOC, **36**), the metabolism of which has been studied most extensively, is excreted in the urine of rabbits at a rate of about 20% in 48 hours, of which 5–6% is voided in the form of the free compound, about 1% as O-conjugate (**37**) and 12% mainly as 2-acetamino-6-methyl-4-nitrophenol O-conjugate (**38**). The metabolites 3-amino-5-nitrosalicylic acid and 4-amino-6-methyl-2-nitrophenol have been observed in trace quantities. The amino groups formed by



36 37 38

reduction are then acylated, and are finally excreted from the organism, probably in the form of O-conjugate glucuronide.

Study of the metabolism of dinoseb and its acetate and of binapacryl in rabbits showed that 2-amino-6-*sec*-butyl-4-nitrophenol (**39**) is formed and excreted as O-conjugate with glucuronic acid, glucuronide (**40**). In rats this metabolism appears only in traces, but for both compounds the oxidation of the side chain — and thus the formation of *β*-methyl-*β*-(2-hydroxy-3,5-dinitrophenyl)propionic acid (**41**) in considerable quantities, also excreted in the urine — has been detected. The evacuation of nitro compounds from warm-blooded organisms is relatively slow.



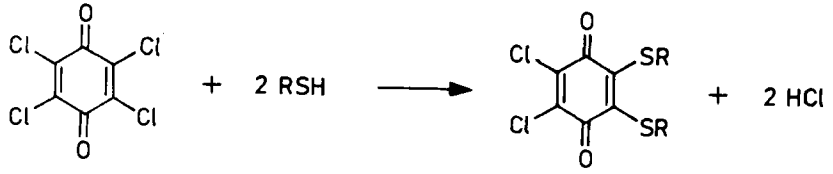
Dinitro compounds or their metabolites are present in the urine even after 10 days. In rats dinoseb decreased by 14–16%, and binapacryl by 7–11% in 48 hours.

Researches have investigated the biological action of other alkyl-dinitrophenols as a function of the structure of the compounds (Byrde *et al.*, 1969; Clifford *et al.*, 1969 and 1972).

5.3.4 Quinones

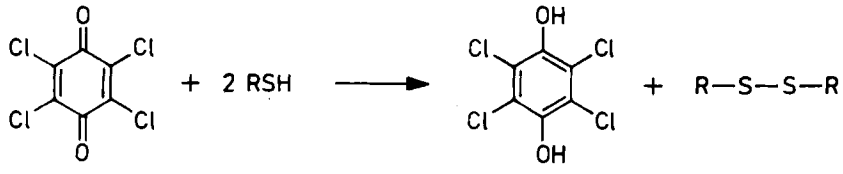
Quinones are important oxidising-formed agents. Natural quinones occurring in fungi and higher plants are, therefore, important in biological redox processes. The best known of these are vitamin K and ubiquinone. The mode of action of chlorinated quinones is based on their reactivity, this occurring primarily with enzymes containing sulfhydryl and with other proteins. The quinone ring behaves

as an α-β-unsaturated ketonic acid, and at the site of the reactive chlorine atom a thioether bond is formed with the sulfhydryl groups (Owens, 1963). With thiols of higher molecular weight, usually only one substitution takes place because of steric hindrance (Owens and Black, 1960a and b).



42

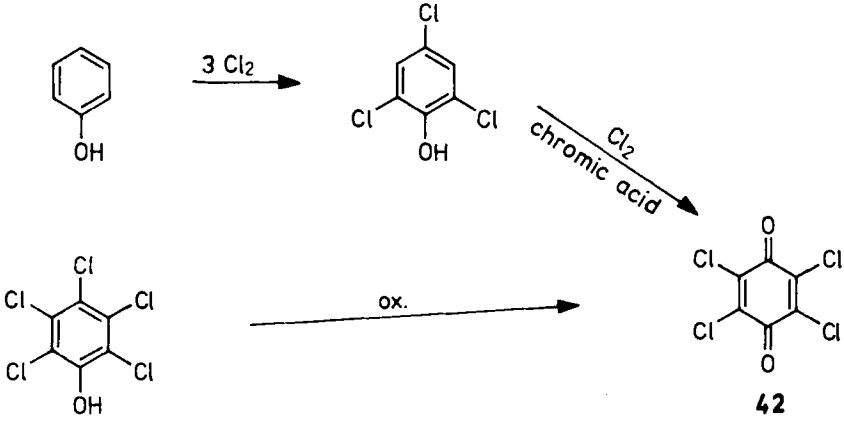
Moreover, quinone may have also an oxidising effect (Gause *et al.*, 1967).



42

McNew and Burchfield (1951) found that of the quinones, napthoquinones are the most toxic to fungi and bacteria. These are followed in decreasing order by phenanthrenequinones, benzoquinones and anthraquinones. Halogenation, primarily chlorination, increases fungitoxicity, and at the same time decreases phytotoxicity; pesticides used in agriculture are therefore chlorinated derivatives of quinones (Van der Kerk, 1956).

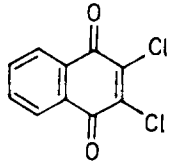
Chloranil (**42**), 2,3,5,6-tetrachloro-1,4-benzoquinone, is prepared either by the oxidative chlorination of 2,4,6-trichlorophenol or by the oxidative hydrolysis of pentachlorophenol.



42

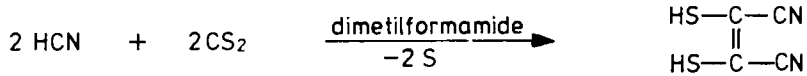
It is used mainly for seed treatment against smut and diseases of vegetable seeds (Schoene *et al.*, 1949). Its use as a foliage fungicide is limited because it decomposes partly by hydrolysis and partly photochemically (Burchfield and McNew, 1950), and sublimates in hot weather. Neither can it be used efficiently as a soil fungicide, because it also rapidly decomposes in the soil (Domsch, 1958). One of its degradation products is chloroanilic acid (**21**), 2,5-dichloro-3,6-dihydroxy-1,4-benzoquinone, which is also biologically inactive. The acute oral LD_{50} chloranil for rats is 4000 mg/kg.

Dichlone, 2,3-dichloro-1,4-naphthoquinone (**43**) (Ter Horst and Felix, 1943) is a more stable compound. Although sensitive to light, this active substance can be used as a foliage fungicide against powdery mildew, apple scab, gray mould, *Phytophtora* spp. and other fungal diseases (Cunningham and Sharvelle, 1940). It cannot be used for the treatment of leguminous seeds because of its toxicity to nitrogen-fixing bacteria. Dichlone is moderately phytotoxic, inhibiting ATP and $NADPH_2$ formation in the plants (Zweig *et al.*, 1972; Saxena *et al.*, 1975). An additional property is its algicidal action, making it suitable for use against blue-green algae in ponds, rivers and industrial water systems (Fitzgerald *et al.*, 1952; Fitzgerald and Skoog, 1954).



43

Dithianon, 5,10-dihydro-5,10-dioxonaphto-[2,3b]-1,4-dithiin-2,3-dicarbonitrile (**46**), is a nonchlorinated quinone derivative. It may be prepared by the reaction of dimercaptomaleinic acid dinitrile (**44**), obtained from carbon disulfide and hydrogen cyanide, with 1,4-naphtoquinone (**45**) (Hahn *et al.*, 1963). Dithianon is a protective fungicide used mainly against apple and pear scab and leaf spot of cherry trees. It is not phytotoxic (Flemming *et al.*, 1963).



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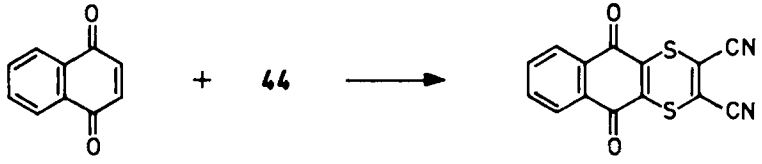
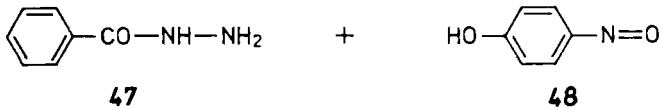
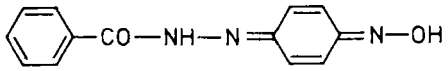


45 **46**

One or both ketone groups of quinones can be substituted for oxime groups (Peterson *et al.*, 1955). Of the oxime derivatives, benquinox, 1,4-benzoquinone-1-benzoylhydrazone 4-oxime **(49)**, made by reacting benzoylhydrazine **(47)** and nitrosophenol **(48)**, is the most important.

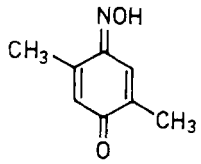


47 **48**



49

The active substance is highly effective mainly in the protection of various plants against *Pythium* spp. It is less suitable for use against seed-borne diseases of cereals, and, because there are several other fungicides which are more effective (Frohberger, 1956), it is used mainly in combinations. "Ceredon special®", a seed dresser combined with phenylmercuric chloride, is used for the dressing of sugar



50

beet. When used against diseases of pea seedlings, a systemic effect was also observed for benquinox (Zsolnai, 1962).

Another member of this group worth mentioning is 2,5-dimethyl-1,4-benzoquinone monoxime **(50)** (El-Tobsky and Sinclair, 1964), which is effective against *Rhizoctonia* and *Pythium* species.

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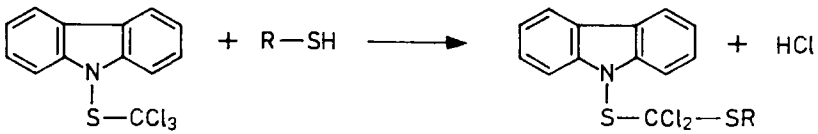
5.4 Compounds with fungicidal properties containing a polyhalogen alkanoic sulfenyl group

Kittleson (1952) discovered a new class of fungitoxic compounds having in common a trichloromethanesulfenyl group (—$SCCl_3$). The first active derivatives found were compounds formed by the reaction of the metal derivatives of carboxamides and imides with trichloromethanesulfenyl chloride, Kittleson (1953) therefore assumed that the N—S bond was essential for fungicidal action. It was later found (Sosnovsky, 1956; Uhlenbroek and Koopmans, 1957; Uhlenbroek *et al.*, 1957) that several compounds containing —S—S—CCl_3, —C—S—CCl_3 and —O—S—CCl_3 bonds were also fungitoxic, and that the —S—CCl_3 group was the toxophore group in the compounds with fungicidal properties. The finding, however, that not all compounds of type R—S—CCl_3 are fungitoxic drew attention to the role of the R group, which influences the physical and chemical properties of the compounds and thus also their biological activity against fungi (Lukens *et al.*, 1965).

The effect of the R group is manifested mainly in two ways. It influences the lipophilicity of compounds of type R—S—CCl_3 and thereby promotes the penetration of the cell membrane by the active substance. Folpet, for example, has an oil–water partition coefficient ten times higher than that of captan; the higher activity of folpet against certain powdery mildew fungi has been attributed to this (Richmond and Somers, 1962). The other role of the R group is to stabilise the R—S bond in compounds of type R—S—CCl_3 and to provide for reactivity with nucleophilic groups (Lukens, 1966). Adequate stability of the compound is needed to prevent hydrolysis of the active substance before it can enter the fungal cell, that is to say, to ensure that the unbroken compound is present at the site of action. On the other hand, if the compound is too stable it cannot react with the biological groups. The more rapid the reaction of the compound with the cell components, the higher is its fungitoxic action. According to Lukens *et al.* (1965), the fungicidal action of N-trichloromethanesulfenyl carbazole (**1**), for example, is weak because the steric configuration of carbazole protects the N—S bond against the attack of thiols, and thiol reacts with one of the chlorine atoms of the trichloromethyl group.



1

The biological activity and stability of compounds of type R—S—CCl_3 are closely related to the rate of hydrolysis of the sulfur bond. The highest fungitoxicity is attained at an optimal hydrolysis rate.

In fungicidal compounds of type R—S—CCl_3, R is generally an imide, hydantoin, 2,4-oxazolidinedione, aliphatic or aromatic sulfonic acid, aliphatic or

aromatic sulfonamide or sulfamide, etc. Of the imides, tetrahydrophthalimide and phthalimide are the most advantageous to activity. The trichloromethanesulfenyl derivates of aliphatic and aromatic sulfonic acids are excellent fungicides, but cannot be used in agriculture because of their high phytotoxicity. Compounds with good fungicidal effects have been developed from aliphatic sulfonamides. The N-trichloromethanesulfenyl derivatives of methane and ethane sulfonic amides are the most active, while the fungitoxic action of the higher homologues is weaker.

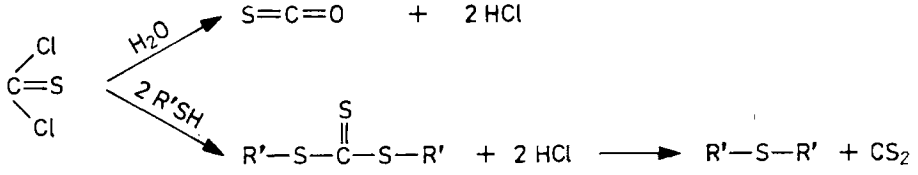
The other substituent on the nitrogen atom also affects activity. However, one or more chlorine atoms introduced into the methyl group do not influence substantially the fungicidal properties of the compound. Active substances with excellent fungicidal action can be obtained in the group of sulfamides.

Recently, Matolcsy and Bordás (1969) investigated the trichloromethanesulfenyl derivatives of urazole and 6-azuracyl. Assuming tautomerism of the compounds, the formation of the hydrophilic metabolite may be expected, which means increasing translocation.

Under physiological conditions, compounds of type R—S—CCl_3 react with thiols:

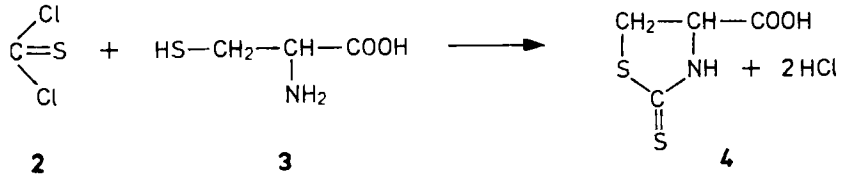
$$R—SCCl_3 + 2R'—SH \rightarrow RH + CSCl_2 + R'—S—S—R' + HCl$$

It is thought that this is the basic reaction of fungitoxicity and, moreover, of the biological detoxication of the fungicides (Owens and Blaak, 1960; Lukens, 1966; Richmond and Somers, 1962). The active substance is reduced during the reaction and free imide is formed, while thiols are oxidised into disulfides. The liberated thiophosgene **(2)** is a very reactive compound. It either hydrolyses rapidly into carbon oxysulfide (COS) or further reacts with thiols, forming trithio-carbonates, which are then decomposed into sulfide and carbon disulfide.



2

Thiophosgene is also able to react with amino acids, with the formation of thiourea, and can even react simultaneously with thiol and amino groups. Thus, for example, with cysteine **(3)**, 2-thiazolidinethion-4-carboxylic acid **(4)** is formed (Lukens and Sisler, 1958a):



2 **3** **4**

However, reactions of compounds of type R—S—CCl_3 with enzymes and other components of the cells containing sulfur are considerably more complex. The reaction mechanism is a question much disputed in the literature (Lukens and Sisler, 1958b; Owens and Novotny, 1959; Owens and Blaak, 1960). More and more experiments are being carried out in attempts to elucidate the processes actually taking place (Siegel, 1970a; 1970b; 1971a, Seifert and Davidek, 1977). According to the experiments of Siegel (1971b), folpet also inhibits isolated α-chymotrypsin, which does not contain any thiol groups. From all of these studies the conclusion can be drawn that there is no specific reaction between compounds of type R—S—CCl_3 and thiols in the cells to which fungitoxicity can be attributed but a complex poisoning process takes place, and it is due to this that resistance to this type of fungicide have not been developed.

The toxophore group, CCl_3—S—, is obtained from trichloromethanesulfenyl chloride, previously called perchloromethyl mercaptan. This compound has long been known but has not been used industrially for some time. Owing to its high toxicity to warm-blooded animals it was used as a gas in chemical warfare during World War I. It attained industrial importance only after 1951, after the discovery of fungicides containing the trichloromethanesulfenyl group.

Trichloromethanesulfenyl chloride (**5**) is a yellow oily substance, volatile with steam, having a very unpleasant odour, with a boiling point of 146–149°C. It is prepared by the chlorination of carbon disulfide below 30°C in the presence of iodine as catalyst (Klason, 1887):

$$2CS_2 + 5Cl_2 \xrightarrow{\text{iodine}} 2Cl—S—CCl_3 + S_2Cl_2$$

5

Nádasy *et al.* (1970) found that under optimal conditions chlorination proceeds according to the following equation:

$$CS_2 + 3Cl_2 \xrightarrow{\text{iodine}} Cl—S—CCl_3 + SCl_2$$

5 **6**

Since 1951 several technological processes have been developed differing only with respect to reaction conditions, their aim being the most advantageous separation from the main product of the sulfur chlorides formed as by-product. The reaction is most suitably carried out according to the second equation, because in this case the sulfur dichloride (**6**) formed as the by-product can be separated from the main product by simple distillation (Harmathy *et al.*, 1968; Nádasy and Harmathy, 1970, Nádasy *et al.*, 1970a, 1970b).

The chlorine atom of trichloromethanesulfenyl chloride is very reactive and can be linked with several organic radicals. The introduction of fluorine into the trichloromethanesulfenyl group can increase the fungicidal activity of compounds of type R—$SCCl_3$, as compared with derivatives containing only chlorine.

Experiments showed that the presence of one fluorine atom represents the optimum, the effect decreasing with the substitution of additional fluorine atoms (Kühle *et al.*, 1964). Dichlorofluoromethanesulfenyl chloride (**7**), prepared according to the method of Petrov and Nejemseva (1959), is suitable for the introduction of the dichlorofluoromethanesulfenyl group.
When suitable conditions are provided, the chlorine atoms of trichloromethanesulfenyl chloride can be selectively exchanged in succession for fluorine atoms by reaction with anhydrous hydrogen fluoride:

$$Cl_3C{-}S{-}Cl \xrightarrow{HF} Cl_2FC{-}S{-}Cl$$

7

In addition to the trichloromethanesulfenyl group, the tetrachloroethanesulfenyl group has also proved to be an excellent toxophore group (Thomas *et al.*, 1962; Lukens, 1962). This group can be attached to the organic radicals with the aid of tetrachloroethanesulfenyl chloride. 1,1,2,2-Tetrachloroethanesulfenyl chloride (**8**) can be obtained more simply and economically than trichloromethanesulfenyl chloride and is also less toxic. It is prepared from trichloroethylene with sulfur chlorides. In one of the methods, trichloroethylene is reacted with disulfur dichloride. In the first step of the reaction bis(tetrachloroethyl)-disulfide isomers are formed, the chlorination of which in the second step gives a tetrachloroethanesulfenyl chloride isomer mixture. However, this mixture contains only 17% of the desired 1,1,2,2-isomer and its separation is cumbersome (Kloubek and Ettel, 1961).

$$2\ CHCl{=}CCl_2 + S_2Cl_2 \longrightarrow \begin{cases} CCl_3{-}CHCl{-}S{-}S{-}CHCl{-}CCl_3 \\ CCl_3{-}CHCl{-}S{-}S{-}CCl_2{-}CHCl_2 \\ CHCl_2{-}CCl_2{-}S{-}S{-}CCl_2{-}CHCl_2 \end{cases}$$

$$(C_2HCl_4)_2S_2 + Cl_2 \longrightarrow \begin{cases} CCl_3{-}CHCl{-}S{-}Cl \\ CHCl_2{-}CCl_2{-}S{-}Cl \end{cases}$$

8

In a second process, trichloroethylene reacts with sulfur dichloride at relatively high temperature and pressure, and the product is formed in a single step (Kohn, 1965):

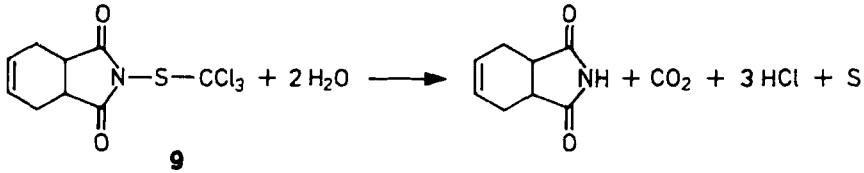
$$CHCl{=}CCl_2 + SCl_2 \longrightarrow CHCl_2{-}CCl_2{-}S{-}Cl$$

8

Pfeifer *et al.* (1974) found that the reaction can be photocatalysed, and that in this way 1,1,2,2-tetrachloroethanesulfenyl chloride can be obtained at room temperature and atmospheric pressure with a yield of 88% (Kovács *et al.*, 1970).

The first active substance containing the trichloromethanesulfenyl group that gained wide application was captan, N-(trichloromethylthio)-1,2,3,6-tetrahydrophthalimide, or N-(trichloromethylthio)cyclohex-4-en-1,2-dicarboximide (**9**). It is a white crystalline compound with a solubility in water at room temperature of less than 5 mg/l.

Captan hydrolyses in aqueous solution. At pH 7 and 28°C its half-life is about 2.5 hours. Lime and other alkaline substances accelerate hydrolysis. Hydrochloric acid formed during hydrolysis may have a phytotoxic effect; thus, carbonates or hygroscopic substances are not to be used for formulation. The addition of a buffer acting in the acid region is favourable.



9

Captan is a fungicide with a very wide range of action. It is effective against almost all of the important fungal pests of plants, being an exception of powdery mildew fungi. It is most effective against *Venturia* sp., where an eradicant effect has even been observed about one and one-half days after infection (Holz and Lange, 1962).

Captan is mainly a foliage fungicide with protective action, but it is used also for seed treatment and as a soil fungicide, because of its effect against *Pythium* sp. The side-effect should be mentioned — it causes thinning of the leaf epidermis, thus increasing the susceptibility of the plant to powdery mildew to a greater extent than even dithiocarbamates. Owing to its lipoid solubility, captan easily penetrates the cell membrane to react with many thiol-containing enzymes essential to the cell (Richmond and Somers, 1966, 1968). It reacts with hexokinase, aldolase, dehydrogenase, pyruvic acid decarboxylase and triose phosphatase, among others (Hochstein and Cox, 1956), blocking their function. Captan presumably binds cell thiols completely for a time and thus stops enzymatic activity so that the cells die. However, it also reacts with thiol-containing compounds nonessential to vitality, probably even before the actual site of action is reached, so that captan is detoxicated and its fungitoxic action reduced. Captan reacts particularly rapidly with glutathione and cysteine. Coenzyme *A* blocked with captan also can be reactivated with glutathione (Owens and Blaak, 1969).

Captan is hydrolysed in the soil depending on the water content of the soil. The degradation is relatively rapid, so that soil microorganisms or the organic matter in the soil have no substantial effect on the reaction (Burchfield, 1959; Griffith and Matthews, 1969).

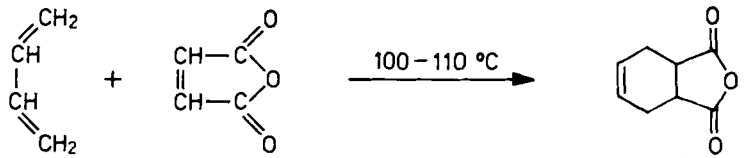
Captan is not toxic to warm-blooded animals. The acute oral LD_{50} for rats is 9000 mg/ kg. No evidence of chronic toxicity has been found (Boyd and Carsky, 1971; Seidler *et al.*, 1971). It is only slightly irritating to the skin. Captan is rapidly absorbed and metabolised in warm-blooded animals, almost the whole quantity being excreted in the feces within 3 days. Unchanged captan could not be detected in rats; tetrahydrophthalimide and tetrahydrophthalic acid were found transitorily in the blood.

Sulfhydryl groups play an important role in the maintenance of the structural integrity of cell membranes. It is therefore probable that because of their high affinity to sulfhydryl groups, captan and similar active substances affect the structure and functions of the cell membranes. Nelson (1971a) observed that captan uncouples oxidative phosphorylation and inhibits the function of single enzymes or enzyme system in the mitochondria of rat liver. He found that captan caused large, passive tumours in mitochondria, thereby changing the permeability of the internal membranes (Nelson, 1971b). In mitochondria affected by captan, internal membranes were missing, and the matrix became completely disorganised.

Three hours after feeding captan to rats, the number of sulfhydryl groups decreased by 54% in red blood cells and in the liver. The specific activity of two enzymes containing sulfhydryl group (glumatic-pyruvic transaminase and lactate dehydrogenase) also decreased (Engst and Raab, 1973).

Kumar *et al.*. (1975) found membrane lesions in human erythrocytes. Captan or captafol in concentrations as low as $5 \cdot 10^{-5}$ M influenced the structure of the membranes and produced a change in permeability, causing a rapid increase in the efflux of intracellular potassium from the red blood cells. Captan inhibits the rate of RNA, DNA and protein synthesis by 50% in the acid-insoluble fraction of Ehrlich ascites tumour cells (Gale *et al.*, 1971). Reports have appeared indicating that captan and folpet and/or their breakdown products are mutagens (Clarke, 1971; Bridges *et al.*, 1972; Herbold, 1978.), interfer with mitosis, induce chromosomal breaks (Legator *et al.*, 1969) and show a weak teratogenic potential (McLanghlin *et al.*, 1969; Verret *et al.*, 1969; Robens, 1970; Martin *et al.*, 1978). These toxic manifestations may involve directly or indirectly the genetic material of an organism (Couch and Siegel, 1977; Couch *et al.*, 1977).

The synthesis of captan starts from tetrahydrophthalic anhydride **(10)** obtained in the classical way from butadiene and maleic anhydride by Diels–Alder synthesis, according to the following reaction (Kohler and Jansen, 1938):

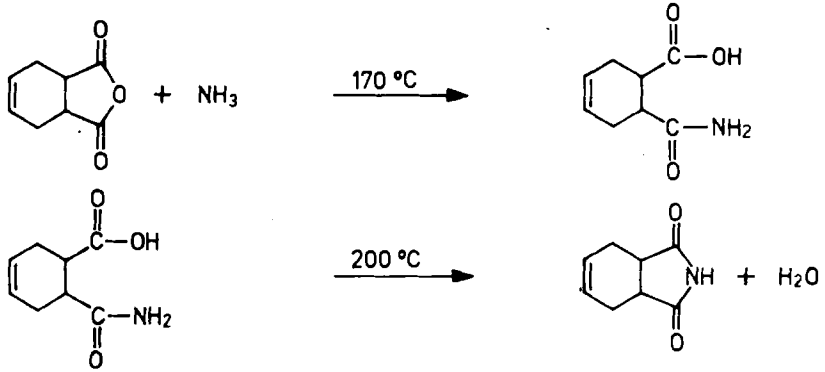


10

Tetrahydrophthalic anhydride can be obtained in a good yield from maleic anhydride and the butadiene-containing gas mixture which is formed during the

manufacture of polyethylene based on benzene pyrolysis. The reaction proceeds at 15–25 atm. pressure in the liquid phase with a conversion efficiency of 99%. The purity of the tetrahydrophthalic anhydride obtained is nearly 100%. The increased pressure considerably decreases the reaction time, and this results in a suppression of undesirable side-reactions (Kovács *et al.*, 1964; Kovács and Pfeifer, 1972).

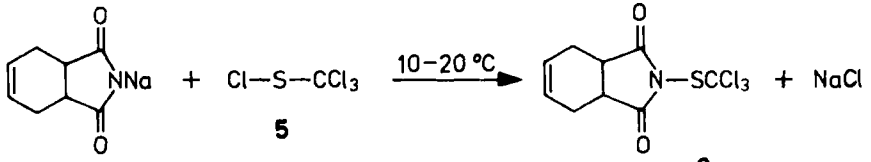
Tetrahydrophthalic anhydrine is converted with gaseous ammonia into tetrahydrophthalimide **(11)** (Kittleson, 1952; Melnikov *et al.*, 1961; Ambrus *et al.*, 1962). According to Dietz and Nusch (1964), the reaction proceeds in two steps. In the first step, tetrahydrophthalaminic acid is formed **(12)**, and in a subsequent step tetrahydrophthalimide is formed by the splitting off of water:



12 **11**

Pfeifer *et al.* (1972) established by derivatographic thermal analysis that not tetrahydrophthalamide acid, but a tetrahydrophthalimide–water adduct is formed, and from this addition compound water is split off, even at lower temperatures. This finding made it possible to avoid the technical difficulties caused by sublimation during the manufacture of thetrahydrophthalimide, because the higher temperature is in fact not needed for dehydration.

The last step in the synthesis is the reaction of the sodium salt of tetrahydrophthalimide with trichloromethanesulfenyl chloride (Kittleson, 1952). The reaction is carried out in organic solvent (benzene, dioxane) or in an aqueous medium. To avoid the hydrolysis of tetrahydrophthalimide, the reaction is carried out at low temperature (10–20°C). In aqueous media the use of emulsifiers considerably increases the yield, which can be as high as 90% (Melnikov *et al.*, 1961). The purity of the technical product is 90–95%.



5 **9**

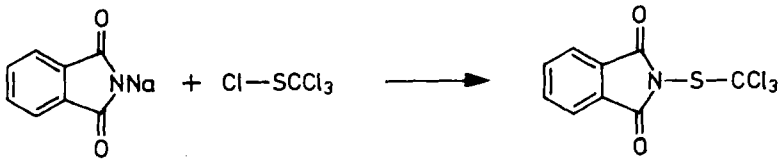
Another important active substance of the group is folpet, N-(trichloromethylthio)phthalimide (**13**), a crystalline substance virtually insoluble in water.

Folpet hydrolyses in aqueous media at room temperature, the rate of hydrolysis increasing in hot or alkaline solutions. Owing to this property, folpet cannot be combined with alkaline pesticides.

It is not toxic to warm-blooded animals, its acute oral LD_{50} for rats being about 10000 mg/kg. It may cause local irritation on contact with the skin. Dogs fed for three years on a diet containing 1100 mg/kg/day showed no histopathological changes. The teratogenic effect has also been investigated in monkeys, rats and hamsters with negative results. According to the experiments of Fischer and Aderhold (1957), folpet even hinders the oxygen uptake of cancerous cells.

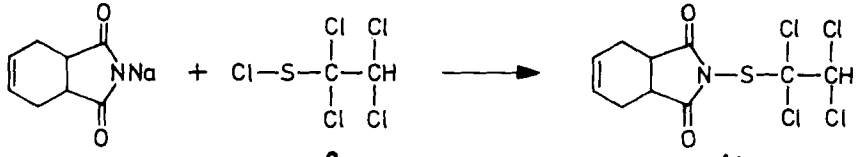
Folpet's mode of action and field of application are similar to those of captan, though it is less widely used in orchards. The most important difference in application of the two active substances is that folpet also has some effect on powdery mildew, or at least does not increase sensitivity to powdery mildew fungi (Lukens and Horsfall, 1967). Folpet is used mainly against downy mildew of vine *(Plasmopara viticola)* and foliage diseases of cereals. It is also used as a wide-spectrum soil fungicide.

Folpet is synthetised from phthalimide with trichloromethane sulfenyl chloride under conditions similar to those of captan synthesis, but the yield of the process and the purity of the product are somewhat lower than is the case with captan, the yield being 85% and the purity of technical folpet 90% (Pfeifer and Kovács, 1972).



13

Captafol, N-(1,1,2,2-tetrachloroethylthio)-1,2,3,6-tetrahydrophthalimide (**14**) also known as N-(1,1,2,2-tetrachloroethylthio)cyclohex-4-en-1,2-dicarboximide, contains a tetrachloroethanesulfenyl group (Thomas *et al.*, 1962). It is synthetised in a manner similar to captan, by the reaction of the sodium salt of tetrahydrophthalimide and 1,1,2,2-tetrachloroethanesulfenyl chloride, with a yield of 95%. The purity of the technical product is 95%.



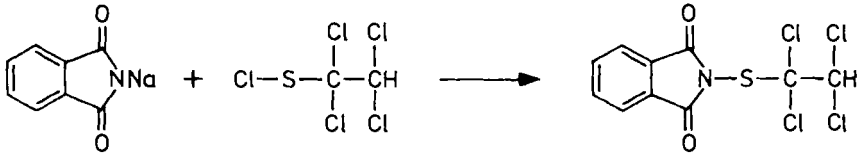
8 **14**

Captafol is a white, crystalline compound. It is practically insoluble in water. It is not toxic to warm-blooded animals, the acute oral LD_{50} for rats being higher than 6000 mg/kg. Sensitive people develop allergies to captafol. In two-year feeding experiments, no toxic effects were found at the 500 mg/kg/day level in the diet of rats or at the 10 mg/kg per day level in the diet of dogs. Captafol hydrolyses slowly in aqueous solutions and rapidly in alkaline solutions. The hydrolysis rate is slower than that of captan or folpet.

Captafol is a protective, wide-spectrum foliage and soil fundicide. It is used mainly for the protection of potato and vine, but it is also effective against vegetable diseases. Its action is long-lasting; the active substance sprayed on the plants is not decomposed by light. It is not phytotoxic, and treatment can be undertaken in the bloom period.

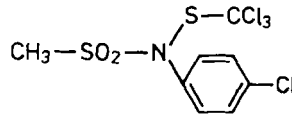
The phthalimide analogue of captafol is difolpet, N-(1,1,2,2-tetrachloroethylthio)phthalimide **(15)** (Pfeifer *et al.*, 1974). It is prepared by the reaction of aqueous · phthalimide sodium solution with 1,1,2,2-tetrachloroethanesulfenyl chloride in the presence of an emulsifier at 0–5°C. The melting point of the product, which has 95% purity, is 118°C.

Difolpet is a fungicide with a range of action similar to that of captafol. It is effective against downy mildew of vine and fungus species that cause tilting of the various seedlings (*Rhizoctonia solani, Pythium* species, etc.).



8 **15**

The other class of active fungicidal subtances containing a polyhalogen alkanesulfenyl group is the family of alkylsulfonic amides (Waeffler *et al.*, 1955). Mesulfan, N-trichloromethylthio-chloro-(methanesulfone) anilide **(16)** (Van der Kerk, 1956); norsulfan, N-trichloromethylthio-(methanesulfone) anilide **(17)** and chlorosulfan, N-trichloromethylthio-(chloromethanesulfone) anilide **(18)** are active substances with good fungicidal properties, but they have found no agricultural application. The most important active substance in this group is dichlofluanid, N'-dichlorofluoromethylthio-N,N-dimethyl-N'-phenylsulfamide **(19)** (Kühle *et al.*, 1964; Grewe, 1968a, 1968b).



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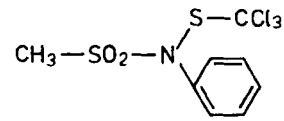

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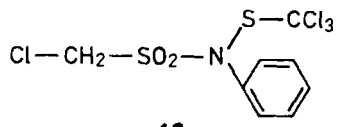

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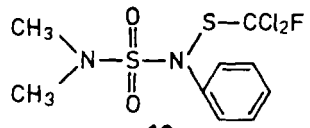


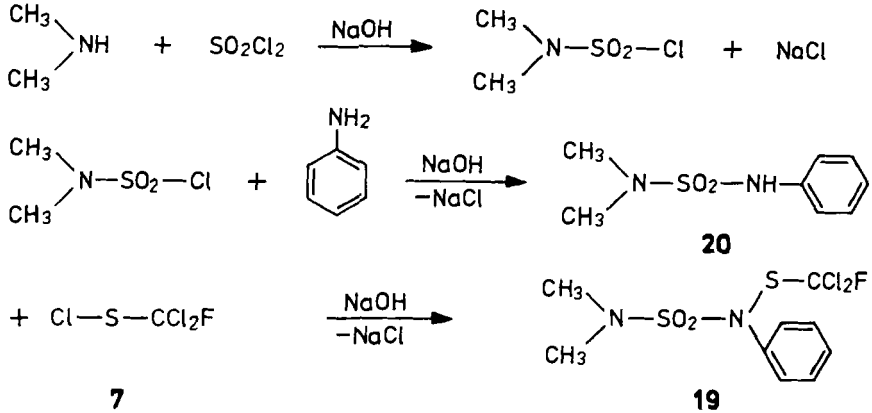
19

Pure dichlofluanid is a white powder, practically insoluble in water. It is hydrolysed easily in sodium hydroxide solution to N,N-dimethyl-N′-phenylsulfamide, and this compound is found under field conditions (Vogeler and Niessen, 1967). Dichlofluanid is much less sensitive to light than captan (Clark and Watkins, 1978).

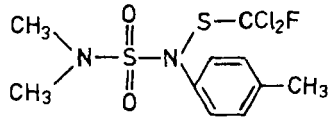
It is a protective fungicide with a broad range of action. It is effective against all the phytopathogenic fungi, including those resistant to other fungicides. It is thus very effective against *Botrytis cinerea*. In orchard it has an eradicant action against scab *(Venturia inaequalis)*. As an advantageous side-effect, it is effective against some powdery mildew fungi in higher concentrations (e.g., *Spherotheca pannose* and *Podosphera leucotricha*) and is also an acaricide (Müller, 1964).

Dichlofluanid has an acute oral LD_{50} of 1000 mg/kg. It is not absorbed through the skin, nor does it cause irritation. No chronic toxicity has been observed.

To synthesise dichlofluanid sulfuryl chloride is reacted with dimethylamide and aniline in turn; N,N-dimethyl-N′-phenylsulfamide formed as an intermediate product (**20**) is then coupled with fluorodichloromethanesulfenyl chloride (**7**) to yield dichlofluanid (**19**):



Tolyfluanid, N-N-dimethyl-N′-(4-tolyl)-N′-(dichlorofluoromethylthio) sulfamide (**21**) is a homologue of dichlofluanid.



21

The pure compound is a yellowish-white powder. It is a protective fungicide with a broad range of action similar to that of dichlofluanid. It is used mainly against scab, but is also active against powdery mildews, and controls, to a certain extent, red spider mites. It even has an insecticidal effect on *Aphis pomi* and *Eriosoma lanigerum* insect (Kolbe, 1972). Its acute oral LD_{50} for rats is higher than 1000 mg/kg; in 90-day feeding experiments, no chronic changes were observed (Kühle *et al.*, 1964).

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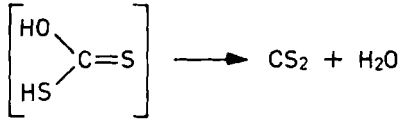
5.5 Dithiocarbonic acid derivatives

The dithio derivative of carbonic acid is xanthogenic acid **(1)**, unknown in the free state, the anhydride of which, carbon disulfide, is in itself an active substance with very good biological properties.

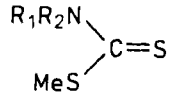


1

Carbon disulfide was first used as a soil insecticide against wine root lice *(Phyloxera)*, and, due to its cheap price and good effect it gained widespread use in

vineyards. Later its fungicidal properties were recognised. It is used mainly as a soil fungicide, because it permeates the soil rapidly due to its high vapour tension and diffusibility. Owing to its disadvantageous properties (low boiling point, fire and explosion hazard, high toxicity to mammals) it has gradually been replaced by other soil fungicides.

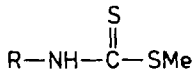
The amide of dithiocarbonic acid is dithiocarbamic acid, which similarly occurs only in the form of its salts and mainly its esters. In the general formula of these dithiocarbamates (2) three substitutions are possible,



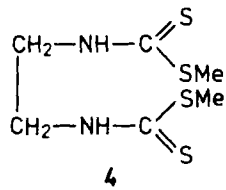
2

R_1 and R_2 = alkyl, alkylene, aryl, aralkyl or hydrogen. Me = Na, NH_4, Cu, Zn, Fe, other metal atoms or alkyl radicals.

Dithiocarbamates can be divided into two main groups different from each other in several respects. Dithiocarbamates, the synthesis of which starts with primary amines, are classified in the first group. Compounds obtained in this way are divided into two subgroups: N-monoalkyldithiocarbamates (3) and N,N'-alkylene-bisdithiocarbamates (4), similarly showing certain differences. Characteristic of dithiocarbamates belonging to the first main group is a tendency to form isothiocyanates due to the active proton remaining on the nitrogen and, according to several authors, their ultimate exertion of fungicidal action as alkylisothiocyanates. Their degradation is continuous, so that their activity is proportional to concentration.



3



4

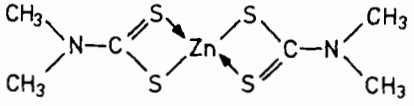
The synthesis of dialkyldithiocarbamates, belonging to the second main group, is accomplished by the reaction of secondary amines with carbon disulfide. These compounds cannot metabolise to isothiocyanates, but are finally decomposed into the initial amine and carbon disulfide. The biological action of the compounds is attributed to the dialkyldithiocarbamate ion, and the activity–concentration curve of the compounds is bimodal. This phenomenon is explained by the dialkyldithiocarbamates first forming 1 : 1 complex conpounds with copper ions, which are always present in trace quantities in nature, and these complexes being comparatively soluble, thus penetrating the cells having excellent fungicidal properties (Janssen and Kaars Sijpesteijn, 1961). With increasing dialkyldithiocarbamate ion concentration, however, the insoluble 2 : 1 dithiocarbamate–copper complex is gradually

formed, and the biological action is reduced. When dithiocarbamate ions are present in excess by a further increase in their concentration, biological activity again increases due to the effect of the unbounded dithiocarbamate (Goksoeyr, 1955; Kaars Sijpesteijn and Janssen, 1958).

It can be similarly attributed to the formation of the complex that dialkyldithiocarbamates can be antagonised with histidine, which also has complex-forming properties. Monoalkyldithiocarbamates are not antagonised, since the complex-formation does not play any role in their effect.

Different properties in the two groups produce only small differences in the range of biological action of dithiocarbamates. Heuberger (1947) found that zinc and iron salts of ethylene-bisdithiocarbamates are more efficient than the corresponding salts of dimethyldithiocarbamates against early blight and late blight of potato and tomato. but are less efficient against enthracnosis of tomato. The salts of dialkyldithiocarbamates are mainly toxic to spores, while the salts of ethylene-bisdithiocarbamates are toxic to both spores and micelia. Iida *et al.* (1951) observed that *Ophiobolus* spores behave differently towards the active substances ziram and zineb.

Several researchers participated in the elucidation of the structure of dithiocarbamates (Van der Kerk *et al.*, 1955; Chatt *et al.*, 1956). Today it has been established unequivocally that the salts of dithiocarbamic acid formed with metals are complex compounds (**5**) and that the compounds of ethylene-bisdithiocarbamate formed with bivalent metals even have a highly polymeric character (**6**). Little information pertinent to their structure is available, but a coordination structure such as (**7**) is conceivable (Vonk, 1975).



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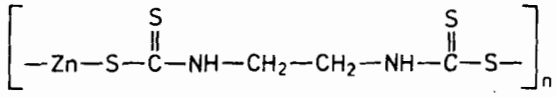

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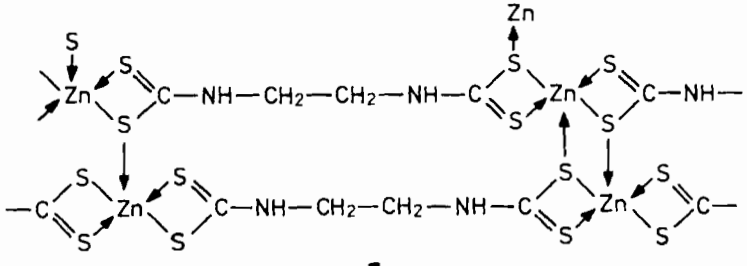


7

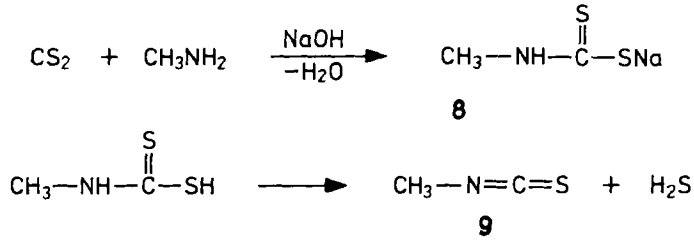
Dithiocarbamates began to play a role in plant protection as early as the 1930s. Tisdale and Williams (1934) in the USA and Martin (1934) in the UK discovered independently the biological activity of dimethyldithiocarbamates, long used as "vulcanisers" in the rubber industry. This finding opened thereby a new chapter in the agricultural application of organic compounds. The first report in the literature on ethylene-bisdithiocarbamates is associated with the name of Hester (1943). Since then several hundred research workers have studied the chemistry, biological action, mode of action and metabolism of dithiocarbamates, and recently also their behaviour in terms of environmental pollution. A number of reviews have also been published (Klöpping, 1951; Thorn and Ludwig, 1962; Owens, 1969).

Dithiocarbamate fungicides attained importance in plant protection after World War II (ziram and ferbam were the first foliage fungicides prepared on a large industrial scale), and even today, in the age of systemic fungicides, their use has not decreased (Tweedy, 1973). Despite much intensive research, however, only a few dithiocarbamate derivatives have found practical application.

5.5.1 N-Monoalkyldithiocarbamates

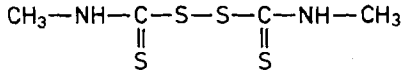
The simplest member of the first subgroup is methyldithiocarbamic acid or metham. The sodium **(8)** or the ammonium salt is formed, depending on whether the reaction of carbon disulfide with methylamine is carried out in a sodium hydroxide or ammonium hydroxide medium. The free acid is not stable.

The salts slowly hydrolyse in dilute aqueous solution, and from the acid liberated methylisothiocyanate **(9)** is formed, which is the carrier of the fungicidal action.



The same reaction also proceeds in the soil. Metham-sodium is a powerful soil disinfectant, because in addition to being toxic to soil fungi (*Pythium, Rhizoctonia* spp.), it is also toxic to soil nematodes and soil insect, and it even inhibits the germination of seeds. Because of this latter property, cultivated plants can be sown or planted in soils treated with metham only after a certain period (biotest). The preparations are formulated as aqueous solutions: the sodium salt under the trade name Vapam® and the ammonium salt under the trade name Ipam®. The ammonium salt is thought to be more advantageous, because its manufacture proceeds at higher efficiency and gives a purer endproduct; moreover, the ammonium hydroxide formed from it in the soil is a nitrogen source (Pfeifer and Nádasy, 1972; Pfeifer *et al.*, 1972b).

The oxidation product of metham, N,N'-dimethylthiuram disulfide (**10**), is also a soil disinfectant. It is very toxic to the microflora (100 mg/kg), particularly against *Actinomycetes* fungi, but is inactive against bacteria (Polovinko, 1970).



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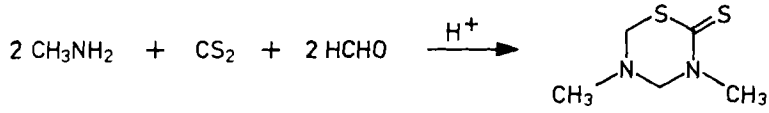
The salts of metham are not stable in solid form, so they are marketed as relatively dilute aqueous solutions, which makes their use rather expensive. When the reaction of methyl amine with carbon disulfide is carried out in the presence of formaldehyde, the stable solid compound 3,5-dimethyl-tetrahydro-1,3,5-thiadiazine-2-thione, or dazomet (**11**), is obtained. It is applied as a dust or as a concentrated prill.



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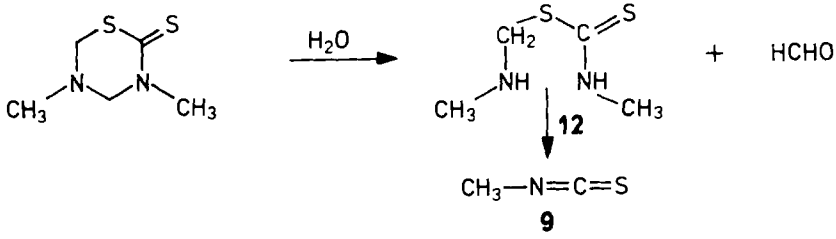
Dazomet is hydrolysed by water; formaldehyde and N-methyldithiocarbamate ester (**12**) are formed, and the latter is converted into methylisothiocyanate (Munnecke and Martin, 1964; Goksoeyr, 1964).



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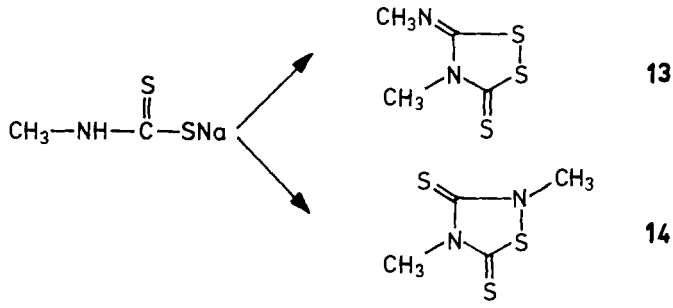
The initial toxicity of a freshly prepared aqueous dazomet solution is low, but after 24 hours, when a substantial quantity of the N-methyldithiocarbamate ester has been converted into methylisothiocyanate, its fungicidal activity increases considerably. A similarly strong fungicidal action develops on the addition of copper ions to the freshly prepared solution, which indicates that the ester bond has been ruptered and the active copper complex of N-methyldithiocarbamate has formed.

The sodium salt of N-methyldithiocarbamate is converted by oxidation into the compounds 4-methyl-5-methylimino-4-aza-1,2-dithiolane-3-thione (**13**) and 2,4-dimethyl-1,2,4-thiadiazolidine-3,5-dithione (**14**) (Thorn, 1960).



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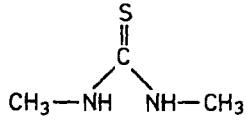
The decomposition of dazomet in the soil proceeds as in aqueous media (Munnecke and Martin, 1964), and the strong activity of methylisothiocyanate formed is enhanced by the formaldehyde liberated, which is also an effective soil fungicide. N,N'-dimethylthiourea **(15)** may also form as degradation product, and a further metabolite, 1,3,5-trimethyl-hexahydro-1,3,5-triazinethione **(16)**, has also been identified in the soil (Drescher and Otto, 1968). The latter also forms in neutral aqueous solution from dazomet. The compound is biologically inactive and is not persistent in the soil.



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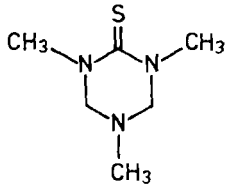

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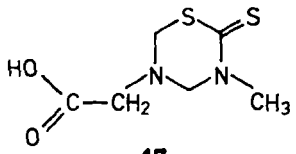
Of the derivatives, 5-carboxymethyl-3-methyl-tetrahydro-1,3,5-thiadiazine-2-thione (thiadiazinethion, **17**), its sodium salt, and 3,3'-ethylene-bistetrahydro-4,6-dimethyl-2H-1,3,5-thiadiazine-2-thione (milneb, **18**) have been used in agriculture, the latter being effective also against apple scab, tobacco peronospora and potato blight.



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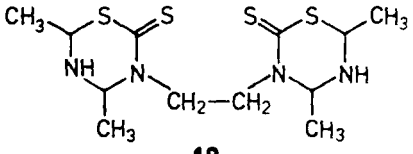

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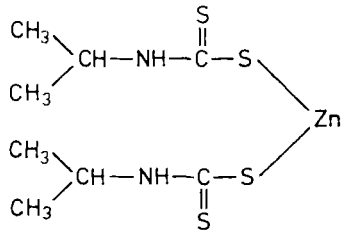
Of the N-alkyldithiocarbamates, neviram, zinc bisisopropyldithiocarbamate **(19)**, also used as a foliage fungicide, has a good fungicidal effect (Pfeifer *et al.*, 1972a). Its fungitoxic action is the same as that of zineb, the dithiocarbamate used in the largest quantity at present. If the hypothesis that N-mono-substituted

dithiocarbamates ultimately act through the isothiocyanates formed from them is accepted (see later), the high activity of neviram is easily understood, because among the isothiocyanates, isopropylisothiocyanate has an outstanding fungicidal action (Pfeifer, 1976).



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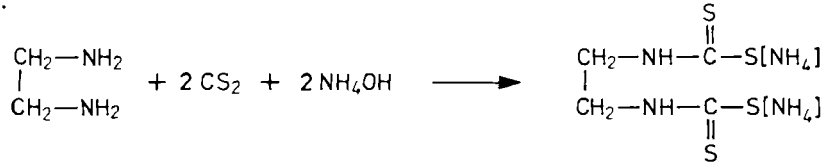
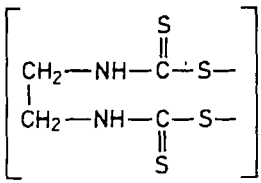
The synthesis of neviram starts with isopropylamine, carbon disulfide and ammonium hydroxide. In the intermediate step, the aqueous solution of ammonium isopropyldithiocarbamate is formed which, on the addition of zinc sulfate, yields zinc bisisopropyldithiocarbamate as a water-insoluble compound. Ammonium hydroxide is more advantageous than other alkalies for this use, because the formation of the trithiocarbamate salt or zinc trithiocarbamate can be avoided, and a purer product is obtained (Pfeifer, 1976). The range of action of neviram is similar to that of zineb. It can be used in vineyards against *Peronospora* and *Botrytis*, and in orchards against apple and pear scab. It is effective also on vegetables (Pfeifer *et al.*, 1972a). It is an active substance with advantages for environmental protection, because its decomposition products do not cause environmental problems (Mezentseva, 1968, Thuránszky and Botos, 1976).

5.5.2 N,N-Ethylene-bisdithiocarbamates

The members of the second subgroup are prepared from ethylene diamine **(20)** or its derivatives by reaction with carbon disulfide. In a sodium hydroxyde medium the disodium salt nabam, in an ammonium hydroxide medium, the diammonium salt amobam is formed **(21)**. The sodium-ammonium salt, nambam, can also be prepared. These active substances are soluble in water. They cannot be used as foliage fungicides because of their phytotoxicity. On the other hand, they can be applied with good results for seed treatment. These compounds are intermediate products of the water-insoluble metal salts of N,N-ethylene-bisdithiocarbamic acid.



20 **21**



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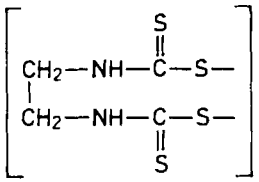

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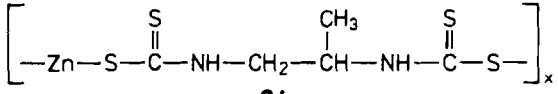
The zinc salt of N,N-ethylene-bisdithiocarbamic acid, zineb (**22**), is obtained with zinc sulfate or with zinc oxide suspension from the aqueous solution of nabam. It is a protective foliage fungicide with a very wide range of action. Though of good tenacity and resistance to rain, its persistence is inferior to that of copper-containing fungicides. It is not phytotoxic and is well tolerated even by the most sensitive of fruits. It is effective against *Peronospora* of vine, *Fusicladium* spp., *Peronospora* of tobacco, *Phytophthora* on potato and tomato, *Alternaria* and *Septoria* spp., and against fungi damaging seedlings. Preparations in combination with copper oxychloride are advantageous not only because of the long-lasting action, but because there is also a synergistic effect between the two active substances, which increases the biological action of the preparation. When combined with nickel salts, its range of action is extended to include rust diseases.

The alkali salt of N,N-ethylene-bisdithiocarbamic acid can be converted with manganese sulfate into the manganese salt. Maneb (**23**) is less stable than zineb, mainly because of the tendency of manganese toward redox catalysis. The pH of the medium must therefore be carefully selected for its preparation, and the preparations must be protected from humidity during storage. On application it rapidly decomposes even in the spray, so that it is phytotoxic to the sensitive apple species. Maneb is more efficient against tobacco *Peronospora* than zineb, and can be used with good effect against the pests of potato and tomato.

Mancozeb is the manganese-zinc double salt of N,N-ethylene-bisdithiocarbamic acid. This compound is more stable than the derivatives described above (Bontoyan and Looker, 1973); this property has been attributed to the polymeric structure of mancozeb. Mancozeb is not phytotoxic. The polymer generally contains 20% manganese and 2% zinc besides ethylene-bisdithiocarbamate ions.

1,2-diaminopropan is the basic compound of propineb (**24**), zinc propylene-1,2-bisdithiocarbamate. Its fungicidal activity considerably surpasses that of zineb, particularly against the pathogens of scab. Its strongest action is directed against *Phycomycetes* species. Its advantageous side-effects are a certain inhibiting action of Oidium, a checking of *Botrytis* spp., and, in repeated treatment, toxicity to red



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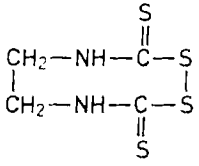
spider mite (Goeldner, 1967). It is superior to zineb also with respect to tenacity. The effect of its mangenese–zinc complex is even more powerful (Grewe. 1967).

When the water-soluble salts of ethylene-bisdithiocarbamic acid are oxidised, ethylenethiuram disulfide **(25)** and a mixture of polyethylenethiuram disulfides **(26)** of different molecular weight are formed. These compounds have not gained widespread use. By the addition of zinc sulfate and simultaneous partial oxidation, however, an active substance can be prepared, which is a polimeric mixture of polyethylene thiuram disulfide and the zinc complex in varying ratios. The length of chain is not defined, but in preparations used in agriculture the ratio of disulfide linkages to the zinc atoms, x : y, is 1 : 3. The best known active substances are metiram **(27)** and its methyl homologue met-metiram. They are powerful fungicides with a wide range of action, particularly in apple orchards, and moreover, have proved to be among the most effective substances against the downy mildew of vine.



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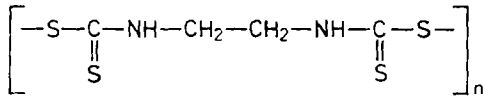

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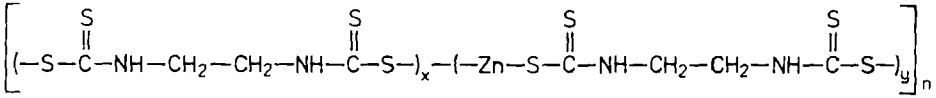

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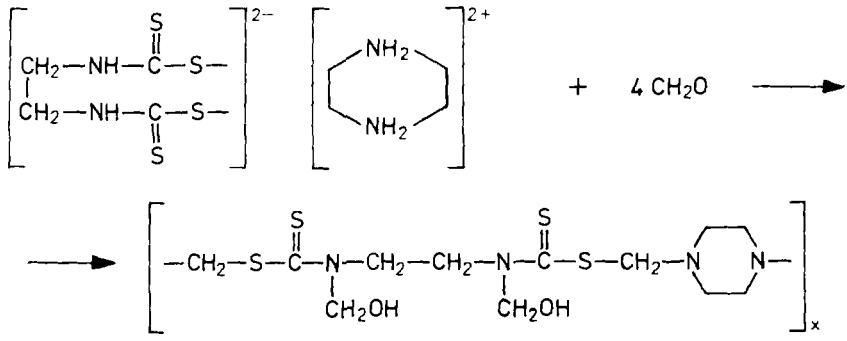
Polycarbazin is the synergistic mixture of 70% zineb and 30% polyethylene thiuram disulfide (Melnikov, 1967). It is prepared by the oxidation of amobam with ammonium persulfate or with hydrogen peroxide in slightly acid medium, in the presence of zinc oxide (Orlov *et al.*, 1975). It is effective against apple scab at lower concentrations than zineb, and favourably affects the growth of apple trees (Chanturiya *et al.*, 1969). Against grey mould, too, it is more effective than zineb (Melnikov *et al.*, 1970), and for the treatment of potato tubers it is better than TMTD **(32)** (Volovik and Borishenok, 1976). The action of polycarbazin is synergised by copper oxychloride (Golyshin and Kolcov, 1975).

Matolcsy *et al.* (1977) prepared the copolymer of linear structure **(28)** by the reaction of the piperazinium salt of ethylene-bisdithiocarbamic acid with formaldehyde. The preparation of this product (proposed common name: pireb) was motivated partly by their earlier finding that the S-aminomethyl derivatives of biologically active dithiocarbamic acids have a strong fungicidal effect, in contrast to the S-alkyl derivatives, because the atomic group $=N—CS—S—CH_2—N=$ facilitates the cleavage of the dithiocarbamate ion ultimately responsible for the action (Matolcsy *et al.*, 1973). The product they obtained is the first pesticide with copolymer structure.



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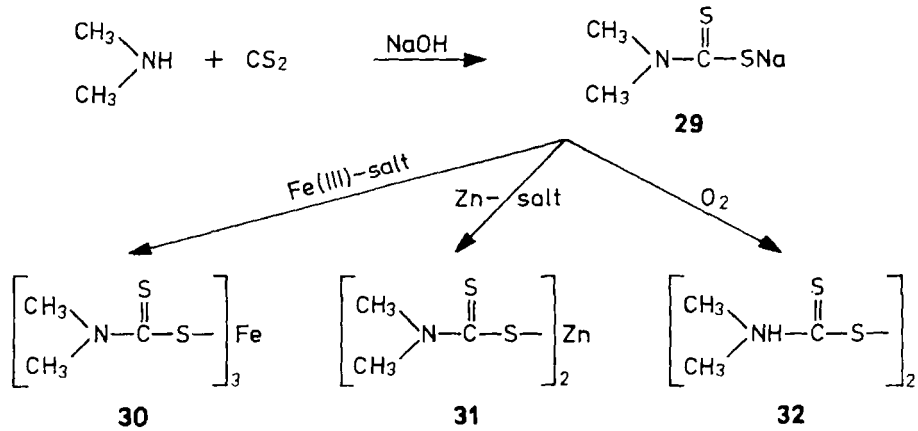
5.5.3 Dialkyldithiocarbamates

Of the dialkyldithiocarbamates belonging to the second group of dithiocarbamates, dimethyldithiocarbamates have the highest activity. With an increase of the alkyl group fungitoxity is rapidly reduced. The compounds are prepared by the reaction of dimethylamine with carbon disulfide and alkali hydroxide. The individual active substance can be obtained by the addition of the alkali salt formed.

The sodium salt of dimethyldithiocarbamate is diram **(29)**, and the ammonium salt is diram-A. Both salts are phytotoxic but can be used for seed treatment. Of this group, too, only the water-insoluble metal salts come under consideration as foliage fungicides. Of these, the iron salt of dimethyldithiocarbamate, ferbam **(30)**, is the most important because it is more stable than the zinc salt, ziram **(31)**.

In the preparation of ferbam an excess of ferric ions must be avoided, because their oxidising action diminishes the stability of ferbam. The metal salts of



30 31 32

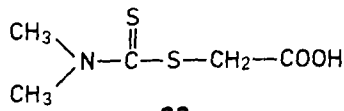
dimethyldithiocarbamates are particularly effective against apple scab and blue mould, but they also give good protection against the seedling diseases of vegetables. The nickel salt also has a bactericidal effect.

The most important member of this group is thiram **(32)**, bis(dimethylthiocarbamoyl) disulfide, also known as tetramethylthiuram disulfide, from the abbreviation of which stems the generally known name TMTD. It is prepared by the oxidation of the water-soluble alkali salts of dimethyldithiocarbamic acid. The oxidising agent may be hydrogen peroxide, chlorine or air. TMTD was the first dithiocarbamate used for plant protection, and even today it plays an important role, although its use shows a decreasing trend. It is a protective fungicide against apple and pear scab, strawberry grey mould and seedling diseases. Today it is used mainly for seed dressing, by itself or in combination with other active substances.

The importance of the alkyl groups in the fungicidal action of dialkyldithiocarbamates can be best characterised by TMTD. These alkyl groups regulate the strength of the disulfide group and partly determine the lipophilicity and volume of the molecule. Whether the molecule can penetrate the fungal cells therefore depends on these groups, and they determine the rate of the reactions within the cells. In this respect, methyl groups are the most favourable, because side-chains with increasing carbon atom number increase the size of the molecule and decrease the reduction potential of disulfide. Dimethyl substitution enhances disulfide activity to a larger extent than monosubstitution.

The excellent fungicidal properties of dithiocarbamates have stimulated research-workers to investigate this area for active substances of improved biological activity, and possibly of higher selectivity.

Part of this research has been directed towards N,N-dimethylthiocarbamoylthioacetic acid **(33)** and its homologues, which have properties similar to those of auxins and have a systemic antifungal effect (Van der Kerk *et al.*, 1955; Garraway, 1965).



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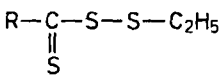
Konečny *et al.* (1971) prepared derivatives characterised by the general formula **(34)**, where R may be a dimethylamine, diethylamine, piperidine or 1,2-ethylene amine group. The compounds showed the same activity as the fungicides used as standards (TMTD, captan). S-Buthylsulfenyldithiocarbamate derivatives of the general formula **(35)** proved less effective.



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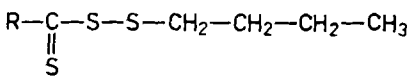

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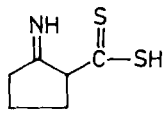
The metabolites of dimethyldithiocarbamid acid play a part in the systemic action of plants (Dekhuijzen, 1964). Pluijgers *et al.* (1969) therefore synthesised several carbohydrate and amino acid derivatives of dimethyldithiocarbamic acid.

Matolcsy and Josepovits (1967) synthesised and tested N-cyanoalkyl- and N-carboxyalkyldithiocarbamates (Bánki *et al.*, 1966). Several hundred dithiocarbamic acid derivatives have been prepared by Carter *et al.* (1963, 1964), and their structure–biological action relationship has been investigated.

In the course of time several combinations of active substances have been introduced. Zineb combined with copper oxychloride exhibits a synergistic effect (Payen *et al.*, 1954). The antifungal action of ziram against *Botrytis* spp. is increased by several orders of magnitude by the addition of complex-forming organic compounds e. g., 2-iminocyclopentane dithiocarboxylic acid **(36)** (Matolcsy *et al.*, 1971).



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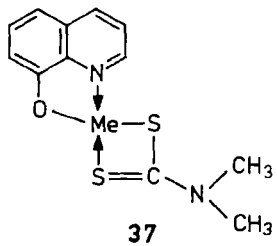
Starting from the finding of Gershon *et al.* (1966) that asymmetric, mixed-ligand metal chelates are biologically more active than the 2 : 1 symmetric metal chelates, Matolcsy *et al.* (1974) prepared the mixed-ligand chelates of structure **(37)** by treating the sodium salts of 8-oxyquinolinate and dimethyldithiocarbamate with



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Me = Zn, Cd, Cu

the salts of bivalent metals. The asymmetric structure of the metal complex has been verified by thermoanalytical tests. The antifungal action of these products was stronger than that of the single 2 : 1 symmetric complexes or that of their physical mixture of molar ratio.

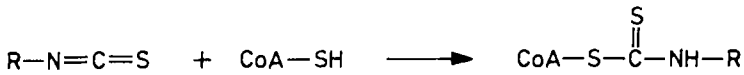
5.5.4 Mode of action and mechanism

Dithiocarbamates react with the HS-containing enzymes and coenzymes of fungal cells. Enzyme inhibition may also occur by complex formation of the active substance with the metal atoms of metal-containing enzymes (Owens, 1953). The inhibition mechanism is not specific — a primary of main reaction cannot be distinguished in the process. The inhibiting effect of the sodium salt of

dimethyldithiocarbamic acid could be best observed on the lipid synthesis of *Xanthomonas oryzae* bacteria (Yoneyama and Misato, 1971). The subgroups of dithiocarbamates show a somewhat different behaviour.

N-Monoalkyldithiocarbamates themselves have a fungicidal effect (Wedding and Kendrick, 1959) because they can react directly with the thiol groups. This is also indicated by the fact that they can be synergised with copper ions. The instability of N-monoalkyldithiocarbamates, however, indicates the activity of isothiocyanates formed from them. With these compounds the free proton adjacent to the nitrogen atom makes possible the formation of isothiocyanates (Van der Kerk, 1955; Rich and Horsfall, 1950). Isothiocyanates are fungitoxic substances with a wide range of action (Zsolnai, 1975). They are characterised by a high vapour pressure even at room temperature. Therefore, methylisothiocyanate (metifum) is used as an active substance alone or in combination with D-D (a mixture of 1,2-dichloropropane and 1,3-dichloropropene) as a soil disinfectant.

At a pH higher than 5.5–6.0, isothiocyanates react *in vitro* and *in vivo* with thiol compounds **(38)**, thereby blocking essential HS-containing constituents in the cytoplasm. It is still an open question whether isothiocyanates are group reagents of all the HS-containing enzymes, but they presumably also react with enzymes of other types, because they also react easily with alcohols and amines.



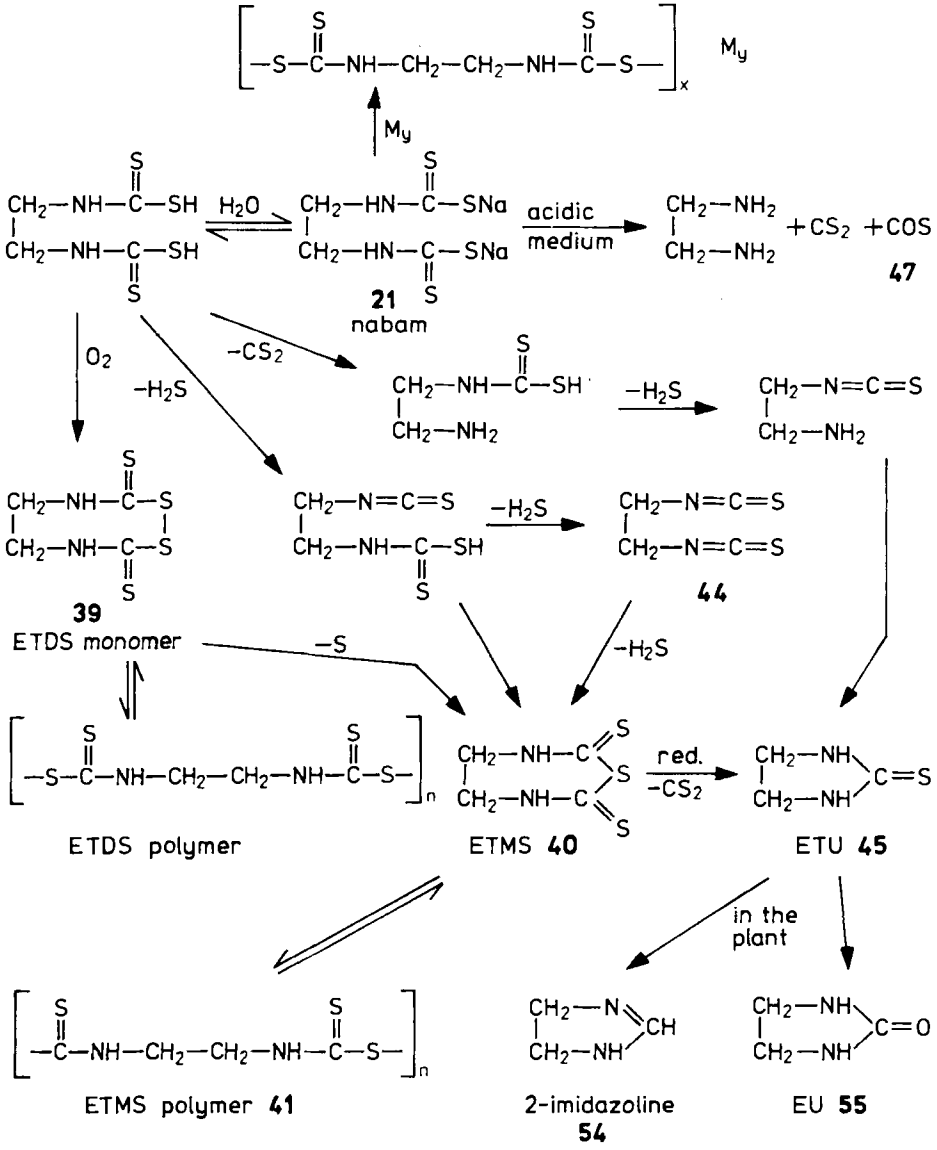
38

Ethylene-bisdithiocarbamates in themselves are only moderately fungitoxic, but they are very unstable, particularly to water and oxygen. Several workers therefore studied the decomposition of these compounds under various conditions to find the carrier of the fungitoxicity. The decomposition mechanism of the well-defined sodium salt, nabam, has been investigated extensively, but similar results were also obtained in the investigations of the decomposition of the metal complexes (zineb, maneb) (Engst and Schnaak, 1970). Results concerning the decomposition mechanism of ethylene-bisdithiocarbamates are summarised in Scheme 5.1.

Klöpping and Van der Kerk (1951) presumed that, analogous to the mode of action of N-monoalkyldithiocarbamates, in the case of ethylene-bisdithiocarbamates, ethylene-bisisothiocyanate is the toxic agent. This decomposition product was detected later by thin-layer chromatography on tomato treated with maneb and in an aerated aqueous solution of nabam (Engst *et al.*, 1968; Engst and Schnaak, 1970). Recently, the attention of the researchers has also turned to the other decomposition products.

Ethylenethiuram disulfide **(39)** is formed by the oxidation of an aqueous solution of nabam (Morehart and Crossan, 1965; Czeglédi-Jankó and Holló, 1967; Engst and Schnaak, 1970; Hylin, 1973).

It is thought, however, that this compound is only an intermediate product converted at pH values lower than 6.0 by elimination of sulfur into ethylenethiuram



Scheme 5.1

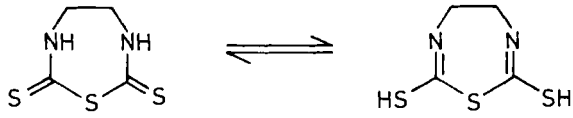
monosulfide **(40)**. This is supported by the detection of elemental sulfur among the decomposition products of nabam (Engst and Schnaak, 1970; Hylin, 1973).

Ethylenethiuram monosulfide can be prepared with good yield directly from the aqueous solution of nabam by mild oxidation. In addition to the monomer, products of various degrees of polymerisation are formed **(41)** and sulfur

precipitates. The process is catalysed by manganese ions (Ludwig *et al.*, 1954; Thorn and Ludwig, 1954).

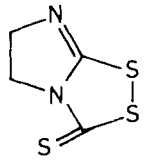
Ethylenethiuram monosulfide can be formed also *via* isothiocyanate (Kaars Sijpesteijn and van der Kerk, 1954), although oxidation plays an essential role in the reaction according to Vonk (1975).

Ethylenethiuram monosulfide (etem) is the degradation product of nabam formed in the largest quantity. It is an active fungicide with the same antifungal range of action as nabam but twice as effective (Matolcsy *et al.*, 1972). Its structure (hexahydro-1,3,6-thia-diazepine-2,7-dithione) has been determined by Thorn *et al.*, and, on the basis of the IR spectrum, they suggested the tautomeric enethiol structure **(42)** (Ludwig and Thorn, 1953; Ludwig *et al.*, 1954; Thorn and Ludwig, 1954; Thorn, 1960).



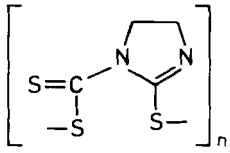
40 **42**

However, inconsistencies arose in connection with this structure and other workers suggested other structures (Pluijgers *et al.*, 1971; Benson *et al.*, 1972). Finally, the structure of ethylenethiuram monosulfide has been verified on the basis of spectral data and the fact that with carbon disulfide the compound gives an adduct. This proved to be 5,6-dihydro-3H-imidazo [2,1-c]-1,2,4-dithiazole-3-thion (DIDT, **43**) (Vonk, 1975).

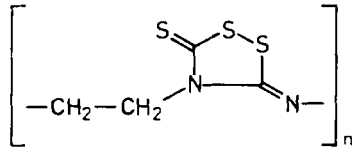


43

The presumed structure of the polymeric compound formed besides DIDT has also been revised. Alvarez *et al.*, (1973) suggested the structure **(41a)**, but Vonk (1975) thinks structure **(41b)** is also possible.

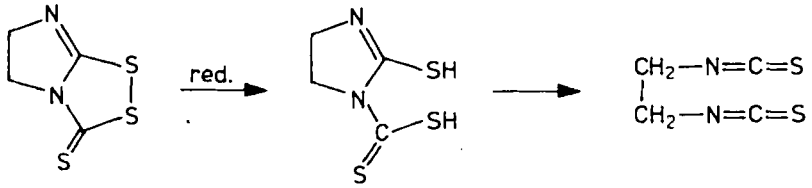


41a



41b

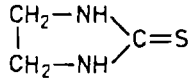
DIDT can be converted in a nonpolar solvent into ethylene-diisothiocyanate (**44**) (Kaars Sijpesteijn and Van der Kerk, 1954).



43 **46** **44**

DIDT easily penetrates the lipid phase of the fungal spores and cells, and its subsequent conversion into diisothiocyanate may be the mechanism of the fungitoxic action of DIDT and ultimately of ethylene-bisdithiocarbamates.

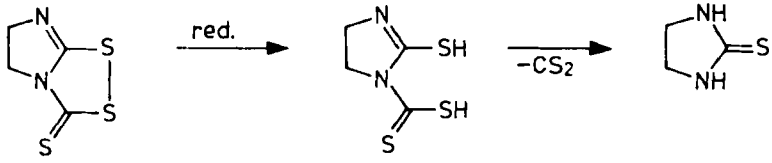
One of the degradation products of ethylene-bisdithiocarbamic acid is N,N'-ethylene thiourea (ETU) (Barratt and Horsfall, 1947; Thorn and Ludwig, 1954; Engst and Schnaak, 1970), also named 2-imidiazolidinethione (**45**):



45

It is formed by aeration of an aqueous solution of nabam in an alkaline medium. Matolcsy (1968) described a new synthesis route.

ETU can also be formed from DIDT by reduction and elimination of carbon disulfide. This reaction is greatly stimulated by the addition of a suspension of bacteria, yeast or filamentous fungi in the presence of glucose. Crude enzyme extracts also bring about this reaction in the presence of NADH. The reducing compounds cysteine, glutathione and ascorbic acid, too, stimulate ETU formation. These observations strongly suggest that an intermediate product (**46**) is formed by reduction of the disulfide bond, resulting in ring opening. This intermediate product would then give rise to ETU (**45**) and CS_2 (Kaars Sijpesteijn and Vonk, 1975).

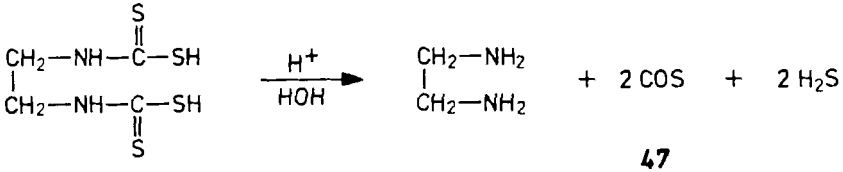


43 **46** **45**

ETU is not fungitoxic—thus, this degradation product cannot be the toxic agent of ethylene-bisdithiocarbamates. Investigations suggest that this product is probably formed from the active substance entering the spores, then rapidly leaving the

cell and accumulating in its environment (Rich and Horsfall, 1954). Ethylene thiourea has systemic properties (Vonk and Kaars Sijpesteijn, 1970; Vonk, 1971; Pluijgers *et al.*, 1971), so that ETU formed in an aqueous solution or in the soil can enter the plant. ETU has carcinogenic, teratogenic and goitrogenic effects on mammals; thus, the elucidation of its role is an important problem from the viewpoint of environmental protection (see later).

Further degradation product of nabam has also been found. The presence of hydrogen sulfide and carbon disulfide in the vapour of the aqueous solution has been observed by several workers (Rich and Horsfall, 1950; Weed *et al.*, 1953; Kendrick, 1960). However, the great fungitoxicity of the vapour cannot be caused by these compounds. Moje *et al.* (1964) showed by IR spectroscopy that carbonyl sulfide (**47**) is also present in the vapour, inhibiting completely the mycelial growth of *Pythium irregulare*. The formation of the compound can be characterised by the following scheme:



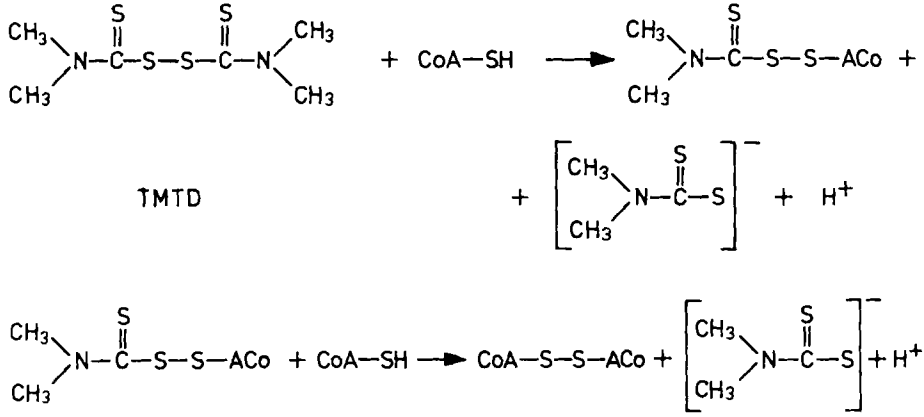
47

Nabam is similarly degraded in the soil (Kaars Sijpesteijn and Vonk, 1970).

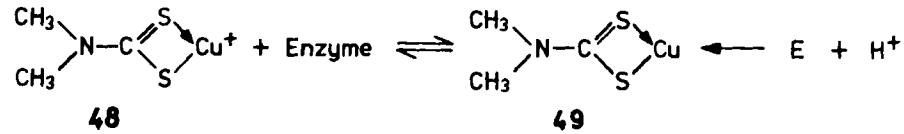
Thus several compounds with powerful fungicidal action have been found among the degradation products of ethylene-bisdithiocarbamates, among them, ethylene-bisisothiocyanate, ethylenethiuram monosulfide (as a result of recent investigations DIDT), their polymers, and carbonyl sulfide. Each of these is responsible for individual aspects of the fungitoxic action of ethylene-bisdithiocarbamates, but essentially their combined action is exerted. Thus, by the application of ethylene-bisdithiocarbamates, an inhibiting system acts on the fungi which is able to perform, on the one hand, the reactions of dithiocarbamates, and, on the other hand, the reactions of isothiocyanates, DIDT and the polymers. Of the dithiocarbamates, therefore, ethylene-bisdithiocarbamates have the widest range of action (Vogeler, 1977).

N,N-Dimethyldithiocarbamates do not form isothiocyanates, so their mode of action as fungicides is different from that of the afore-mentioned substances. TMTD penetrates the cell membrane of fungi more easily than dimethyldithiocarbamates, and is then reduced within the cell (Richardson and Thorn, 1961) so that its action is the same as that of dimethyldithiocarbamates. However, the fact that TMTD is more toxic to several microorganisms than the sodium salt of dimethyldithiocarbamic acid indicates that there must be a certain nonessential difference between the two active substances. Owens and Rubinstein (1964) proved *in vitro* the different reactivity of TMTD and of the other dimethyldithiocarbamates towards 4-nitrothiophenol. However, in the primary reaction of TMTD dimethyl-

dithiocarbamate ion is also formed, which also reacts with the cell components. The inhibiting action of TMTD proceeds in two steps:



TMTD reacts spontaneously with sulfhydriles, because of the favourable change in free energy of the reaction. On the other hand, the reaction possibility between the dimethyldithiocarbamate ion and sulfhydriles is less favourable and, indeed, less probable. It is therefore thought that from the point of view of fungitoxicity dimethyldithiocarbamates come into consideration only as heavy metal chelate formers (Kaars Sijpesteijn *et al.*, 1975). Some researchers explain the fungicidal action by the formation of a 1 : 1 complex of the dimethyldithiocarbamate ion with copper ions **(48)**, this complex then binding chemically the essential enzymes **(49)** (Van der Kerk, 1953, 1958, Van der Kerk and Klöpping, 1952, Pluijgers, 1959). Histidine exerts its antagonistic action by replacing competitively the enzyme.



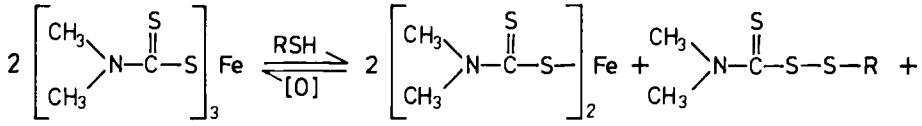
48 **49**

The antifungal effect of the 2 : 1 complex nontoxic in itself, is an unsettled question. According to certain authors, it is converted within the cell into the 1 : 1 complex. However, this is inconsistent with the fact that the 2 : 1 complex cannot penetrate the cell with its very low water solubility. According to recent theories, the stabilities of the complexes play the decisive role. The stability of the metal complexes of identical dialkyldithiocarbamates depends on the metal. The order of stability of dimethyldithiocarbamate complexes used as fungicides is, according to Eckert (1957), Mn < Zn < Fe < Ni < Cu.

Manganese, zinc and iron dithiocarbamates, whether they are 1 : 1 or 2 : 1 complexes, react with copper-containing complex compounds, thus with proteins,

and block them. If the stability of the metal complex formed during the reaction is higher than that of the original compound, the reaction will proceed. The copper ions present will replace first the metal ions of the fungicide, and will then react in this form with the copper-requiring enzymes. The more stable enzyme-complex is always formed.

In the mode of action of the dimethyldithiocarbamate, ferbam (**30**), reduction and the atmospheric re-oxidation of iron also play a role (Owens and Rubinstein, 1964). The end-products of this process are dimethylamine and carbon disulfide.



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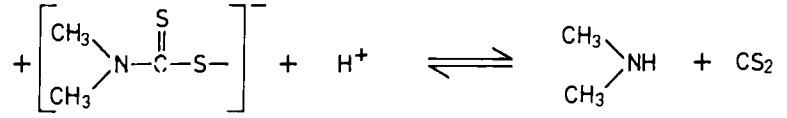
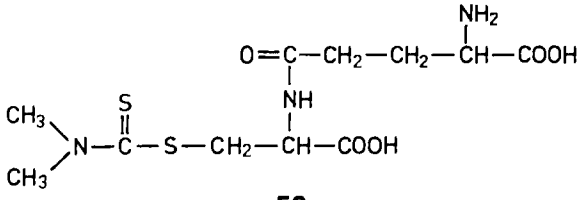


All of the dithiocarbamates are decomposed in acid media into corresponding amine and carbon disulfide. Their analytical determination is based on this reaction (Clarke *et al.*, 1951).

5.5.5 Aspects of environmental protection

Dithiocarbamates are protective fungicides. Only in the case of TMTD have some specific properties been observed. (Pluijgers and van der Kerk, 1961; Kaslander, 1966). In plant tissues dimethyldithiocarbamic acid forms conjugates enzymatically, which preserve their fungitoxic action after hydrolysis by the fungal enzymes. The conjugates identified so far are N,N-dimethylthiocarbamoyl-1-thio-β-D-glucopyranoside (**50**) (Kaslander *et al.*, 1961) and β-(N,N-dimethyl-thiocarbamoyl-thio)-L-α-alanine (**51**) (Kaslander *et al.*, 1962), and the non-fungicidal thiazolidine-2-thione-4-carboxylic acid (**52**), formed from the latter (Dekhuijzen, 1961, 1964; Kaslander, 1966).

A conjugate of probable dipeptide structure, dimethyldithiocarbamoyl-(N-γ-glutamil)alanine (**53**), has also been detected.



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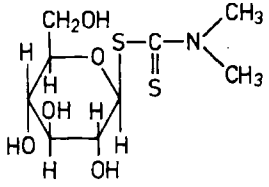

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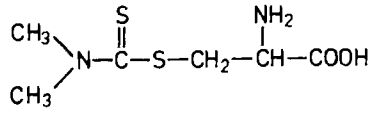

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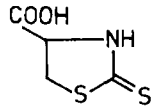
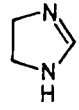
HOH



52

Ethylene-bisdithiocarbamates do not form conjugates with plant constituents because of their instability, but their decomposition products are present on the plant surfaces treated with them (Engst *et. al.*, 1968; Vonk, 1975), and, in the case of root treatment, even inside the plant. Nabam, unstable in an aqueous environment, is converted into ETU and DIDT, and the plant is exposed primarily to the action of these two principal decomposition products. ETU has a systemic effect and can thus penetrate the plant through the root and the leaves (Sato and Tomizawa, 1960; Hoagland and Frear, 1976), but it is then metabolised within a relatively short time into 2-imidazoline **(54)** and ethylene urea EU **(55).** Both compounds are also formed photochemically from ETU by the action of sunlight in the presence of photosensitisers (acetone, chlorophyll) (Cruickshank and Jarrow, 1973; Ross and Crosby, 1973). The mechanism of their formation in the plant, however, is different, because these metabolites can also be detected in plants treated in the dark (Vonk and Kaars Sijpesteijn, 1970, 1971; Vonk, 1975). In the green parts of the plant polar metabolites have also been detected, which are presumably formed from DIDT in the root and translocated into the leaves.



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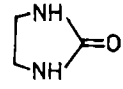
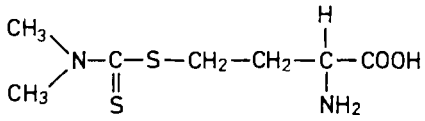


55

The quantity of ETU at the surface of the plant rapidly decreases and could not be detected after three weeks (<0.5 mg/kg) (Yip *et al.*, 1971; Blazquez, 1973; Hoagland and Frear, 1976). Recently, the fate of ETU and other metabolites in the plant has been studied by several workers (Newsome *et. al.*, 1975; Nash, 1976, Rhodes, 1977; Pease and Holt, 1977; Ripley and Cox, 1978; Ripley, 1979). Generally, the quantity of metabolites in the plant increases for six days following the treatment (in the case of the usual quantities used for spraying from 0.05 mg/kg

to 0.1 mg/kg), and then decreases rapidly (Klisenko and Vekshtejn, 1971; Engst and Schnaak, 1975).

Dimethyldithiocarbamates are metabolised by fungi and bacteria to γ-N,N-dimethylthio-(carbamoylthio)-L-α-aminobutyric acid **(56)** (Kaslander, 1966).



56

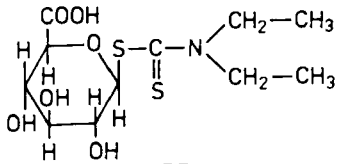
Dithiocarbamates, with the exception of metham and dazomet, are not directly toxic to plants, but they thin the epidermis of the leaves, making them susceptible in particular to powdery mildew fungi and to mites.

The direct toxicity of the fungicides to mammals is low. The acute oral LD_{50} values of the single active substances for rats are:

metham	820 mg/kg
dazomet	500 mg/kg
neviram (in mice)	4250 mg/kg
nabam	395 mg/kg
maneb	6750 mg/kg
mancozeb	8000 mg/kg
zineb	5200 mg/kg
propineb	8500 mg/kg
ziram	1400 mg/kg
ferbam	17 000 mg/kg
TMTD	750 mg/kg

The dermal toxicity of dithiocarbamates is similarly very moderate, though on longer contact it may cause irritation of the skin in sensitive individuals, while its vapour may cause conjunctivitis and bronchitis.

Dialkyldithiocarbamates inhibit the function of aldehyde oxidase; thus alcohol consumed simultaneously with their uptake produces toxic reactions. The oxidation of alcohol proceeds only to acetaldehyde, which accumulates to cause poisoning. Tetraethylthiuram disulfide (Antabuse) is used for this property for the curing of alcohol addicts. Investigation of the fate of the active compounds in human tissues has also yielded data on the metabolism of dialkyldithiocarbamates. A conjugate, N,N-diethylthiocarbamoyl-1-thio-β-D-glucopyranoside uronic acid **(57)** is formed in the largest quantity, and is excreted in the urine (Kaslander, 1966).



57

Ethylene-bisdithiocarbamates do not inhibit the function of aldehyde oxidase (Van Logten, 1972), nor do they form conjugates in mammals, but all their decomposition products are present. These metabolites are excreted within a relatively short time in the urine and the feces. Twenty-four hours after feeding, 55% of the nabam introduced into the stomach of rats was excreted in the urine and feces, while the thyroid, liver, kidney, spleen and brain contained only 1.2% in the form of metabolites, and even this quantity was reduced after 5 days to 0.18% (Seidler *et al.*, 1970). Carbon disulfide has also been detected in the breath of rats fed with neviram (Thuránszky and Botos, 1976; Botos, 1979).

Chronic toxicity tests with ethylene-bisdithiocarbamates have had more alarming results, especially recently. Prolonged feeding of high dosages of zineb and maneb to rats and dogs increased the mortality rate, and produced kidney damage, hypotonicity and goitrogenic activity (Blackwell-Smith *et al.*, 1953; Syrowatka *et al.*, 1971). In six-month feeding tests with a weekly dose of 500 mg/kg of maneb a weak blastomogenic activity was observed (Balin, 1970; Chernov *et al.*, 1972). Zineb, maneb and mancozeb exhibited embryotoxic and teratogenic effects in rats (Ivanova-Chemishanska, 1969; Chepinoga *et al.*, 1970; Antonovich *et al.*, 1972; Petrova-Vergieva and Ivanova-Chemishanska, 1973), and caused disturbances in the growht of *Xenopus laevis* embryos (Bancroft and Prahlad, 1973). Maneb in high concentrations affected the activity of testicular lactate dehydrogenase isoenzymes in rats, while zineb did not cause significant changes compared to the control. These results may support the proven mutagenic action of maneb, which has not been found for zineb (Mosheva-Izmirova *et al.*, 1969 and 1972).

The general action of ethylene-bisdithiocarbamates is centred on the thyroid gland. A series of goitrogenic effects has been observed in animal experiments (Seifter *et al.*, 1948; Blackwell-Smith *et al.*, 1953; Ivanova-Chemishanska *et al.*, 1968; Bankowska *et al.*, 1970).

The conversion product formed, ethylene thiourea, has been held responsible for all of these toxic effects (Innes *et al.*, 1969; Engst *et al.*, 1971). ETU inhibits the functions of the thyroid gland, interferes in iodine metabolism and thus has a goitrogenic effect (Sobotka, 1971; Graham and Hansen, 1972). In twelve-month feeding experiments at an ETU level of 125 mg/kg, modular hyperplastic growth was found in the thyroid of rats. The development of thyroid carcinomas at a level higher than 250 mg/kg proves the carcinogenic effect of ETU (Graham *et al.*, 1973). A carcinogenic effect was observed by Ulland *et al.* (1972) and by Chernov *et al.* (1972), while Khera (1973) and Chernoff *et al.* (1979) found a teratogenic effect and Seiler (1974) a mutagenic effect.

ETU is rapidly excreted from experimental animals (Newsome, 1974, Jordan and Neal, 1979). The residue value of ETU in the liver, heart, kidney and muscles ranged between 0.01 and 0.086 mg/kg, but was considerably higher in the thyroid gland (0.751–0.824 mg/kg) (Newsome, 1974). According to other authors, however, ETU and its metabolite did not accumulate in the thyroid tissues (Lyman and Lacoste, 1975).

There is evidence to suggest that long-term consumption of food containing ETU could be inimical to health, although Graham *et al.* (1975) concluded from a two-year feeding study that ETU was not biologically deleterious to the rat at 5 and 25 mg/kg dietary levels.

An investigation of the effect of dithiocarbamates on the chromosomes of bone marrow cells showed that ziram and, particularly, TMTD causes chromosomal aberrations. The effect of ethylenebisdithiocarbamates is considerably milder. All of the aberrations produced by these compounds were of the chromatoid type (Kurinnyi and Kondratenko, 1972).

The decomposition products of ethylene-bisdithiocarbamates were also detected in formulations of the active substances (Clarke *et al.*, 1951; Bontoyan *et al.*, 1972). The quantity of ETU varied between 0.02 and 2%, but this quantity can increase during storage, partly through an increase in temperature, partly through higher atmospheric humidity (Petrosini, 1962; Czeglédi-Jankó and Holló, 1967; Bontoyan and Looker, 1973).

The derivatives of dithiocarbamates are not toxic to bees. In poultry they may reduce egg production and result in shell-less eggs. Feeding 35 mg/kg of TMTD daily to hens may produce this effect (Waibel *et al.*, 1955). Other pathological changes have been observed in chicken embryos as well (Van Steenis and Van Logten, 1971).

In acid soils dithiocarbamates are degraded into amine and carbon disulfide. Carbon disulfide is volatile and rapidly leaves the soil. Amines generally serve as a nitrogen source for certain bacteria *(Aerobacter aerogenes, Pseudomonas aminovorans)*.

As has been mentioned, of the decomposition products DIDT is reduced in the soil by glucose bacteria and fungi, and, after elimination of carbon disulfide, is converted into ETU.

In acid soil (pH = 6) ETU is rather stable (Kaars Sijpesteijn and Vonk, 1970), but it is rapidly decomposed in neutral and alkaline soils, and ethylene urea is formed (Lyman and Lacoste, 1975). Microorganisms that degrade ethylene thiourea have not yet been isolated from the soil (Kaars Sijpesteijn and Vonk, 1975).

Due to the presence of ethylene thiourea, which is toxic to mammals, the agricultural application of ethylene-bisdithiocarbamates has raised new problems. Ethylene thiourea may be present on or in the produce because of its presence in the preparation, or it may form *in situ* during the decomposition of the active substance. Special attention must therefore be given to the prevention of contamination with ethylene thiourea of foodstuffs that are sprayed with fungicides of the bisdithiocarbamate type. Fortunately ETU is readily biodegradable. Accumulation of ETU in plants, soils or water is very unlikely, and little if any ETU (< 0.06 mg/kg) is likely to be present in raw agricultural commodities treated with dithiocarbamates under normal conditions. On the other hand, there are data indicating that up to 25% of ethylene-bisdithiocarbamate residues on fruits or vegetables can be converted into ethylene thiourea during cooking and baking (Blazquez, 1973; Newsome and Laver, 1973; Watts *et al.*, 1974; Newsome, 1976;

Marshall, 1977). Fortunately, the active substances themselves are not persistent on the plant. Finally, it is important to keep the ETU content of the preparations to a minimum. Of the metal complexes, the coordination complex of zinc and manganese, mancozeb, is the most stable; therefore, the preparations of this active substance contain the smallest amount of ETU (Blazquez, 1973). The potentiation of the activity of metal dithiocarbamates may allow the levels of ETU to be reduced by permitting a reduction in the amount of dithiocarbamate needed to control a fungal pathogen. Clifford and Bruyns-Haylett (1978) reported that zineb 1 : 1 complex with 2-(2-aminoethylamino)ethanol was shown to be more active than zineb in greenhouse and field trials against *Plasmopara viticola*.

It follows then, that the lower amount of dithiocarbamate applied with the zineb complex should be reflected in lower amounts of ETU residues in a post-harvest treatment such as boiling.

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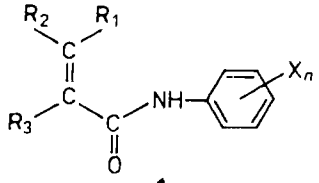
5.6 Carboxamides and carboximides

5.6.1 Carboxamides

Fungicides of carboxamide type became known in 1966 with the discovery of carboxin (which has an oxathiin skeleton), which began a new chapter in the chemotherapy of plant diseases. This group actually has a much longer history —

the first completely organic compound with fungicidal action, salicylanilide, discovered in 1930 and introduced under the trade name Shirlan®, is also a carboxamide. A more detailed investigation of the relationship between the structure of carboxamides and their fungicidal action began when it was realised that the fungitoxic properties of carboxin could not be attributed to the oxathiin skeleton. Toluanilide proved to be nearly as toxic to *Rhizoctonia solani* as carboxin (Snel *et al.*, 1970), and even butyranilide has some fungitoxic effect. The results of several workers unequivocally showed that the fungitoxic effect of the molecules is provided by the α,β-unsaturated anilide structure (**1**) (Snel *et al.*, 1970; ten Haken and Dunn, 1971; Hardison, 1971a; Pommer *et al.*, 1974; White and Thorn, 1975).



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In the basic skeleton each part of the molecule is essential from the point of view of fungicidal action. Another condition of fungitoxicity is the R_1 substitution at the β-carbon atom *cis* to the carboxamide group. If there is no substitution in the *cis* position at the 3-carbon atom ($R_1 = H$), or if the substituent group is too large (e.g., R_1 = phenyl), the molecule has no fungicidal effect. In the case of the R_1 group, it is the dimensions of the radical which play an important role and not the electrophilic or nucleophilic properties of the group. The effect of the R_1 group on the fungitoxicity of the molecule depends also on the R_2 and R_3 groups. R_2 may be a methyl group and R_3 hydrogen (open-chain unsaturated acid), or R_2 and R_3 may form a ring. In the latter case the double bond may be part of a planar aromatic system (e.g., benzene, furane, thiazole and oxazole), or of a nonplanaring system (e.g., dihydrooxathiin, dihydrofuran, dihydropyran).

In the case of benzanilides, the fungitoxicity of the molecule is influenced by the R_1 group in the order: $R_1 = I >$ ethyl $> Br > CH_3 > Cl > OH > F = H$. This order is almost the same as the order of the space requirement of the atom or the atomic group. With carboxanilides of other basic skeletons the methyl derivative generally has the greatest effect.

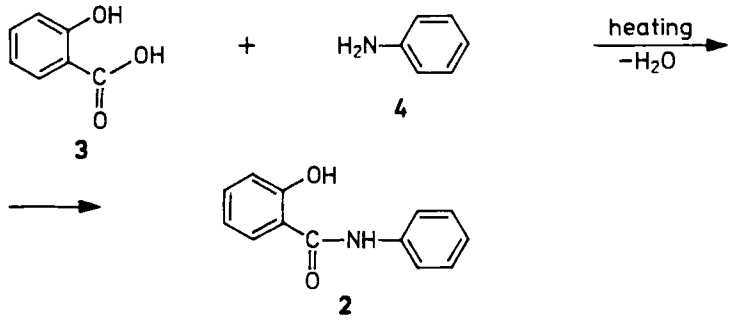
The aromatic ring attached to the carboxamide is also essential from the point of view of fungitoxicity. Its replacement with cyclohexyl radical reduces the effect, and aliphatic radicals make the molecule inactive. The aromatic ring may carry substituents (X); however, these do not change decisively the fungitoxic activity of the molecule either quantitatively or qualitatively. Nucleophilic substituents in the aniline ring increase the electronegativity of the nitrogen atom, which increases the possibility of the formation of a hydrogen bond, and thus fungitoxicity (Schönenberger *et al.*, 1962). *Ortho* substitution has a better effect than *para* substitution.

Lipid–water distribution coefficients play an important role in the action of fungicides. Similar phenomena have also been seen in the case of carboxamides (Mathre, 1971a). The sulfoxide of carboxin, for example is an inactive compound, due to its low lipid solubility. However, a closer relationship between the fungicidal action and the distribution coefficient of carboxamides has not yet been established.

The most thoroughly investigated and best known carboxamides at present are discussed below.

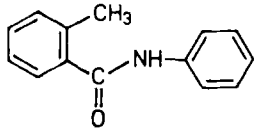
Hydroxybenzoic acid, and particularly its ester and amide derivatives, are compounds with good fungicidal action. Salicylic acid has long been used for the conservation of fruits and vegetables. Its anilide, salicylanilide (Shirlan®, **2**), is a selective protective fungicide against certain *Ascomycetes* and *Phycomycetes* fungi, particularly against leaf mould of tomato *(Cladosporium fulvum)* and certain powdery mildew fungi (hop, cucumber). It has also been used in the textile industry for the protection of textiles against mould fungi (Martin and Salmon, 1934).

Salicylic acid (**3**) and aniline (**4**) are condensed in the presence of a catalyst at a raised temperature to salicylic acid anilide (2-hydroxy-N-phenylbenzamide).



When the OH group of salicylanilide is replaced by a methyl group, the fungicidal range of action of the carboxamide is changed, and the mebenil (**5**) is mainly effective against *Basidiomycetes* (*Puccinia* spp., *Rhizoctonia solani*). This crystalline compound of the composition 2-methyl-N-phenylbenzamide has gained importance for seed treatment of cereals and potato; however, a phytotoxic effect has been observed in several cases (Pommer and Kradel, 1969). Its metabolism has been investigated by Warrander and Waring (1977).

2-Iodo-N-phenylbenzamide, benodanil (**6**), has a more powerful effect on rust fungi of cereals (*Puccinia* spp.) than mebenil, and is also effective against the rust fungi of coffe, tobacco, vegetables and ornamental plants (Pommer *et al.*, 1973; Löcher *et al.*, 1974). This active substance is better tolerated by plants than mebenil. It has a curative and systemic action. Its absorption through the leaves depends on the formulation of the active substance. It is more rapidly absorbed from emulsions and oily preparations than from suspension. Its translocation is relatively slow (Frost *et al.*, 1973).



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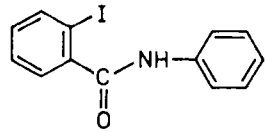

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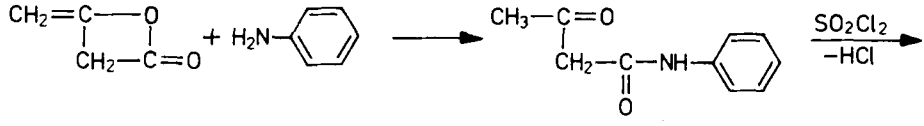
The most widely used fungicide of the carboxamide group, carboxin (**9**), contains an oxathiin ring. Its composition is 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (Von Schmeling and Kulka, 1966). Its synthesis starts with acetoacetanilide (**7**), which with sulfuryl chloride gives 2-chloro-3-oxobutyranilide (**8**). This intermediate product is cyclised with 2-thioethanol in a weakly alkaline medium. The purity of the technical product is not less than 97%.



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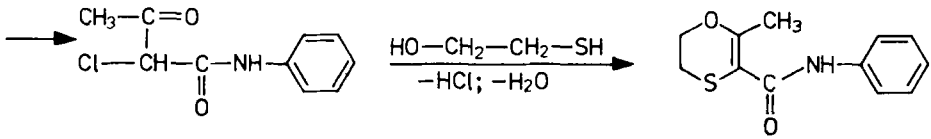

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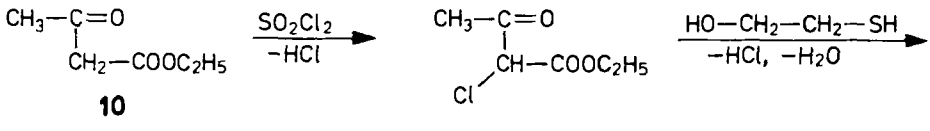
Synthesis can also be carried out from acetoacetic ester (**10**) through the corresponding 1,4-oxathiin-3-carboxylic acid (**11**) by the following reaction:



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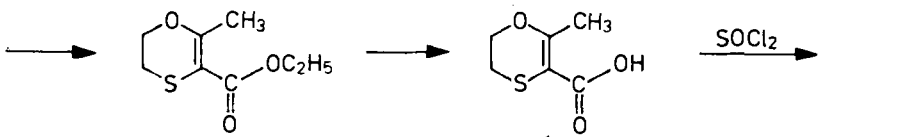

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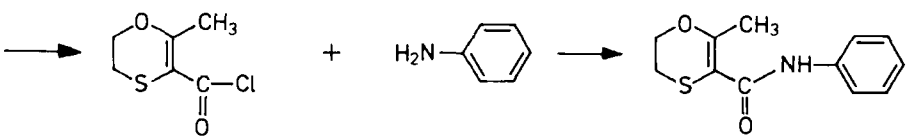

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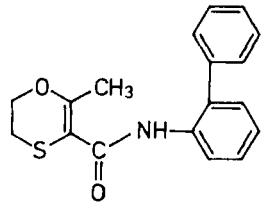
Carboxin is a white crystalline product. The acute oral LD_{50} for rats is 3820 mg/kg. It is a selective fungicide used against *Basidiomycetes* fungi and particularly against bunts of wheat and barley. Its economic importance lies in the fact that it was the first active substance giving effective protection against the loose smuts *Ustilago nuda* and *Ustilago tritici* (Van Tate and Von Schmeling, 1968). The systemic action of carboxin was first established in conjunction with bean rust (*Uromyces faseoli*). The active substance is taken up by the roots of the plant; it is then translocated in the xylem, accumulating mainly in the epicotyl. Carboxin is effective against wheat bunt, oat smuts, wheat seedling blight, oat leaf stripe, brown foot rots of oat and the malseco diseases of lemon trees (Macer *et al.*, 1969). It is used mainly for seed dressing and as a soil fungicide. It is less effective as a foliage fungicide, because it is rapidly oxidised by environmental factors into the biologically almost inactive sulfoxide.

The closely related derivative of carboxin, 5,6-dihydro-2-methyl-N-2-diphenyl-1,4-oxathiin-3-carboxamide (F-427, **12**), has an even wider range of action being effective against several *Deuteromycetes* fungi (*Aspergillus* spp.) (Edgington and Barron, 1967).



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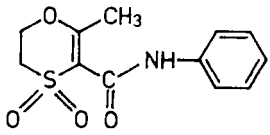

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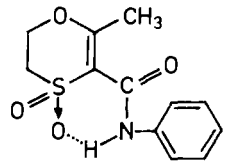
The sulfon of carboxin, oxycarboxin (**13**), 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide-4,4-dioxide, is prepared by the oxidation of carboxin with hydrogen peroxide. It is more soluble in water than carboxin (1000 mg/kg). The selectivity of its action is similar to that of carboxin, and though its fungitoxicity is lower, it is more efficient against rust fungi, particularly as a foliage fungicide, because it is stable under environmental conditions. Its stability is due to the formation of an internal hydrogen bond (**14**) (ten Haken and Dunn, 1971). Oxycarboxin is a specific fungicide for the treatment of wheat against leaf and stem rust. It is used for seed dressing or as a soil fungicide and protects the plant from infection for at least two months.



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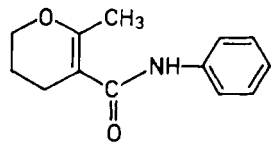

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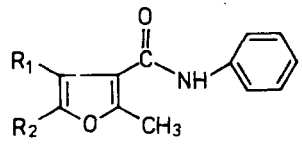
Pyracarbolid **(15)**, 3,4-dihydro-6-methyl-N-phenyl-2H-pirane-5-carboxamide, has a range of action similar to that of the oxathiines but is somewhat more effective in seed dressing against smuts, rust fungi and *Rhizoctonia solani*. It has a systemic action; the active substance is taken up by leaf, shoot and root alike, but its translocation in the plant is relatively moderate (Oeser *et al.*, 1975). It is a stable compound, less sensitive than carboxine to light and heat (Stingl *et al.*, 1970; Jank and Grossman, 1971). It is used primarily for the protection of coffee, tea and cereals (Kataria *et al.*, 1976).

Of the carboxamides with a furan skeleton, furcarbanil, cyclafuramid, fenfuram and methfuroxam are of the most practical importance. An analysis of the relationship between structure and fungicidal action shows that substitution on the furan skeleton in position 2 is also essential here **(16)**. Against *Basidiomycetes* spp. 2,5-dimethyl substitution enhances effectiveness; 2,4,5-trimethyl substitution somewhat diminishes effectiveness; only 3-methyl- and 5-methyl-N-phenylfuran-3-carboxamides are completely ineffective. Methyl substitution in the aniline ring reduces the fungicidal action of the compound by 30–50%, and substitution of chlorine or bromine by 70–100% (Pommer, 1971).



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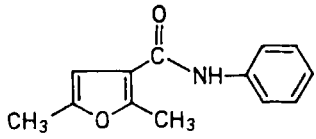
Furcarbanil **(17)**, 2,5-dimethyl-N-phenylfuran-3-carboxamide, is most effective against loose and covered smuts of cereals (Hardison, 1972); moreover, it is also effective against several fungi not belonging to the *Basidiomycetes* class (*Fusarium nivale, Helminthosporium* spp.). The active substance has a systemic action, but its translocation in the plant is relatively slow, and one part of the active substance is already fixed during transport in the stem tissues. The effect against fungi infecting the leaves is unsatisfactory, so it is used mainly for seed dressing and as a soil fungicide. Certain barley species are stunted after seed dressing under certain climatic conditions; these sensitive species tolerate, however, the cyclohexyl analogue of the active substance, cyclafuramid **(18)**, N-cyclohexyl-2,5-dimethylfuran-3-carboxamide (Pommer *et al.*, 1971).

Fenfuram **(19)**, 2-methyl-N-phenylfuran-3-carboxamide is a compound very slightly soluble in water and stable to heat and light. It is highly active as a seed



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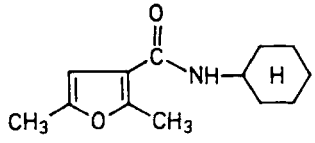

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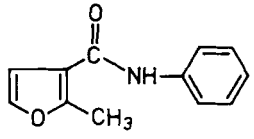
dressing against the smuts and bunts of temperate cereals. It controls *Tilletia* and *Ustilago* spp. including *U. nuda*. The acute oral LD_{50} is 12 900 mg/kg for rats. The Ames test for mutagenecity was negative (Dobrat, 1979).



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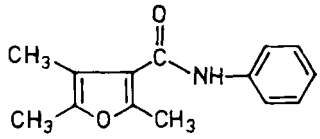

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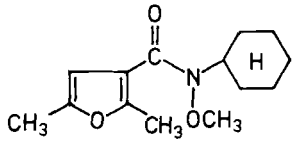
It is prepared by the reaction of 2-acetoxypropion aldehyde with acetic acid anilide in benzenic medium in the presence of sulfuric acid (Merkle and Siegel, 1973).

Methfuroxam (**20**), N-phenyl-2,4,5-trimethyl-3-furancarboxamide, is a new systemic fungicide active against *Basidiomycetes* pathogens. It is used as a seed treatment against loose smut of wheat, barley and oats and bunt of wheat. Methfuroxam is also active against *Rhizoctonia solani* and rust fungi, but a higher rate of use, similar to that for carboxin and oxycarboxin, seems to be needed. It has a low mammalian toxicity (acute oral LD_{50} 4300 mg/kg for male rats) (Jackson, 1979; Mitchell and Paulson, 1982).

The structure-action investigation of N-cyclohexyl-2-methyl-3-furamides resulted in the discovery of a new active substance (Pommer and Zeeh, 1977).

N-Cyclohexyl-N-methoxy-2,5-dimethyl-3-furancarboxamide (common name: furmecyclox, **21**) gives good protection against *Fusarium nivale* and *Helminthosporium gramineum* fungi, among others, and comes under consideration mainly as a component of mercury-free seed dressing (Papavizas *et al.*, 1979 and 1980).



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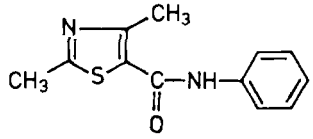
Of the carboxamides containing a thiazole ring, the active substances 2,4-dimethyl-N-phenyl-5-thiazole-carboxamide (G 696, **22**) and 2-amino-4-methyl-N-phenyl-5-thiazole-carboxamide (F 849, **23**) are thought to be promising according to the literature. Both are fungicides of systemic action, particularly against smuts and rust fungi. Their range of action is similar to that of carboxin and oxycarboxin (Hardison, 1971b).



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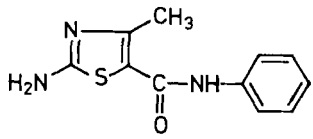

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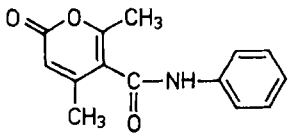
Anilides of isodehydroacetic acid (**24, 25**) were of medium overall antifungal activity and did not show a specific high activity against any of the fungi used as test organisms. Introduction of two ethyl groups in *ortho* position in the anilin ring, a factor resulting in the prevention of free rotation, increased the antifungal activity somewhat. This result indicates that coplanarity cannot be considered a decisive factor in the activity of this type of compound (Kovács *et al.*, 1976).



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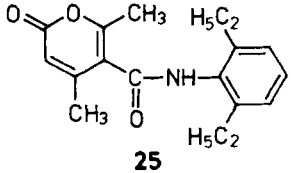

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The carboxamides are excellent systemic active materials. They are taken up primarily through the roots and are then translocated in the xylem, accumulating mainly in the epicotyl (Thapliyal and Sinclair, 1971; Ambro-Bálint and Nádasy, 1975). Moreover they can penetrate deep into the seeds and also destroy fungus micelia which infiltrate the interior of the seeds. They are therefore effective mainly for seed treatment and as soil fungicides. They are less efficient as foliage fungicides, because the active substances become photoinactivated. According to the investigations of Buchenauer (1975), carboxin is the least stable carboxamide, due to the oxidisability of the sulfur atom. Oxidation is strongly catalysed by light. The photostability of the other carboxamides increases in the order furcarbanil $\leqslant$ cyclafuramid $<$ pyracarbolid $<$ mebenil $\leqslant$ benodanil $<$ oxycarboxin. The last four carboxamides are sufficiently photostable to be used as foliage fungicides in the control of rust fungi.

The metabolism of carboxin has been studied most extensively. Carboxin is oxidised into sulfoxide in water, soil, plants and animals alike (Chin *et al.*, 1969, 1970a). Its oxidation into sulfon in plants has also been observed in certain cases, though to a very small extent (Chin *et al.*, 1970b). The carboxanilide group may be split by hydrolysis (Snel and Edgington, 1970).

No active substance could be detected in plants treated with carboxin six weeks after the treatment. The major part of the residue found was sulfoxide. Actually, sulfoxide can occur in the plant in two ways. On the one hand, carboxin is oxidised relatively rapidly in the soil, and the plant takes up its sulfoxide, and, on the other hand, carboxin is metabolised within the plant to sulfoxide, presumably by enzyme systems producing hydrogen peroxide, such as riboflavin or flavin enzymes (Lyr *et al.*, 1975a). It has been proved by extraction with hot dimethyl sulfate that sulfoxide formed in the plant is gradually bound in the form of a water-insoluble complex to lignin and is thus detoxified. No hydrolysis of carboxin in the plant has been observed (Chin *et al.*, 1973).

The range of action of carboxamides depends partly on the basic skeleton and partly on the substituents. With a few exceptions, carboxamides are effective

against *Basidiomycetes* fungi, of which smuts and rust fungi, as well as *Rhizoctonia solani*, are also economically important pests. By appropriate modification of the molecular structure, the fungitoxic action can be extended also to *Ascomycetes, Deuteromycetes, Oomycetes* and *Zygomycetes*. The interesting observation was made that 2-amino benzanilide has some effect on *Plasmopara viticola* (Snel *et al.*, 1970). Lyr *et al.* (1975b) attribute the selective action of carboxamides to differences in their affinity to the receptor. In this respect, not lipophilicity but presumably the steric arrangement of the molecules and their electron configuration play a decisive role.

The range of action of carboxamides can be extended also to fungus species less sensitive to them by combination with protective fungicides, which also produce a partial synergistic effect in the combined seed-dressings. Copper oxine, chloroneb, mancozeb and other fungicides are used in combination with carboxamides (Richard and Vallier, 1969; Ranney, 1972; Baicu and Nägler, 1974).

As regards the mode of action of carboxamides it has been suggested that salicylanilide exerts its action by the reaction of the anilide hydrogen with the various enzymes (Baichwal *et al.*, 1960). According to Williamson and Metcalf (1967), salicylanilides are new uncouplers of the oxidative phosphorylation.

Extensive investigations showed that active carboxamides primarily inhibit the oxidation of acetate, pyruvate and succinate in fungi (Mathre, 1971b). They inactivate succinate dehydrogenase (White, 1971; Lyr *et al.*, 1972; White and Thorn, 1975), thus, succinate accumulates in fungal cells treated with carboxin. The recent investigations, mainly in *Ustilago maydis* cultures, confirmed that the site of carboxin action is the succinate dehydrogenase enzyme system, involving either the enzyme itself or some electron acceptor attached to it. White (1971) and Ulrich and Mathre (1972) place the site of action between the succinate and coenzyme Q. Based on further investigations, Schewe *et al.* (1975) suggest the iron-sulfur proteins in the electron transport system as site of action of carboxin. Carboxin reacts with the Fe(II) form of iron-sulfur proteins, inhibiting subsequent oxidation through the respiratory chain. The main sites of action are presumably not the Fe(II) atoms but the sulfur bridges between iron and the polypeptide chain (Lyr *et al.*, 1975a).

From a study of the development of strains tolerant to carboxin it can be followed that this phenomenon depends on the penetration of the fungal cells by the fungicide (Mathre, 1968). But recently, the kinetics of carboxin uptake by the fungal cells have been investigated in various carboxin-sensitive and carboxin-tolerant strains of *Ustilago hordei*, and no difference in penetration rate has been found. (Lyr *et al.*, 1971). On the other hand, Georgopoulos *et al.* (1972) have reported that high resistance to oxathiin and thiazole carboxanilide fungicides in *Ustilago maydis* is obtained with a single-gene mutation that modifies the mitochondrial succinate dehydrogenase system. Data on the inhibition of succinate-2,6-dichlorophenol indophenol reductase indicate that mitochondria of the heterozygous diploid probably contain a mixture of carboxin-sensitive and carboxin-resistant succinate dehydrogenase complexes (Georgopoulos *et al.*, 1975). It is supposed that the development of carboxin-tolerant strains in *Ustilago hordei*

depends on the development of alternative metabolic pathways, such as the glyoxylate cycle, or carboxin-tolerant phosphate uptake, and only partly on the development of carboxin-tolerant succinate-dichlorophenolindophenol reductase (Ben-Yephet *et al.*, 1975). Owing to their systemic action, carboxamides permeate the interior of the plant and have a certain effect on plant tissues (Karchik *et al.*, 1975). Thus oxathiin derivatives stimulate protein synthesis in wheat (Karchik, 1975). Certain active substances are detrimental to photosynthesis (Mathre, 1972), while carboxin enhances the growth of cultured plants, mainly by increasing the chlorophyll content of the leaves (Carlson, 1970).

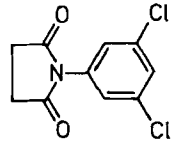
An interesting side effect of carboxin is its ability to protect plants from the injurious effect of atmospheric ozone contamination (Rich *et al.*, 1974). Soil treatment with carboxin is phytotoxic to tobacco plant (Taylor and Rich, 1974).

Certain *Phycomycetes* soil fungi are able to decompose carboxamides. Thus, *Rhisopus japonicus* metabolises the 90 per cent of carboxin to butiranilide within a three-week period (Wallnöfer, 1969).

Carboxamides are not toxic to mammals, their acute oral LD_{50} generally being more than 2000 mg/kg. Chronic or subchronic toxicity has not been observed. These active substances are also advantageous for environmental protection, partly because they are rapidly decomposed, the average half-life of carboxin in the soil is two days, and partly because they form metabolites which are biologically inactive to mammals. The protective effect of carboxin ceases completely 50–60 days after sowing. No traces of carboxin were found in harvested seeds.

5.6.2 Dicarboximide derivatives

Due mainly to the wide resistance of *Botrytis cinerae* to fungicides primarily of benzimidazole type, the realisation that compounds of dicarboximide type, particularly N-(3,5-dichlorophenyl)heterocyclic derivatives, have a very efficient systemic action against *Botrytis cinerea, Cochliobolus miyabeanus, Pellicularia sasakii* and *Sclerotinia sclerotiorum* fungi became very important. The parent compound, N-(3,5-dichlorophenyl)pyrrolidine-2,5-dione (dimetachlon, **26**) is a protective and curative fungicide used in Japan for the control of *Corticium sasakii* and *Cochliobolus miyabeanus* fungi in rice cultures, in orchards and for vegetables (Anonym, 1971; Fujinami *et al.*, 1972).



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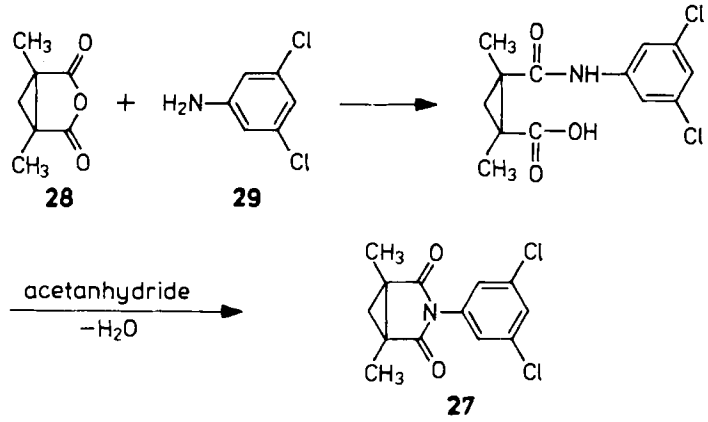
More recently a whole series of derivatives with excellent fungicidal action has been discovered, in which the heterocyclic part is mostly pyrrolidine dione, oxazolidine dione or imidazolidine dione, while the analogous functional group is N-(3,5-dichlorophenyl) dicarboximide.

Procymidone, N-(3,5-dichlorophenyl)-1,2-dimethyl-cyclopropane-1,2-dicarboximide (**27**), is a fungicide with moderate systemic action (Fujinami *et al.*,1969). The active substance is a white crystalline material stable to the action of light, heat and humidity. It is slightly soluble in water. It is moderately toxic to mammals, the acute oral LD_{50} for rats being 6800 mg/kg. It is not toxic to fish or bees.

Procymidone is rapidly absorbed, mainly through the roots but in a small measure through the stem or the leaves also, and is acropetally translocated in an unchanged form. A certain degree of basipetal translocation has also been observed. According to Cooke *et al.* (1979), the action of procymidone used as foliage fungicide is not satisfactory against *B. cinerea*. Its spectrum of action includes *Sclerotinia, Botrytis, Helminthosporium* and *Monilia* spp. fungi. It has a powerful effect on *Botrytis cinerea* fungi resistant to benzimidazole derivatives (Hisada *et al.*, 1976, Durand, 1979). It shows promise for the control of storage rots of fruits and vegetables. It can be prepared by the reaction of *cis*-1,2-dimethyl-cyclopropane-1,2-dicarboxylic acid (**28**) with 3,5-dichloroaniline (**29**).

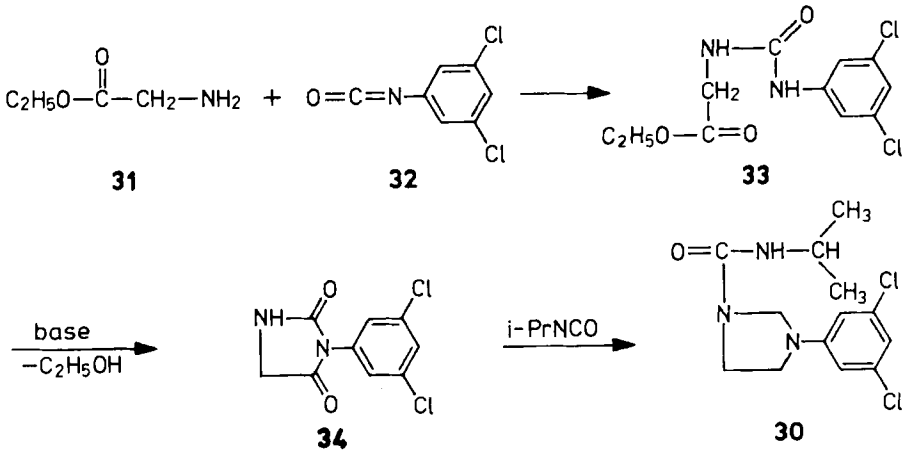


28 **29** **27**

Iprodione, 3-(3,5-dichlorophenyl)-N-isopropyl-imidazolidine-2,4-dione-1-carboxamide (**30**), is actually a hidantoin derivative (Sauli, 1970).

Glycine ester (**31**) is reacted with 3,5-dichlorophenylisocyanate (**32**) to yield the ethyl ester of 5-(3,5-dichlorophenyl)hidantoic acid (**33**). By the cyclisation of this product 3-(3,5-dichlorophenyl)imidazolidine-2,4-dione (**34**) is formed, which with isopropylisocyanate, yields the end product.

The active substance is a white, odourless, non-hygroscopic crystalline compound with a water-solubility of 13 mg/l at 20°C. It has a very low oral and dermal toxicity and is practically non-irritating to mucous membranes. The acute oral LD_{50} for rats is 3500 mg/kg. In eigtheen-month feeding tests no significant pathological changes were observed in rats at a dietary level of 1000 mg/kg. Iprodione, in ethanolic solution, was found to undergo structural rearrangement over a period of days, giving a solid product which was shown by mass spectrometry to be an isomer (Cooke *et al.*, 1979).



Iprodione is primarily a contact fungicide, inhibiting simultaneously the germination of spores and the growth of fungus mycelium. It gives excellent protection particularly against grey mould on vine, strawberry and vegetables (Soper and Cox, 1977; Davis and Dennis, 1979). It was also successful in experiments against other phytopathogenic fungi (*Sclerotinia* spp., *Peronospora* spp., *Alternaria* spp., *Monilia* spp., *Rhizoctonia solani, Phoma solanicola* and *Pellicularia sasakii*). Thus its range of action is rather wide. Absorbed through the roots it has a systemic action and gives good protection against *Phoma exigua foveata* (Cayley and Hide, 1980).

It is not phytotoxic. It does not affect the alcoholic fermentation of must (Lacroix *et al.*, 1974). It is efficient against storage rot of apples (Bompeix *et al.*, 1979). Combined with carbendazime it is very effective for the seed dressing of cereals. It gives excellent protection against *Helminthosporium gramineum, H. avenae, H. sativum, Tilletia caries, Fusarium roseum* and *Septoria nodorum* (Chalandon *et al.*, 1979).

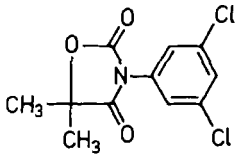
Owing to its low water solubility and low volatility, iprodione is a promising active substance from the viewpoint of environmental protection. Moreover, it is degraded in the soil to biologically inactive compounds (Burgaud *et al.*, 1975).

Dichlozoline (**35**), 3-(3,5-dichlorophenyl)-5,5-dimethyl-1,3-oxazolidine-2,4-dione, is a white, crystalline compound, stable to heat and almost insoluble in water (2.5 mg/kg at 25°C). Its acute oral LD_{50} for rats is higher than 10 000 mg/kg. In 90-day feeding tests a daily diet of 70 mg/kg produced no pathological changes in mice and rats (Iwami *et al.*, 1969 and 1974). The active substance is rapidly metabolised in rats and excreted. The metabolites are hydroxylated at position 4 of the benzene ring, and the oxazoline can also be modified (Sumida *et al.*, 1973). Dichlozoline is not toxic to fish, bees or earthworms.

Dichlozoline inhibits primarily the mycelial growth of pathogens. Used preventively, it has a long-lasting action and a high efficiency. Used after infection, it is a locosystemic fungicide with curative action. It has a specific action against

Botrytis cinerea, Sclerotinia sclerotiorum and *Monilia* spp. fungi. It gives excellent protection against downy mildew of the vine (Kokovic, 1972), among others. It is not phytotoxic and does not inhibit alcoholic fermentation. It can be used as a fumigant in greenhouses.

Vinclozoline **(36)**, 3-(3,5-dichlorophenyl)-5-methyl-5-vinyl-1,3-oxazolidin-2,4-dione, is not toxic to mammals, fish or earthworms.



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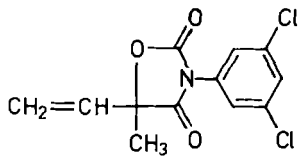

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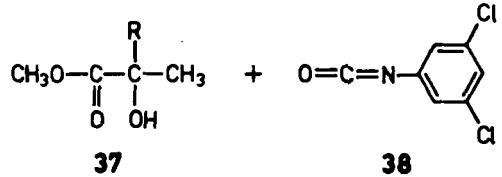
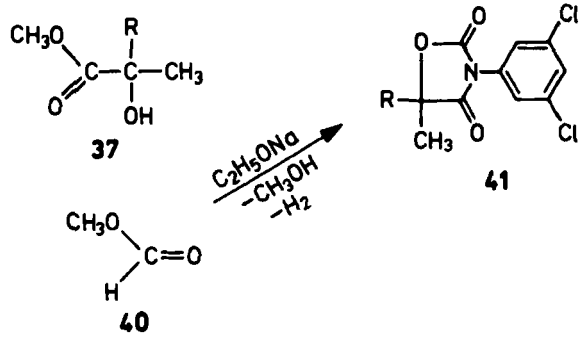
Its acute oral LD_{50} for rats is 10 000 mg/kg. Its main fields of application are vine, orchards, hop and ornamental plants. In protecting against gray mould of strawberry vinclozoline is more effective than dichlofluanid. (Davis and Dennis, 1979). It does not inhibit alcoholic fermentation. A curative effect on begonia has been observed (Pommer and Mangold, 1975; Hess and Löcher, 1975).

Oxazolidins **(41)** can be prepared from the methyl ester **(37)** of the respectively substituted glycolic acid with 3,5-dichlorophenyl isocyanate **(38)** or from dichloroaniline **(39)** with substituted glycolic acid ester **(37)** and formic ester **(40)** in the presence of alkaline metal alcoholates (Sato *et al.*, 1968a, 1968b).



37 **38**



37 **41**

39 **40**

Procymidone, iprodione and vinclozoline all inhibit mycelial growth much more than spore germination. None of the compounds affect respiration, membrane permeability or RNA production, but iprodione inhibits DNA synthesis. Although chitin biosynthesis is inhibited by all of these fungicides, it is barely affected at the LD_{50} concentrations, and it is thus unlikely that it is the primary target. The fungicides alter fungal lipid composition. Procymidone and vinclozolin inhibit triglyceride production, but iprodione has no effect on it. Iprodione reduces sterol biosynthesis (Pappas and Fisher, 1979; Buchenauer, 1979).

Regrettably, resistance phenomena have already been observed for these active substances, too. Fungi adapt rapidly to the compounds, and cross-resistance has also been observed. Similar phenomena have been observed under field conditions. (Davis and Dennis, 1979; Lorenz, 1979; Spengler *et al.*, 1979; Vogt-Müller *et al.*, 1979).

Iprodione, procymidone and vinclozoline are very active in increasing the number of mitotic recombination in diploid colonies of *Aspergillus nidulans*. The recombinogenetic activity of the N-(3,5-dichlorophenyl)dicarboximides may be as high as for any other member of the "aromatic hydrocarbon group".

The similarity of action between the N-(3,5-dichlorophenyl)dicarboximides and the chlorinated benzene and chloronitro-benzene members of the group indicates that the 3,5-dichlorophenyl group is essential for the action of iprodione, procymidone and vinclozoline. The dicarboximide moiety may increase either membrane permeability or affinity for internal sites (Georgopoulos *et al.*, 1979).

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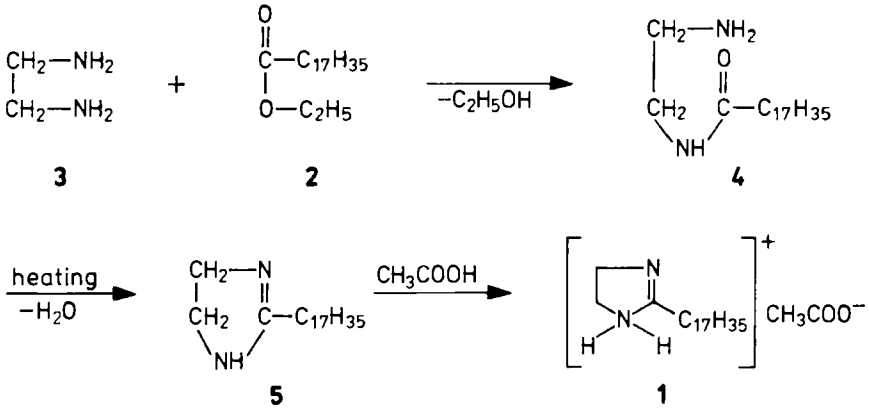
5.7 Azole compounds

5.7.1 Imidazole and its derivatives

Imidazole (1,3-diazole, glyoxaline) is present in several biologically active compounds. Imidazole forms the basic skeleton of histamine, L-histidine, allanthion and compounds with a purine skeleton. It is also a component of vitamin B_{12}. The pharmaceutical industry has therefore been engaged for a long time in research concerning the derivatives of heterocyclic rings, and several excellent drugs with bacteriostatic, anaesthetic or circulatory (e.g. vasodilatory, vasoconstrictor) action have been found among them. This research has also formed the basis for the application of these compounds to plant protection.

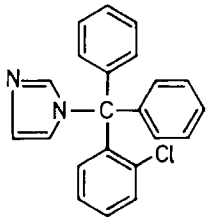
Although imidazole itself is biologically inactive, the group with fungicidal action is to be found in the imidazole ring, and substituents serve to increase the lipoid solubility of the compounds and thus to carry the toxophoric group to the site of action. Biological activity increases with increasing length of the 2-alkyl chain, which reaches a maximum at C_{17} (Woodcock, 1959). The imidazole derivative glyodin, containing a $C_{17}H_{35}$ alkyl chain, is a fungicide used in agriculture (Wellman and McCallan, 1946). Glyodin (**1**), 2-heptadecyl-2-imidazoline acetate, is prepared from ethyl stearate (**2**). Its acide amide (**4**) formed with ethylene diamine (**3**) is cyclised by heating (**5**) and forms a salt with acetic acid.



Glyodin is a foliage fungicide with a curative effect against apple scab. It is effective also against cherry anthracnose and leaf spot. The pure compound is not phytotoxic, but the technical product damages certain plants. This phytotoxicity is attributed to the oleic acid contamination of stearic acid.

The mode of action of glyodin is presumably its effect on the biosynthesis of purine, of which it is the competitive inhibitor. Indeed, the fungitoxicity of glyodin can be eliminated with guanine and xanthine (West and Wolf, 1955).

The triarlymethyl derivatives of imidazole have a good fungistatic effect against powdery mildew fungi and *Phytophthora infestans*, but their agricultural application is limited. One of the most potent derivatives is clotrimazole, 1-(2-chlorophenyl-diphenylmethyl)-imidazole **(7)**, which, however, is used primarily against human pathogenous fungi (Tolkmith *et al.*, 1967; Büchel *et al.*, 1972).



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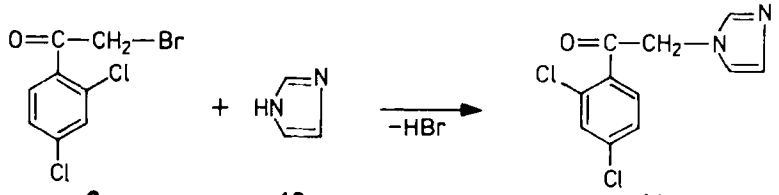
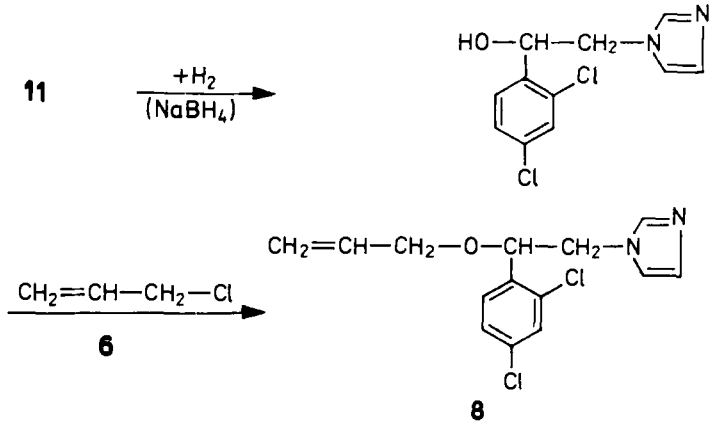
One of the more recently discovered members of the N-substituted imidazole-group is imazalil, 1-(β-propenyloxy-2,4-dichlorophenethyl)-1H-imidazole **(8)** (Laville, 1973, 1974). The base is scarcely soluble in water, while its salts (nitrate, sulfate, acetate) are soluble in water. It is a fungicide with systemic action, effective against several phytopathogenous fungi, but it has a specific action against *Helminthosporium, Fusarium* and *Septoria* spp. It is used as a seed dresser against diseases of cereals by itself or in combination with several other fungicides (Melin *et al.*, 1975 Reisdorf *et al.*, 1983). It is very effective against *Penicillium* spp. strains resistant to fungicides of the benzimidazole type, and is therefore used also for the protection of oranges, lemons and other stored fruits (McCornack *et al.*, 1977; Gestel and Reempts, 1979). The efficiency of imazalil is dependent on the pH. This fungicide markedly inhibits ergosterol biosynthesis. Simultaneously ergosterol precursors accumulate in *sporidia* of *Ustilago avenae*. It is assumed that imazalil acts as a selective inhibitor of demethylation at C-14 position during ergosterol biosynthesis in *sporidia* of *U. avenae* (Buchenauer, 1977c; Siegel and Ragsdale, 1978). The acute oral LD_{50} for rats is 320 mg/kg (Barlett and Ballard, 1975, Kerkenaar *et al.*, 1984, Gestel and Van der Ven, 1984).

Imazalil can be prepared by the reduction of the intermediate product **(11)**, formed in the reaction of chlorophenacyl bromide **(9)** with imidazole **(10)**, and subsequent alkylation with allyl chloride **(6)** (Godefroi and Schuermans, 1970).



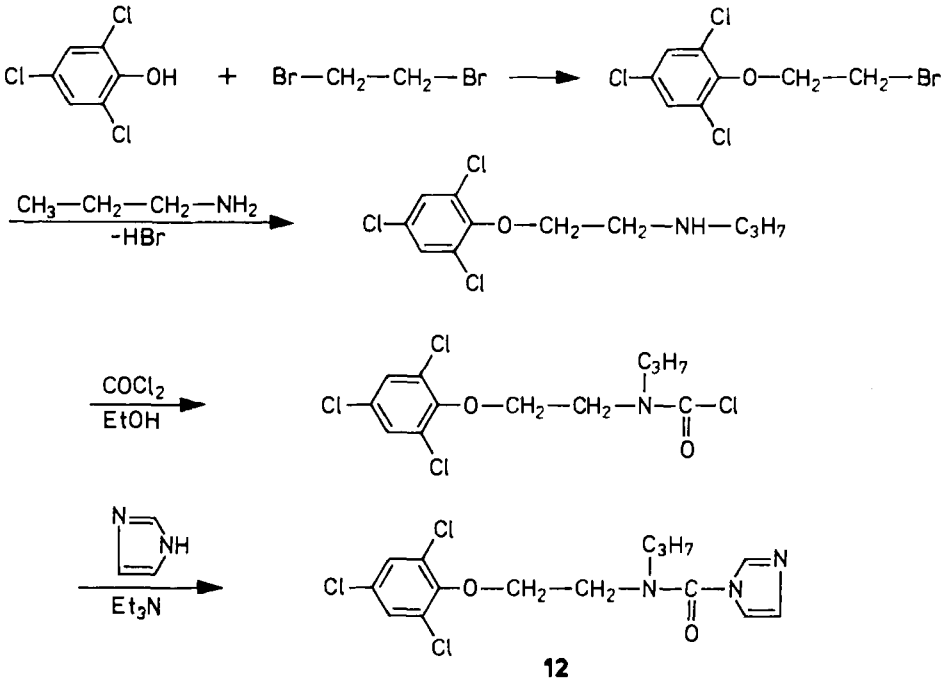
9 **10** **11**



Several related derivatives of imazalil (miconazole, econazole) show *in vitro* a broad antimicotic spectrum against fungi pathogenic to man and animals (Buchenauer, 1977c).

Of the 1-carbamoyl imidazole derivatives The Boots Company found the compounds BTS 40 542 to be the most potent fungicide (Birchmore *et al.*, 1977).

The scheme of preparation of prochloraz is the following (Brookes *et al.*, 1973):

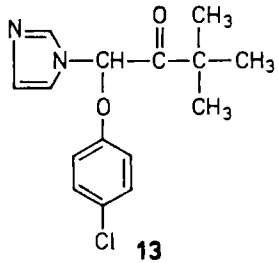


Prochloraz **(12)**, N-propyl-N-[2-(2,4,6-trichlorophenoxy)ethyl]imidazole-1-carboxamide, demonstrates excellent eradicant and protectant activity against a wide range of important foliar, stem and ear diseases attacking cereal crops. Effective control is obtained against the early season diseases eyespot, leaf blotch and powdery mildew. Prochloraz also shows considerable potential for the control of the late season disease complex of glume blotch, leaf spot, *Fusarium* spp. and the black and sooty moulds (Weighton *et al.*, 1977; Harris *et al.*, 1979). It is particularly active against members of the *Ascomycetes* and *Fungi imperfecti*, although it shows less activity against *Basidiomycetes*.

Prochloraz is also effective against pathogens of broad-leaved crops. Several of these crops have proved sensitive to foliar applications, however, and related compounds were therefore synthesised with the aim of retaining high activity while increasing the margin of crop safety. This was achieved with a series of metallic complexes, as exemplified by a prochloraz-manganese(II)chloride complex (Birchmore *et al.*, 1979, Schneider *et al.*, 1981, Copping *et al.*, 1984).

The acute oral LD_{50} of prochloraz is 1600 mg/kg for rats.

The trade mark of the compound 1-(4-chlorophenoxy)-1-(imidazol-1-yl)-3,3-dimethylbutanon is Baysan® **(13)**. This fungicide is effective against *Aspergillus*, *Penicillium*, *Candida* and *Paecilomyces* spp. on various household materials, utensils and parts of buildings. The acute oral LD_{50} for male rats is 400 mg/kg. (Worthing, 1979).



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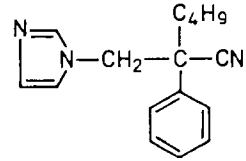


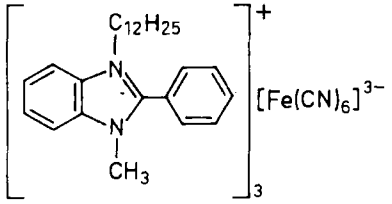
14

α-Butyl-α-phenyl-1H-imidazole-1-propanitrile (fenopanil, **14**) has a protective and curative action against many phytopathogenous *Ascomycetes* spp., *Fungi imperfecti* and *Basidiomycetes* spp. It is recommended for both seed dressing and as a foliage fungicide. It is not toxic, its oral LD_{50} being 1590 mg/kg for rats (Martin and Edgington, 1982).

5.7.2 Benzimidazole derivatives and precursors

With a view to the relationship between the structure and action of glyodin, the research in the benzimidazole series was first centred on active substances containing long alkyl chains. Of these, 1-methyl-2-phenyl-3-dodecylbenzimidazolium ion has been used in plant protection in the form of its insoluble salts. These salts such as the

hexacyanoferrate of the former cation **(15)** or 1-methyl-3-dodecylbenzimidazolium halides **(16)**, have a curative effect, particularly against apple scab, and are well tolerated by plants (Grewe, 1965).



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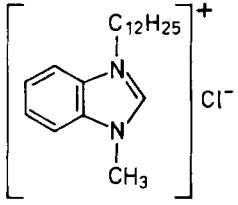

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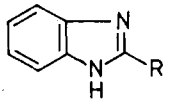
The most important derivatives used in agriculture are 2-substituted benzimidazoles **(17)** and 2-substituted aminobenzimidazoles **(18)**.



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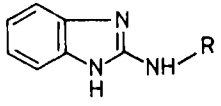
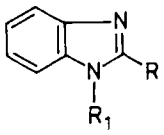


18

Of the latter particularly those in which R is an alkoxycarbonyl group, that is, the N-benzimidazol-2-yl-carbamic acid esters, are good fungicides. The fungicidal action diminishes with increasing carbon atom number of the R alkoxy group, and hexyl and octyl esters are already inactive. The 2-acylaminobenzimidazols are less active than the analogous alkyl benzimidazol-2-yl-carbamates. The antifungal activity ceases if a methylene bridge is introduced between the benzimidazole ring and the 2-methoxycarbonylamino group into the molecule. The methylation of either the carbamate nitrogen or the imidazole nitrogen similarly results in inactive compounds (Eckert and Rahm, 1979).

The derivatives of the above two parent compounds also substituted in position 1 represent a further group of compounds **(19, 20)**.



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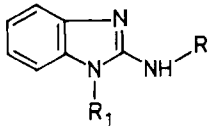

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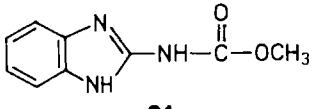
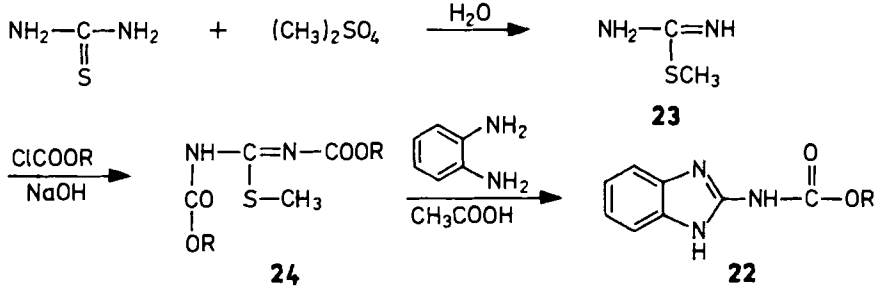


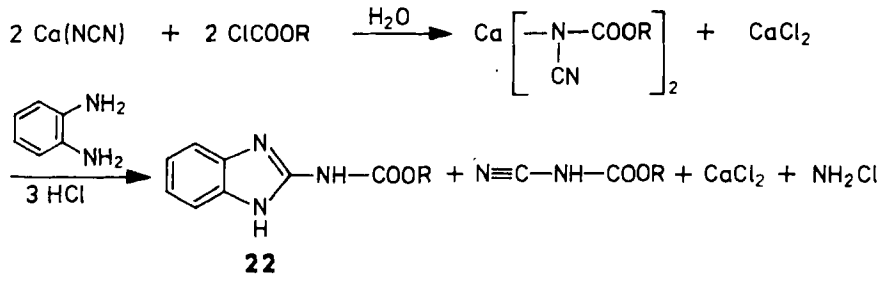
21

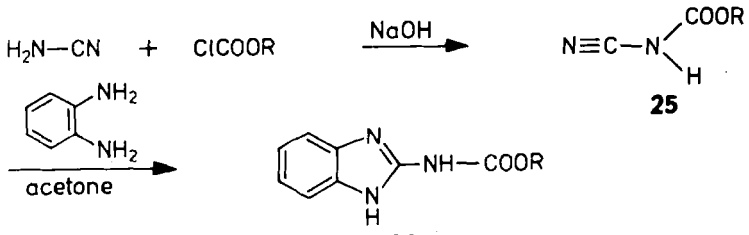
Carbendazim **(21)**, methyl-N-benzimidazol-2-yl-carbamate (MBC) is a light gray powder which decomposes slowly in alkaline solution, while forming a stable watersoluble salt in acid solution. Its water solubility depends on the pH (at pH 4, 28 mg/kg; at pH 8, 7 mg/kg). Carbendazim is a foliage fungicide with a specific action also used for seed treatment. It has a very broad spectrum of action. It protects orchards, vineyards, vegetables, ornamental plants and field crops against many fungal diseases which cause very significant damage. It is very efficient against the leaf and ear diseases of wheat (*Erysiphe, Septoria* and *Fusarium* spp.), but it is inactive against rust. Seed treatment of cereals increases the crop by 10% (Hampel and Löcher, 1973).

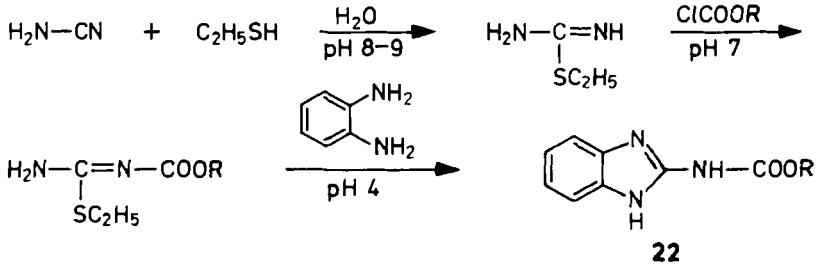
The alkyl esters of N-benzimidazol-2-yl-carbamic acid **(22)** can be prepared by the methylation of thiourea with dimethyl sulfate and the subsequent N-acylation in alkaline medium of the S-methyl-isothiourea formed **(23)** with the alkyl ester of chloroformic acid. Finally, N,N'-bis(alkoxycarbonyl)-S-methylthiourea **(24)**, obtained as an intermediate product is condensed with *o*-phenylene diamine in glacial acetic acid.



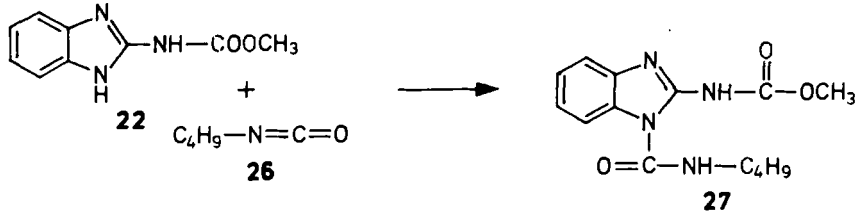
The product can be filtered off as a dark brown crystalline substance (Harvey, 1959; Klopping, 1960; Littrell *et al.*, 1967). They can also be synthesised by the reaction of calcium cyanamide with chloroformic acid alkyl ester and *o*-phenylene diamine (Adams and Schlatter, 1966; Tóth *et al.*, 1972; Burmakin *et al.*, 1974), or by the reaction of alkyl cyano carbamates **(25)**, produced by the treatment of cyanamide with chloroformic acid alkyl ester, with *o*-phenylene diamine (Adams and Schlatter, 1969), or by the reaction of cyanamide with alkyl mercaptan, chloroformic acid alkyl ester and *o*-phenylene diamine (Schlatter, 1970):





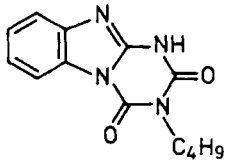


Benomyl **(27)**, N-(1-butylcarbamoyl-benzimidazole-2-yl)methylcarbamate or *methyl-N-[1-(butylcarbamoyl)-2-benzimidazole]*carbamate (Delp and Klopping, 1968), is produced by the reaction of MBC **(21)** with butyl isocyanate **(26).**



Benomyl is practically insoluble in water. It hydrolyses rapidly in aqueous media into methyl-N-benzimidazol-2-yl-carbamate (MBC) (Clemons and Sisler, 1969; Sims *et al.*, 1969; Fuchs *et al.*, 1972, 1974). In the alkalyne hydrolysis of benomyl, 1,2,3,4-tetrahydro-3-butyl-2,4-dioxo[1,2a]-*s*-triazinobenzimidazole (STB, **28**) and 1-(2-benzimidazolyl)-3-*n*-butylurea (BBU, **29**) are also formed (Ogawa *et al.*, 1971). According to White *et al.* (1973), the reaction catalysed by the dilute alkali and the formation of the monobasic salt of STB during the reaction proceeds rapidly and quantitatively. According to the patent of Bose and White (1971), STB is a fungicidal compound with systemic action.

Benomyl is readily soluble in organic solvents but is unstable in these solutions (Kilgore and White, 1970; Chiba and Doornbos, 1974; Chiba and Cherniak, 1978). Calmon and Sayag (1976a) found that in the solvents investigated the final decomposition product of benomyl was MBC. The solvolysis of benomyl is a spontaneous intramolecular catalysis in which the interaction of benomyl and the solvent molecules plays a role.



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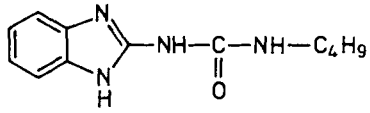

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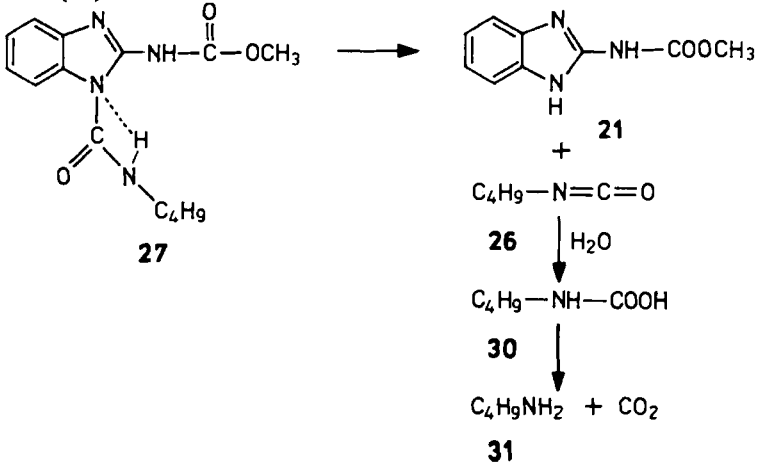
Benomyl absorbed by plants is rapidly metabolised in the tissue fluids into MBC (Sims *et al.*, 1969; Peterson and Edgington, 1970), so that benomyl itself can be detected only rarely in the tissue fluids. Sunlight, heat and various solvents enhance the transformation. At the same time, Baude *et al.* (1973) showed by the chemical approach that benomyl has adequate stability in aqueous suspensions at a concentration usual in sprays. An aqueous suspension of the benomyl preparation Benlate® at 23°C contained more than 90% of the original benomyl even after 48 hours. After a longer time, the larger part of the residue found on the leaves consisted of intact benomyl. No other metabolites were found in the plant in addition to MBC, even if benomyl was used in combination with alkaline pesticides (basic copper sulfate or lime sulfur solution) in the spray. Thus, because of its low solubility, the hydrolysis of benomyl in practice is not as rapid as has been measured in dilute solutions by several authors (Jhooty and Singh, 1972; Brown and Albrigo, 1972).

Recently, Calmon and Sayag (1976a and 1976b) studied the decomposition mechanism and kinetics of benomyl as functions of pH. The breakdown of benomyl into MBC begins by a spontaneous intramolecular process in slightly acid or neutral media. A hydrogen bond is formed between the free electron pair of the N_1 atom of the benzimidazole ring and the hydrogen on the nitrogen of the butylcarbamoyl side chain, forming thereby an unstable four-membered ring which opens to yield MBC and butylisocyanate. The isocyanate rapidly forms butylcarbamic acid with water **(30)**, and this is decomposed into carbon dioxide and butylamine **(31)**.



27

21

+

$C_4H_9-N=C=O$

26

H_2O

$C_4H_9-NH-COOH$

30

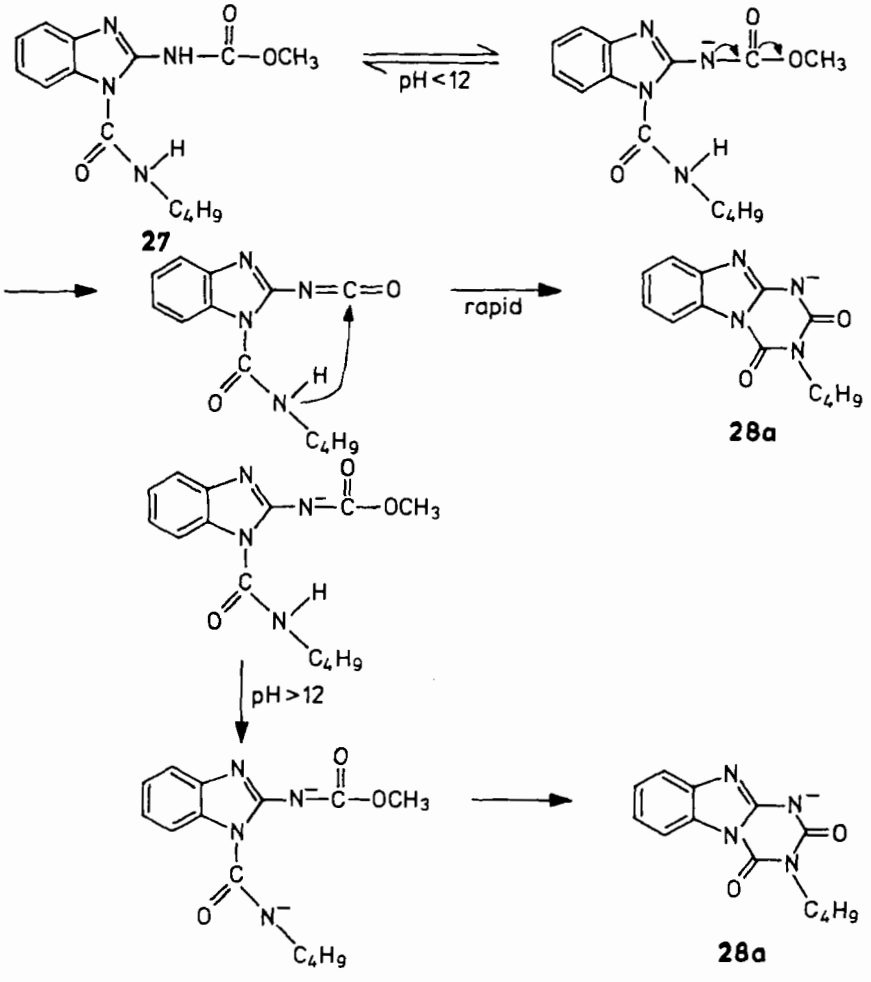
$C_4H_9NH_2 + CO_2$

31

Strongly acid media can prevent the decomposition, which can be explained by protonation of the benomyl molecule. Protonation occurs at the N_3 atom of the imidazole ring, inhibiting intramolecular H-binding by reducing the elctronegativity of the N_1 atom of the ring.

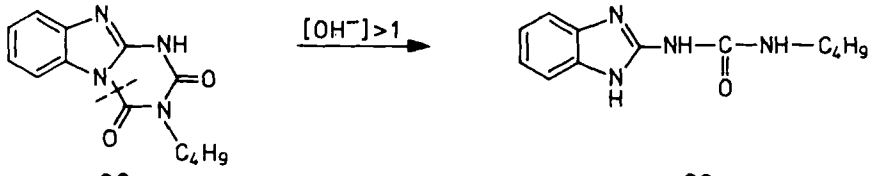
In weakly alkaline media (pH < 12), deprotonation occurs, which theoretically can take place on the nitrogen atom of either of the two side-chains. The authors have demonstrated that the proton of the methoxycarbamoyl group is more mobile, and the conversion mechanism is E_1cB elimination followed by a fast cyclisation. The end-product is the monobasic salt of STB **(28a).**

In strongly alkaline media (pH > 12) deprotonation also occurs on the nitrogen atom of the butylcarbamoyl group, and a dianion is formed. The intramolecular nucleophilic attack of this nitrogen on the carbonyl of the methoxycarbamoyl group also results in the formation of STB.



In the pH range 12–14, an equilibrium is established between the monoanionic and the dianionic mechanisms.

In very strongly alkaline media ($c_{OH^-} > 1$), the rapid reactions are followed by a much slower reaction. The triazine ring is split open and BBU **(29)** is formed. The opening of the triazine ring is caused by nucleophilic attack of the OH^- ions on the carbonyl group next to the N_1 atom of the imidazole ring.

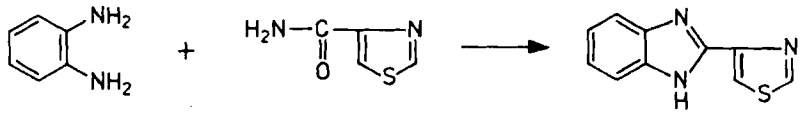


28 **29**

In normal foliage spraying with benomyl, the pH of the aqueous suspension is close to neutral, so that the conversion time on the plant and in the plant fluids is probably of the same order of magnitude as under aqueous neutral or slightly acid conditions. However, in the suspension applied the persistency of benomyl is incereased by rapid drying of the spray, which prevents further decomposition of the active substance.

Benomyl is a foliage and soil fungicide, and is also an effective seed protectant. Its range of action is very close to that of MBC. It is effective against gray mould, apple scab and powdery mildew, and against *Gloeosporium* dieseases during storage. It is also used against *Cercospora beticola* on sugar beet and against other pathogenic fungi on tomato and cucumber. According to Edgington *et al.*, (1971), benomyl is very effective against *Phialosporae, Arthrosporae, Sympodulosporae* and *Aleurisporae* belonging to the *Deuteromycetes* class. In the group of *Blastosporae, Cladosporium fulvum, Botrytis* spp. and *Monilia cinerae* are very sensitive. On the other hand, benomyl has but a weak action or is inactive against *Phycomycetes (Phytophtora infestans, Plasmopara viticola), Alternaria* and *Helminthosporium* spp. It proved to be a suitable seed protectant against *Erysiphe graminis*. It is sold under the trade names Benlate® (Du Pont) and Fundazol® (CHINOIN).

Thiabendazole, 2-(4′-thiazolyl)benzimidazole **(32)**, is prepared from *o*-phenylenediamine and 4-thiazole carboxamide **(33)** in polyphosphoric acid (Brown *et al.*, 1961).



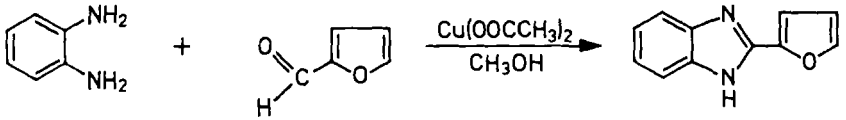
33 **32**

Thiabendazole has been known since 1962 as an anthelmintic against dermatophytes fungi. Its bactericidal activity is low. It was found later that thiabendazole has a fungistatic and fungicidal effect on many phytopathogenic

fungi (Robinson *et al.*, 1964; Staron and Allard, 1964). Its main field of application is the protection of apples and pears against fungi causing rot during storage (Pleisch *et al.*, 1971; Spalding and Hardenburg, 1971; Ben-Arie, 1975). It is also very effective for seed treatment against bunt of wheat and against the steadily spreading dwarf bunt fungi *(Tilletia contraversa)*, protecting the plant against infection for several months (Hoffmann, 1971). Thiabendazole is inactive against *Phycomycetes* (*Pythium* and *Phytophthora*), *Deuteromycetes (Phoma betae)*, bacteria, yeasts and *Actinomycetes*.

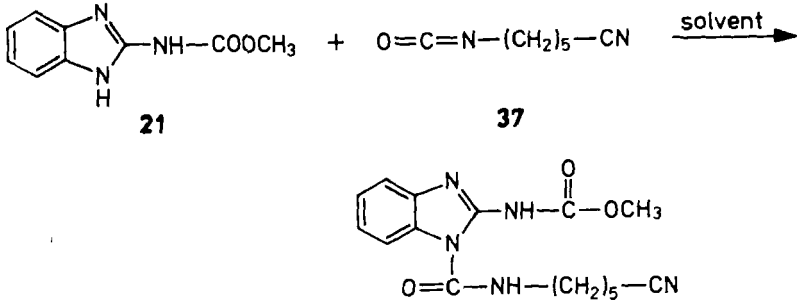
The active substance has a systemic effect. It is translocated (Weinke *et al.*, 1969), but more slowly than benomyl or MBC (Wang *et al.*, 1971; Ben-Arie, 1975). The metal salt complexes of thiabendazole also have a fungicidal effect (Miller *et al.*, 1973).

Synthesis of fuberidazole, 2-(2'-furyl)benzimidazole (**34**), starts with *o*-phenylene diamine, which gives the end-product directly with furfurol (**35**) and cupric acetate, as oxidising agent, in a medium containing methyl alcohol (Weidenhagen, 1936). Its range of action is similar to that of thiabendazole (Von Schumann, 1967). It is effective for the treatment of seeds mainly against *Fusarium* diseases *(F. nivale, F. culmorum)*, leaf rust *(Puccinia triticina)* and powdery mildew on barley *(Erysiphe graminis)* (Von Schumann, 1968). Fuberidazole has a systemic effect.



35 **34**

Cypendazole, methyl-N-[1-(5-cyanopenthylcarbamoyl)-2-benzimidazole]-carbamate (**36**), is prepared by the reaction of MBC (**21**) with 5-cyanopenthyl isocyanate (**37**) (Daum *et al.*, 1968a, 1968b). A yellowish-white crystalline substance, it is a fungicide with protective and eradicant action and a range of action similar to that of benomyl (Melin, 1973).

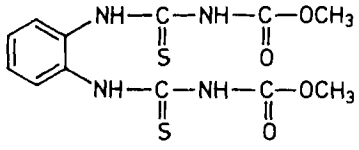


21 **37**

36

Thioallophanic acid derivatives

These active substances, although chemically not benzimidazole derivatives, will be discussed in this chapter because their fungicidal metabolites are benzimidazole derivatives. Substances of importance belonging to this group are thiophanate-methyl (**38**), 1,2-bis(3-methoxycarbonyl-1-thioureido)benzene, its ethyl homologue thiophanate (**39**) and NF-48 (**40**).



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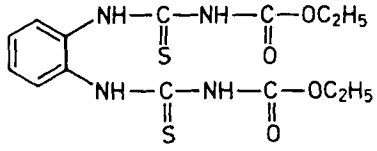

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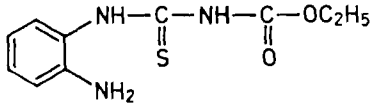

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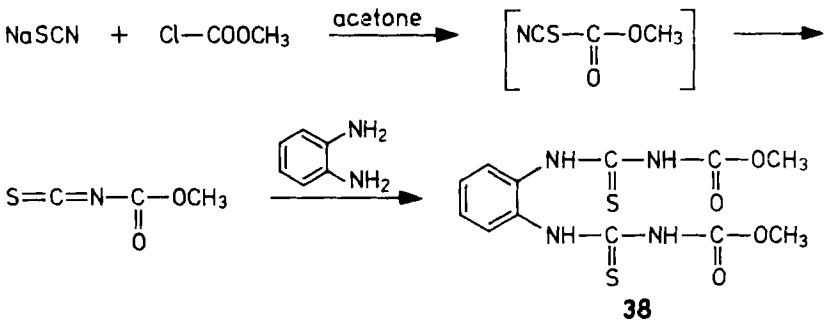
All of these derivatives are 1,2-disubstituted benzenes, which are converted by chemical reaction, for example, in aqueous medium with sodium hydroxide or with dimethyl sulfate, into alkyl N-benzimidazol-2-yl-carbamates (Koyamada *et al.*, 1969; Adams and Wommack, 1970). Thiophanate derivatives themselves are inactive (Nogutsi *et al.*, 1971), but in plants they are converted into benzimidazole derivatives, exerting their effect in this form (Selling *et al.*, 1970; Vonk and Kaars Sijpesteijn, 1971; Soeda *et al.*, 1972). The lack of activity of 1,3- and 1,4-bis(3-alkoxycarbonyl-1-thioureido)benzenes can be explained by their inability to cyclise the benzimidazole ring. Thioallophanic acid derivatives are thus the precursors of alkyl N-benzimidazol-2-yl-carbamates. Further substitutions on the benzene ring decrease the fungitoxicity of the compounds.

Of the thiophanates, thiophanate-methyl (**38**) is the most active compound (Ishii, 1970). It is prepared by the reaction of sodium or potassium thiocyanate with chloroformic acid methyl ester, and the intermediate product reacts with *o*-phenylene diamine to form the thiophanate. Thiophanate-methyl is a colourless, crystalline compound hardly soluble in water. It forms unstable salts and complexes with bivalent ions in alkaline solutions. The range of action of each thioallophanic acid derivative is identical with that of the benzimidazole derivative into which it is converted in the plant. Thiophanate-methyl has both a preventive and a curative action.



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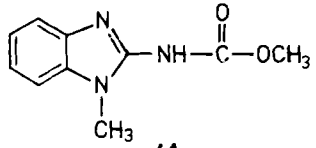
Particularly good results are attained against apple and pear scab and on various crops against powdery mildew, *Botrytis* and *Sclerotinia* spp. The thiophanates are also effective against diseases that occur in the period after harvest, such as rotting of banana and apple caused by *Gloeosporium* spp., rotting of orange and citrus fruits caused by *Penicillium* spp., and the brown rot of pears (Meredith, 1977). When used systematically, thiophanate-methyl substantially decreases acarus populations because the compound is an effective ovicide against *Tetranychus urticae* (Cole *et al.*, 1971).

Thioallophanic acid derivatives are endotherapeutic active substances with a specific action. They are taken up mainly by the roots and remain in the plants for a relatively long time. They are suitable for seed treatment, for example, on barley against *Ustilago nuda* (Mercer, 1971), and have been found to be active also against tobacco mosaic virus (Noguchi *et al.*, 1972).

The similarity of the range of biological action of benzimidazole derivatives is very remarkable (Edgington *et al.*, 1971; Kaars Sijpesteijn, 1972). Eckert and Rahm (1974) explain this similarity by their identical structure, and compare the structure–activity relation of 2-substituted benzimidazoles with that of the herbicidal N-phenylcarbamates. In the case of herbicides of the general formula R_1—NH—CO—R_2 it is assumed that in plant cells the active substances are bound to the site of action by a hydrogen bond or by a charge-transfer complex formed through the amino group. The R_1 group promotes the penetration of the molecule into the cells, while the R_2 group provides for optimal electron density at the carbonyl group. Roughly the same role can be attributed to the single parts of the molecule in the explanation of the fungitoxic effect of alkyl benzimidazole-2-yl-carbamates. For example, the binding of the hydrogen of the amino group results in biological inactivity. A —CH_2 group introduced between the benzimidazole ring and the amino group weakens hydrogen bounding tendency at the amino group and, accordingly, reduces the antifungal action of the active substance thus modified. The ester group does not substantially affect activity; however, the fungicidal effect decreases with increasing length of the alkyl chain.

The role of the benzimidazole nucleus in the active substances is not only to provide for hydrophobic–hydrophilic equilibrium, but also to bind the molecule to the site of action. In the benzimidazole ring, the opportunity for binding at the

nitrogen atoms and the planarity of the benzimidazole nucleus should lead to a strong affinity for a complimentary site. The participation of hydrogen bonds through the imino-nitrogen is indicated by the fact that derivatives in which ability to the bond hydrogen at this site is impaired or lacking have a decreased fungicidal activity. This is the case, for example, for methyl-N-(1-methylbenzimidazol-2-yl)-carbamate (**41**). On the other hand, those 1-substituted derivatives degraded spontaneously under environmental conditions to MBC reveal *in vivo* an excellent fungicidal action (Edgington and Schooley, 1972). Substitutions in the benzene ring could have pronounced electronic and steric influences, or could shift the hydrophilic–hydrophobic balance of the molecule. Strongly electron-withdrawing substituents in positions 5,6 may drastically reduce the fungicidal activity of the molecule.



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The actions of the individual active substances on identical fungi differ to a certain degree, which can be explained by the properties of the active substances and the processes that occur during the period required for the compound or its fungitoxic metabolite to reach the site of action. According to certain workers, benomyl acts only after its degradation to MBC. Sims *et al.* (1969) did not find benomyl either in the leaves or in the stem of cotton plants treated with benomyl four weeks after treatment, but they detected MBC, which moves faster in the plants. According to Peterson and Edgington (1970), benomyl is decomposed in five days in beans. Moreover, they attribute even the systemic action of benomyl to MBC formed from it.

According to other workers, the notion that the action of benomyl can be simply traced back to the action of MBC is not unequivocal. Although it is true that the growth of most fungi is identically decreased by the two active substances, they nevertheless show certain differences. MBC is less effective against *Saccharomyces pastorianus* fungi than benomyl. Hammerschlag and Sisler (1972) found that MBC is considerably less fungistatic than benomyl, but is a more efficient fungicide. As concerns the metabolism of the organisms, benomyl inhibits the oxidation of glucose or acetate, and rapidly blocks the synthesis of DNA, RNA and proteins. MBC, on the contrary, does not affect the oxidation of glucose or acetate, and inhibits the synthesis of DNA, RNA and proteins only after a rather long delay. In spite of the fact that benomyl inhibits growth to a greater extent than MBC initially, MBC eventually reduces the vitality of the cells to a higher degree than benomyl. The differences in the action of MBC and benomyl can be explained by the slower penetration of the former into certain fungal cells (Upham and Delp, 1973).

However, according to recent investigations by Hammerschlag and Sisler (1973), differences in the activity of the two active substances might be explained by the

presence of the other metabolite, butyl isocyanate, formed during the metabolism of benomyl. The toxicity of butyl isocyanate is probably influenced by the cell: inhibitor ratio, since the reactivity of the compound makes it inclined to become inactivated by the thiol compounds in the cells.

Butylisocyanate, as methyl isothiocyanate (see dithiocarbonic acid derivatives), inhibits the respiration of yeast cells. Isothiocyanates react with thiol compounds, and their fungitoxicity is reversible. Mailman *et al.* (1971) found that the toxicity of benomyl to yeast can be decreased by the addition of thiol compounds.

Butylisocyanate formed is a very reactive and unstable compound, so that its action is local and of short duration. Butyl isocyanate, as well as butylamine, may contribute to the phytoalexin-inducing properties of benomyl preparations observed by Reilly and Klarman (1972).

Benomyl has been frequently reported to be more effective than MBC although both compounds exhibited similar toxic effect. Köller *et al.* (1982) found that benomyl, but not MBC inhibits cutinase from *Fusarium solani* by the reaction of butylisocyanate and prevents under controlled conditions of a bioassay, the fungal penetration into its host suggesting the possibility of a dual mode of action for this fungicide.

The slower biological activity of thiophanate-methyl is due to its slower conversion to MBC. Important factors in this conversion are the pH of the medium and the temperature. The less acidic the medium, the more rapid is the conversion (Vonk and Kaars Sijpesteijn, 1971). In plant tissue fluids this conversion is rapid (Matta and Abbatista Gentile, 1971); moreover, certain fungi may accelerate the metabolism. Conversion is also catalysed by sunlight (Buchenauer *et al.*, 1973). Thiophanate-methyl is also metabolised in fungi to MBC (Yashuda *et al.*, 1973).

Fungicides of the benzimidazole type have a systemic action. Generally, they are taken up by the roots of the plants, and the active substances are then acropetally translocated through the xylem to the leaves. In the leaves they travel peripherically and accumulate at the edges and tips (Peterson and Edgington, 1970 and 1975; Ben-Aziz and Aharonson, 1974; Leroux and Gredt, 1975; Knoll, 1978). It has been shown experimentally that benomyl, MBC, thiabendazole and thioallophanic acid derivatives are translocated to a small extent from one leaf to another, then basipetally into the stem and the roots (Solel, 1970; Noguchi *et al.*, 1972). Part of the benzimidazole fungicides thus penetrates, albeit to a small extent to the cytoplasm and phloem (Solel *et al.*, 1973).

The distribution of the active substances in the plants is different. Thiabendazole remains in the highest concentration mainly in the roots, while benomyl accumulates in the epicotyl. This explains the finding that benomyl is less effective against seedling diseases (Gray and Sinclair, 1970). The hydrochloric acid salts of benzimidazoles are more soluble in water than the free bases and can therefore penetrate the cuticle about four times as rapidly. Therefore, in the case of acid salts the concentration of the active substance increases in the xylem and in the phloem, so that the hydrochloric acid salts of the active substances give efficient protection to cotton even against *Verticillium* (Buchenauer and Erwin, 1971 and 1972). The

translaminar translocation of benzimidazole active substances can be improved with nonionic surfactants and oil–water formulations (Brown and Hall, 1970).

The action of these active substances on plant cells has been studied by Richmond and Phillips (1975) using onion *(Allium cepa)* as test object. Benomyl and carbendazim induce identical aberrations in the cells of onion root. Benomyl acts considerably more rapidly than carbendazim. However, the proportion of abnormal mitosis caused by them is presumably insufficient to cause irregular plant growth. On the other hand, a property of benomyl and MBC similar to that of cytoquinine has been noted (Skene, 1972; Thomas, 1973 and 1974).

Benzimidazole fungicides presumably penetrate the fungal organism by diffusion. Their passage through the membrane is a function of the lipoid solubility of the molecule and of the pH. At pH 4.5 their fungitoxicity is generally low, because the majority of the molecules are in the ionised state. At pH 8.6, however, the molecules are in the nonionised state and can rapidly penetrate the membrane and the cell nucleus to exert its fungicidal effect (Bartels-Schooley and McNeill, 1971).

Benzimidazoles influence DNA synthesis and processes closely related to it such as nucleus or cell division. This hypothesis is increasingly supported by the research results of recent years. It is further substantiated by the structural similarity of the benzimidazoles to the two purine bases of DNA, adenine and guanine. The experiments of Clemons and Sisler (1971) were the first to call attention to the fact that benomyl and carbendazim, and fungicides of the benzimidazole type in general are specific mitosis inhibitors. According to these workers, in the presence of carbendazim, the number of nuclei in the cells of conidia of germinating *Neurospora crassa* is lower than in control cells. In the synchronous cultures of sporidia of *Ustilago maydis* growth stopped in the doublets in the presence of carbendazim, and the doublets contained only a single nucleus. Davidse (1973) did not find separated nuclei in the hyphae of *Aspergillus nidulans* treated with carbendazim. Hastie (1970) found that benomyl causes instability of the diploidal cell lines. Benomyl in a solution with a concentration as low as 0.5 mg/kg decreased the number of conidia and the size of the colonies. Styles and Garner (1974) also observed mitotic abnormalities caused by carbendazim (spindle poison) in cell cultures of mammals (Davidse, 1975).

Richmond and Phillips (1975) found in the case of *Botrytis cinerea* that the conidia of the fungi produced distorted germ tubes in the presence of benomyl. In most of the fungi, cell division differed from classical mitosis, the normal states of which were not seen clearly in any of the treated material. Chromosomes became visible at the prophase-metaphase, but they did not completely separate. Finally, the chromatin became stretched into long threads, daughter nuclei did not separate completely and chromatin was often present as irregular shaped masses.

According to Kumari *et al.* (1977) benomyl severely decreases DNA synthesis when applied at $3.5 \cdot 10^{-6}$ M during the *G1* phase of germinating conidia of *Fusarium oxysporum*. Nuclear divisions are completely inhibited at a fungicide

concentration of $10 \cdot 10^{-6}$ M. The same concentration applied only after the *S* phase also completely inhibits nuclear divisions. This dual interference of benomyl with DNA formation and mitosis might be related to a disturbed phosphorus metabolism. Davidse and Flach (1977, 1978) found in recent investigations that benzimidazole derivatives are bound to the tubuli of the fungi (Davidse, 1977).

In the mode of action of benzimidazoles, the carrier of the fungicidal action is the benzimidazole ring, common to all of the derivatives. The substituents, however, particularly in position 2, strongly influence this action. Therefore, in addition to the common mode of action, different side-effects can be observed for certain active substances. Thus, a respiration-inhibiting action was observed for thiabendazole (Allen and Gottlieb, 1970) and an acaricidal action for benomyl, thiophanates and MBC (Nakashima and Croft, 1974), while 2-trifluoromethyl benzimidazole are primarily acaricides.

The nearly identical mode of action of benzimidazoles, evidenced by the similarity of their fungitoxic range of action and of their structure, is also supported by the development of cross-resistance. Resistance developed rather rapidly to systemic fungicides has also been observed for benzimidazole derivatives.

Resistance to benomyl was already known before it was put on the market (Schroeder and Provvidenti, 1969).

Resistance to all of the benzimidazole derivatives has been produced in the laboratory (Bartels-Schooly and MacNeill, 1970; Hastie and Georgopoulos, 1971; Bollen and Scholten, 1971). Since then, several fungal strains not sensitive to some fungicides of the benzimidazole type have also been isolated from the field and the problem steadily becomes more serious (Smoot and Brown, 1974; Jordan and Richmond, 1974; Littrell, 1974; Vantuyl *et al.*, 1974; Bollen and Van Zaayen, 1975). Abelentsev and Golyshin (1973) studying fungi grown in a medium containing 5 μg benomyl, found that in 290 days the resistance of *Botrytis cinerea, Monilia cinerea, Monilia fructigena* and *Venturia inaequalis* increased 2.5-, 2.8-, 3.6- and 2.7-fold, respectively. The acquired resistance was very specific for the first three fungi, while in the case of *Venturia inaequalis* a cross-resistance to dithiocarbamate fungicides was observed.

According to the experiments of Bartels-Schooley and MacNeill (1971), mutants tolerating benomyl and thiabendazole proved to be tolerant also to fuberidazole, but fuberidazole-tolerant mutants of *Fusarium oxysporum* showed the same sensitivity to benomyl and thiabendazole as the wild isolates. It follows from this that fuberidazole and the benzimidazoles have a common mode of action, but benomyl and thiabendazole also act according to a further mechanism different in effect. Research is under way on the mechanism of resistance (Gessler, 1976; Davidse, 1976; Davidse and Flach, 1977; Tripathi and Schlösser, 1982; Kovács and Tüske, 1982).

Benzimidazole derivatives are taken up to a limited extent by plants from the soil (Erwin, 1973; Baude *et al.*, 1974). Uptake from sandy soil is greater than from loamy soil (Fuchs *et al.*, 1970), and the rate of uptake increases with the decrease in

organic matter content and the increase in pH of the soil (Schreiber *et al.*, 1971). Aharonson and Kafkafi (1975a, 1975b) investigated the absorption mechanism, mobility and persistency of the fungicides in different soils and found that absorption is the greater the more acid the soil (Süss and Pritzl, 1977).

Thiabendazole is bound more strongly to the soils than is MBC. Its motility is also lower, so that is available for a longer time for the plants as a fungicide reservoir. Thiabendazole is very persistent, particularly in dry soils. In both aerobic and anaerobic soils it is degraded by only 10–25% over a period of nine months. The decomposition of MBC is somewhat more rapid, 25–30% being degraded in nine months. In wet soils both are degraded more rapidly. 70–80% in the nine months (Rhodes and Long, 1974; Helweg, 1977).

A possible degradation product of MBC is 2-aminobenzimidazole **(42)**, which has been detected in the soil in very small quantities (Baude *et al.* 1974). Benomyl is also decomposed in the soil into MBC. Thiophanates decompose rapidly into MBC in the soil as well (Fleeker *et al.*, 1974), this conversion is dependent on the pH value. At pH 7.4 cyclisation proceeds four times as rapidly than at pH 6.5. Benomyl does not affect the bacterial population of the soil (Siegel, 1975); it does, however, reduce the action of phytopathogenic nematodes *(Xiphinema americanum, Tylenchorhynchus dubius)* and increases the efficiency of certain nematicides (dazomet) (Romanenko, 1974).

Thiabendazole is metabolised in plants only in sunlight, being decomposed by photolysis. Jacob *et al.* (1975) found that the photolysis products are benzimidazol-2-yl carboxamide and benzimidazole. The decomposition of MBC is also accelerated by sunlight (Fleeker and Lacy, 1977).

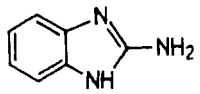
Benzimidazole derivatives are not toxic to mammals. Their acute oral LD_{50} is generally higher than 2500 mg/kg for rats. Below 400 mg/kg subchronic toxicity cannot be detected in 90 days. They are not hazardous to bees and are toxic only above 100 mg/kg to fish. The active substances do not accumulate in the organism. Rats and dogs excrete 99% of the benomyl administered orally in the urine and feces within 72 hours.

The main metabolite of benomyl is methyl N-(5-hydroxybenzimidazol-2-yl)-carbamate **(43)** (Watkins, 1976), which nas been detected in the urine conjugated with glucuronic acid or sulfate. Two-year chronic feeding tests similarly proved that there is no accumulation in warm-blooded animals. Residues in milk and eggs can be detected only at a feeding level of 25–50 mg/kg of benomyl (Gardiner *et al.*, 1974). The irreversible acetylcholinesterase-inhibiting effect of benomyl is attributed to its other metabolite, butylisocyanate (Krupka, 1974). Its metabolism in rats has been studied by Axness and Fleeker (1979). Fuberidazole is rapidly absorbed by mammals through the digestive system. Its biotransformation is also very rapid, so that 4–5 hours after its administration the original compound cannot be detected in the plasma. Its metabolites vary, depending on the animal. Three metabolites have been identified in rabbits, and seven in rats and goats. The main metabolic pathway is hydroxylation of the benzene ring and the splitting off and subsequent hydroxylation of the furan ring (Adrian, 1971).

Benomyl applied to the soil reduces the earthworm population quickly and considerably, but after a few months the reproduction of the earthworms is restored again. After one to two years, no substantial difference can be detected between the earthworm pupulations in treated and untreated areas (Black and Neely, 1975).

The mutagenic and teratogenic effects, however, which have been demonstrated on various bacterial test organisms (Seiler, 1972; Seiler and Limacher, 1973), and have been observed by Styles and Garner (1974) even in mammalian cell cultures, however may cause problems with this type of active substance. It is of interest that methyl N-(5-*n*-butyl-benzimidazol-2-yl)carbamate, parbendazole (**44**), used as an anthelmintic caused abnormalities in a large number of sheep (Lapras *et al.*, 1973a). A significant teratogenic effect was also found in rats (Lapras *et al.*, 1973b).

However, mutagenic damage of the chromosomes by application of fungicides of the benzimidazole type has not yet been observed (Makita *et al.*, 1973; Hashimoto *et al.*, 1972a, 1972b).



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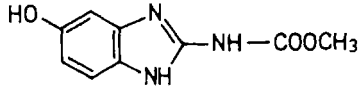

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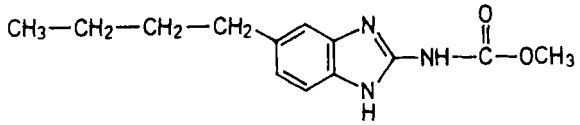

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Whether used as soil or foliage fungicides, benzimidazole derivatives reduce damage to plants caused by atmospheric ozone (Taylor, 1970; Pellissier *et al.*, 1972).

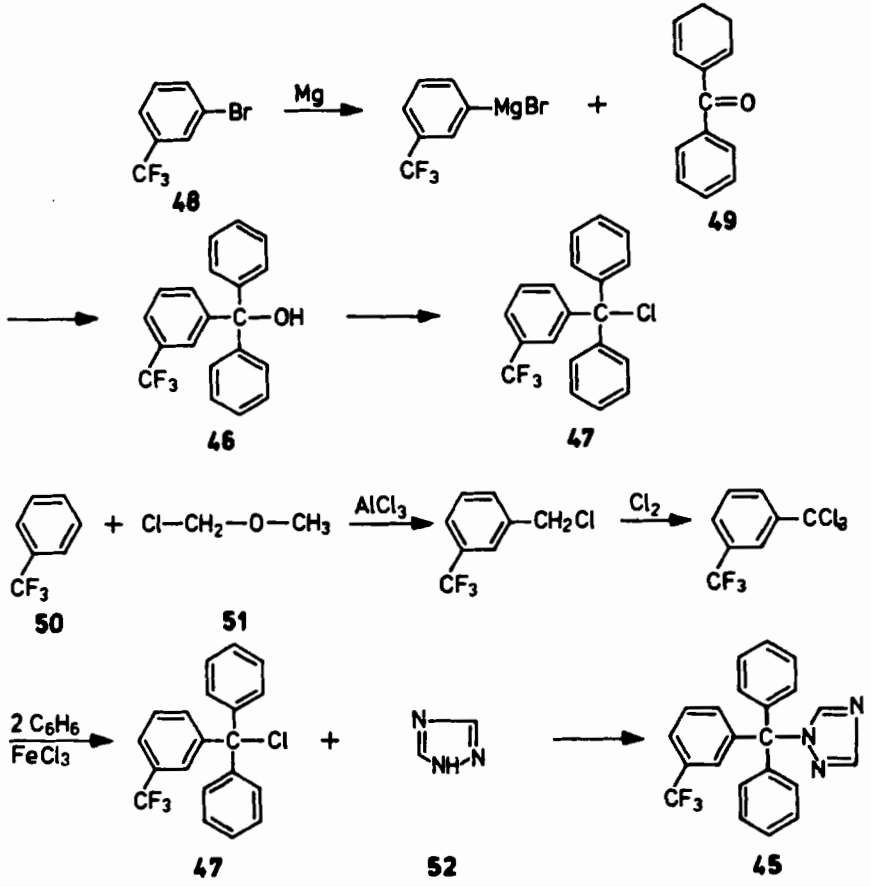
5.7.3 Triazoles

Starting from the hypothesis that azo compounds with an ability to form active carbonium ions *in vivo* are biologically active, Büchel *et al.* (1972, 1975) synthesised several derivatives of 1-trityl azoles. They established in extensive research work that the derivatives particularly active are those which contain only one substituent in one of the phenol rings, and in which the azole ring remains unsubstituted. This led to the very active antimycotic clotrimazole (see Section 5.7.1), which nowadays plays an important role in the local therapy of human mycoses, and to fluotrimazole, of specific activity against powdery mildews.

The initial basic substance for the synthesis of fluotrimazole (**45**), 1-(3-trifluoromethyltrityl)-1H-1,2,4-triazole, may be *m*-trifluoromethylphenyl bromide (**48**), which reacts in Grignard synthesis with benzophenone (**49**), the 3-trifluoromethylphenyl-bis(phenyl)methylcarbinol (**46**) obtained being converted into trityl chloride (**47**).

The substituted trityl chloride can also be synthesised by Friedel–Craft reaction from trifluoromethyl benzene (**50**) and chloromethyl ether (**51**). The product obtained is chlorinated and reacted with benzene in another Friedel–Craft reaction (Büchel and Singer, 1975).

Nucleophilic substitution with triazole (**52**) of the substituted trityl chloride in polar solution (ketone) yields the end-product (**45**) (Büchel *et al.*, 1972).



Fluotrimazole gives effective protection against all important powdery mildew fungi on cereals, apples, cucumber and roses. It shows some activity against brown rust *(Puccinia hordei)* in spring barley and against yellow rust *(Puccinia striiformis)* in spring barley and winter wheat (Jeffrey *et al.*, 1975). Its effect is essentially protective, but it also has a certain curative effect. The toxicological properties are very favourable, the acute oral LD_{50} for rats being higher than 5000 mg/kg (Kaspers *et al.*, 1975).

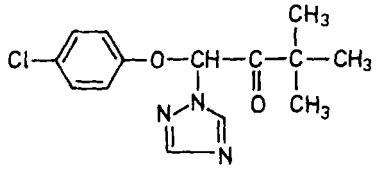
Fluotrimazole seriously inhibits ergosterol biosynthesis and concomitantly caused an accumulation of immediate ergosterol precursors. Fluotrimazole is a

specific inhibitor of the oxidative demethylation of the ^{14}C-methyl group during ergosterol biosynthesis in *Ustilago avenae* (Buchenauer, 1978a).

Owing to its selective action, the low quantity applied and its favourable toxicological properties, fluotrimazole is a very advantageous active substance from the point of view of environmental protection. Its use in agriculture is promising (Grewe and Büchel, 1973, Clark *et al.*, 1983).

In the study of trityl-azole derivatives the phenol groups have been found to be replaced by ketones, carboxyl esters, nitriles and carboxamides (Büchel *et al.*, 1975). Of these new derivatives, the triazolyl-O,N-acetals **(53)** particularly have good fungicidal properties, similar to those of fluotrimazole. Unlike trityl triazoles, these compounds have not only a protective, but also a systemic action. The systemic action and the range of action of these compounds depend on the number and nature of the substituents in the phenyl nucleus. When two chlorine substituents are incorporated in the phenyl ring, the systemic action of the compounds decreases, but their range of action is shifted towards fungi other than powdery mildews. Systemic activity is further reduced if the chlorine substituent is replaced by a phenyl ring, another alkyl group or a cycloalkyl group (Anderson *et al.*, 1984).

Triadimefon **(54)**, 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)butan-2-one, excels in its broad spectrum of action and its potency (Grewe and Büchel, 1973; Krämer *et al.*, 1978).



54

Triadimefon is a fungicide with excellent systemic action. It is translocated primarily acropetally in the plant, and to a lesser degree basipetally (Buchenauer, 1975 and 1976a; Brandes *et al.*, 1978; Führ *et al.*, 1978). Thus it can be applied as a foliage fungicide, for seed treatment, and even as a soil fungicide. Its action *in vitro* is moderate; *in vivo*, however, it has a powerful effect, particularly against powdery mildew fungi. When used for seed treatment, the direct systemic action lasts for about two months, so that it protects spring cereals from infection for almost the whole growth period, while at harvest time no residue is present in either the straw or in the grain (Hardison, 1974; Kolbe, 1976; Scheinpflug *et al.*, 1978).

It is also very effective as a foliage fungicide. In greenhouse experiments a concentration as low as 1 mg/kg was sufficient for a protective and curative effect against *Erysiphe graminis*. It has been used with good effect against powdery mildew fungi of vine *(Uncinula necator)* (Dörtlein and Rota, 1978) and against powdery mildew of apple trees (Kolbe, 1978b).

The range of action of triadimefon is actually much broader. In addition to the control of powdery mildew fungi, this active substance completely protects cereals

against all kinds of smuts — *Ustilago nuda, U. tritici,* and even against *U. avenae* and *U. nigra.* It has a powerful action against *Helminthosporium* spp., spreading with the seeds, particularly in barley and oat, which is of great practical importance. In the treatment of barley seeds it was used to remarkably good effect against *Typhula incarnata,* surpassing the action of all the fungicides used so far (Ebenebe and Fehrmann, 1974; Frohberger, 1975; Kampe, 1975). Treatment with triadimefon made possible for the first time the protective, curative and eradicant control of rust fungi in cereals (Siebert, 1976; Morris *et al.,* 1977; Rowley *et al.,* 1977).

At normal temperatures triadimefon gives complete protection to untreated barley plants against powdery mildew up to a distance of 50 cm from treated plants due to its vapour emission (Schlüter, 1977).

A disadvantage of triadimefon is that it may cause certain growth disturbances in plants. In effective concentration it is not phytotoxic either on spraying or in seed dressing, but some retardation of germination and some inhibition of the initial growth of plants can often be oberved, particularly under nonoptimal germination conditions. These effects are only transitory, however, and are later overcome completely by the plants, so that the deleterious side-effect of triadimefon does not ultimately affect the yield (Buchenauer, 1977a).

The triadimefon content of mycelia accumulates to 20 to 40-fold that of the external concentration, irrespective of the sensitivity of the fungus. During its metabolism a highly fungitoxic product, triadimenol **(55)**, was formed (Clark *et al.,* 1978). In mycelia of sensitive fungi this transformation took place at a high rate, whereas it could be demonstrated to only a limited extent or not at all in resistant types. The material produced by the sensitive fungi was also effective against fungi basically resistant to triadimefon. Based on these observations, triadimefon must be regarded as the precursor of triadimenol. In the species investigated, selectivity may be related mainly to the rate of action. In higher plants the metabolism of triadimefon showed a similar pattern, but was slower than in fungi. Thus, as the transformation into triadimenol (activation) begins early in the host tissues, the systemic fungitoxic effect is also influenced by the host plant itself (Gasztonyi and Josepovits, 1979). According to Büchel and Singer (1975) the stereochemistry of a molecule is an important factor in determining the fungitoxicity of azole fungicides. The reduction of triadimefon to triadimenol increases the number of chiral centres. Thus, from the two optical isomers of triadimefon (*R* and *S*), two pairs of triadimenol enantiomers are produced: (1*R*,2*S* and 1*S*,2*R*) and (1*R*,2*R* and 1*S*,2*S*). The dissimilar physical properties of the diastereomers made possible their separation by gas-liquid chromatography and the ratio of the diastereomers in the triadimenol formed is characteristic for each of the fungal species (Gasztonyi 1981; Deas and Clifford, 1982; Buchenauer and Grossmann 1982; Gasztonyi and Josepovits 1984; Deas *et al.,* 1984a,b).

The inhibition of the conversion of immediate sterol precursors to ergosterol may be regarded as the primary target for the action of triadimefon in *Ustilago avenae* (Leroux and Gredt, 1976; Buchenauer, 1976b, and 1977b).

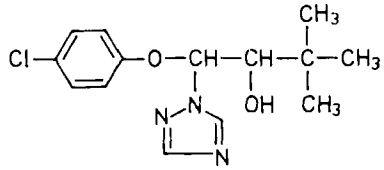
From the standpoint of environmental protection, triadimefon is one of the most promising of all fungicides. Toxicologically it is not hazardous, it is a moderate poison for warm-blooded animal (LD_{50} acute oral 568 mg /kg for rats). Absorbed through the skin or inhaled it has a very low toxicity, and it does not irritate the mucous membranes. In subchronic tests no pathological changes could be detected (Frohberger, 1973). It is not toxic to bees.

Photolysis causes cleavage of the C-1 to triazole bond, liberating 1,2,4-triazole, 4-chlorophenol and 4-chlorophenyl-methyl carbonate, none of which are fungitoxic (Clark *et al.*, 1978).

Triadimenol **(55)** 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)butan-2-ol (Krämer *et al.*, 1973), is structurally very closely related to triadimefon and has been indentified within fungal and plant tissues as a metabolite of triadimefon (Clark *et al.*, 1978; Buchenauer, 1979). The mode of action appears to be similar to that of other members of the triazolyl-O,N-acetale group in that the biosynthesis of ergosterol is affected in susceptible fungal strains (Buchenauer, 1978b).

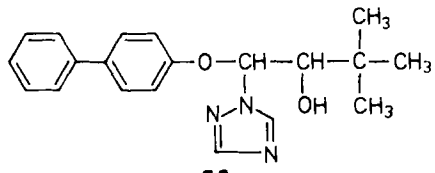
Triadimenol has been shown to be biologically active *in vivo* against a number of fungal diseases in plants, the spectrum of activity being particularly useful in the control of seed-borne and foliar dieases of cereals (Frohberger, 1978; Trägner-Born and Boom, 1978; Wainwright *et al.*, 1979).

The acute oral LD_{50} is 1100 mg/kg for rats.



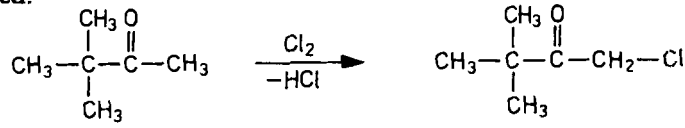
55

Another member of this family of compounds, bibertanol **(56)**, 1-(1,1'-biphenyl-4-yloxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)butan-2-ol, is primarily a protective foliage fungicide, but it also has curative and eradicative effects. Its action, however, is not systemic. It has a very wide range of action. Its main field of application is protection against *Venturia* spp. the foliar diseases of ground nut, *Mycosphaerella* spp. damaging banana, and powdery mildew and rust fungi. Its curative and eradictive effects were observed mainly in the control of apple scab (Brandes *et al.*, 1979; Trägner-Born *et al.*, 1981). Bibertanol exerts its fungitoxic action by inhibiting sterol biosynthesis (Kraus, 1979). It has advantagenous toxicological properties for mammals, the acure oral LD_{50} being 5000 mg/kg in rats. It is not toxic to bees, fish or birds.



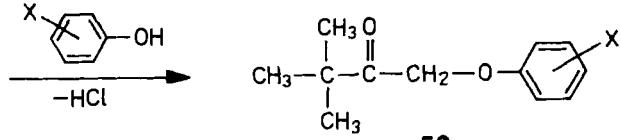
56

Triazolyl-O,N-acetals (**53**) can be synthesised by several methods (Meiser *et al.*, 1972; Krämer *et al.*, 1973). Synthesis generally starts from pinacolone (**57**), which is halogenated:



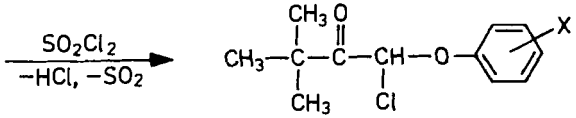
57

The next step is nucleophilic substitution with substituted phenol:

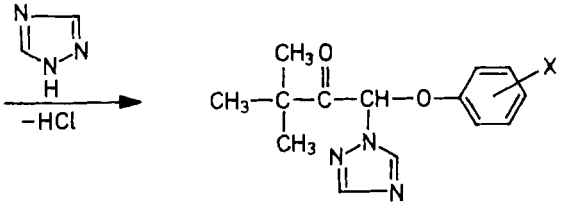


58

The phenol ether ketone formed (**58**) is halogenated:

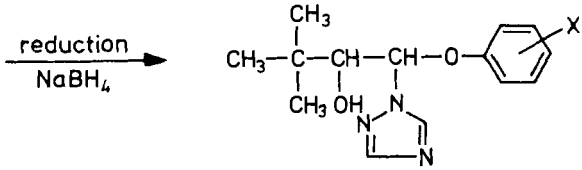


The following step is again nucleophilic substitution with 1,2,4-triazole:



53

Finally, in the case of (**53**) an alcoholic end-product, the compound is reduced with complex metal hydrides:



Diclobutrazol (**59**), (2*R*,3*R*)- and (2*S*,3*S*)-1-(2,4-dichlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)pentan-3-ol is highly active against rust, powdery mildew and other fungal pathogens of plants.

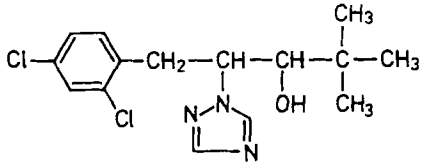
X-ray crystallography revealed that diclobutrazol has the 2*R*, 3*R* and 2*S*, 3*S* *(threo)* configuration. The corresponding 2*R*, 3*S* and 2*S*, 3*R* *(erythro)* form was found to be less active as fungicide. Spray applications on wheat and barley crops

have given excellent control of diseases of the foliage and ears, resulting in large increases in yield. Protection of barley against winterkill has been observed in some situations. Diclobutrazol sprays appear promising for the control of coffee rust, apple mildew and scab, grape powdery mildew and various other crop diseases (Baldwin and Wiggins, 1984).

Diclobutrazol has a systemic action and is translocated mainly acropetally. Its eradicative action, increased by vapour effect, is very strong (Zitzewitz and Heckele, 1979).

Diclobutrazol is of low toxicity to mammals and other animals. The acute oral and dermal LD_{50}s for rats are about 4000 mg/kg and > 1000 mg/kg, respectively. Ames and cell transformation tests gave negative results. Diclobutrazol is also of low toxicity to birds, fish and invertebrates.

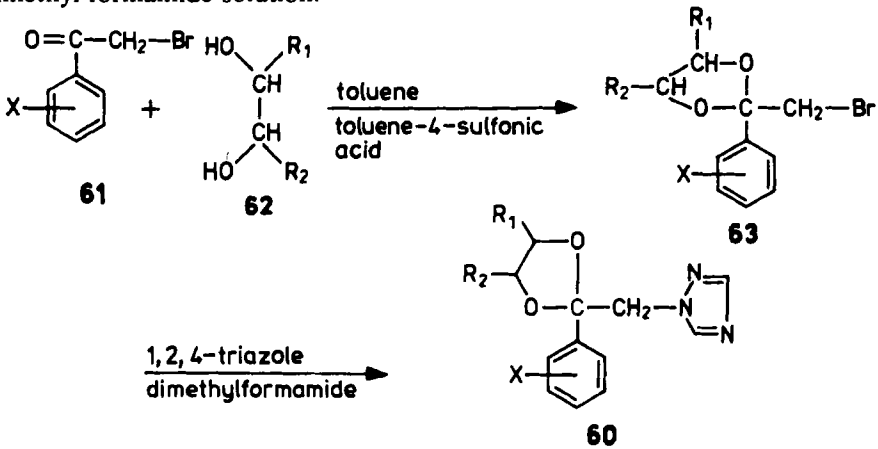
Diclobutrazol inhibited spore germination and mycelia growth of a wide range of fungi. Mode of action studies on *Ustilago maydis* indicated marked and specific interference with ergosterol biosynthesis in the fungus at the 14α-demethylation stage (Bent and Skidmore, 1979, Baldwin and Wiggins, 1984).



59

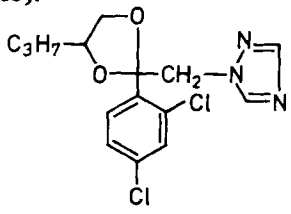
Van Gestel *et al.* (1980) prepared a series of substituted 1-(2-phenyl-1,3-dioxolan-2-yl-methyl)-1,2,4-triazoles **(60)**, and evaluated them in the greenhouse for fungicidal activity. Compounds with 2,4-dichloro substitution on the phenyl ring and with a lower alkyl side chain on the dioxolane ring were found most promising for the control of powdery mildew on gherkins and barley, and for the control of bean rust.

Substituted phenacyl bromides **(61)** were condensed with vicinal diols **(62)**, and the resulting bromoketals **(63)** were then coupled with sodium 1,2,4-triazole in dimethyl formamide solution.



61 **62** **63** **60**

Of this group two active substances have been developed: propiconazole, 1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1,2,4-triazole **(64)** and etaconazole, 1-[2-(2,4-dichlorophenyl)-4-ethyl-1,3-dioxolan-2-ylmethyl]-1,2,4-triazole **(65)**.



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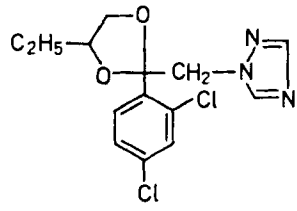

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Due to its high level and wide spectrum of activity, etaconazole is particularly suited for the control of powdery mildews and scab of deciduous fruit and *Monilia* spp. on cereals and peanut, while propiconazole shows superior activity against the foliar and ear diseases attacking cereal crops (Urech *et al.*, 1979). Both fungicides are systemic and have curative and protective properties (Speich and Urech, 1980; Elmsheuser and Flemming, 1981; Henry and Sisler, 1981).

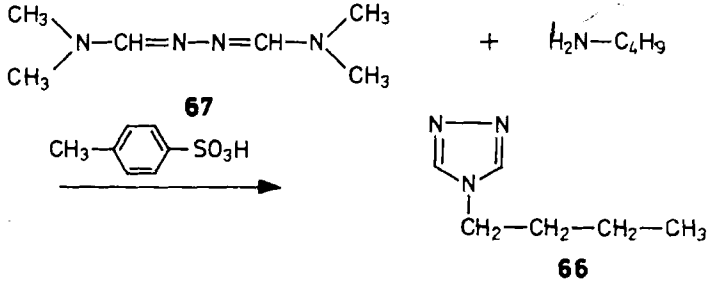
Structure–activity relationship in a group of azoles with special reference to 1,3-dioxolan-2-yl-methyl derivatives is discussed by Heeres (1984).

These products are slightly toxic to mammals, the acute oral LD_{50}s for rats being 1300–1500 mg/kg.

The compound RH-124 (triazbutil, **66**), 4-*n*-butyl-1,2,4-triazole is a systemic fungicide for the control of wheat leaf rust, which is caused by *Puccinia recondita tritici* (Meyer *et al.*, 1970). In foliar, seed and soil applications this active material was superior to benomyl, triarimol or oxycarboxin against leaf rust, though the duration of effectiveness inside the wheat plant was relatively short (Rowell, 1976).

As a foliar spray or seed dresser the compound is rapidly absorbed and translocated to younger tissues. The antifungal activity of RH-124 was exhibited by swollen, distorted hyphae in the leaves of treated plants, so that the compound caused a reduction or inhibition of metabolic activity in the developing hyphae and haustoriae (Watkins *et al.*, 1977).

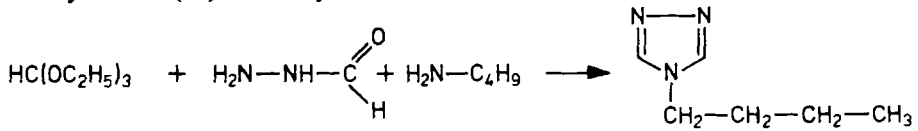
Synthesis starts with the symmetric hydrazone of dimethylformamide **(67)**, which is converted with *n*-butylamine in the presence of a small amount of toluene sulfonic acid into the end-product (Barlett and Humphrey, 1967).



67

66

According to the process of Bayer *et al.* (1969), the compound can also be obtained by the single-step reaction of orthoformic acid triethyl ester **(68)**, formic acid hydrazine **(69)** and butylamine:



68 **69** **66**

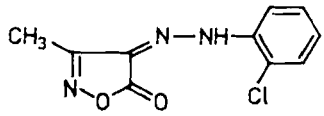
5.7.4 Oxazoles and thiazoles

Of the 1,2-oxazole compounds, the arylhydrazone-1,2-oxazole derivatives exhibit high antifungal activity (Summers *et al.*, 1968; Matolcsy *et al.*, 1969; Eckhard *et al.*, 1973).

Drazoxolon **(70)** is a fungicide effective mainly against powdery mildew also showing a certain eradicant action. It is also used as a seed dresser for the control of *Pythium and Fusarium* on peas, maize, grasses, vegetables and cotton (Geoghegan, 1967). The active compound, 4-(2-chlorophenylhydrazono)-3-methyl-5-isoxazolone, may be prepared by the coupling of *o*-chlorobenzenediazonium chloride with ethyl 3-oxybutyrate and by the reaction of the intermediate product with hydroxylamine. The compound is almost insoluble in water, but readily soluble in alkalies to form relatively stable salts. It is fairly soluble also in acidic solutions, an intramolecular hydrogen bond being formed between the C=O and NH groups. The hydrolysis products are also fungicides, but their antifungal action is weaker than that of drazoxolon (Lehtonen *et al.*, 1972).

It is rather toxic to mammals, its acute oral LD_{50} being for rats 126 mg/kg. Its vapour causes lung irritation. The 4-(3-chlorophenylhydrazono)-3-methyl-5-isoxazolone analogue, which is considerably less toxic to mammals, has therefore been synthesised. The acute oral LD_{50} of metazoxolon **(71)** for femal rats is 3340 mg/kg, its dermal toxicity is higher than 1000 mg/kg (Purnell, 1973).

The fungicidal range of action of metazoxolon is wide, but the best action is attained against soil fungi and fungi spreading with seeds, thus against *Pythium* spp., *Rhizoctonia solani* on cotton, *Phytophthora capsici, Tilletia caries* and *Fusarium nivale*. It is not systemic, so it gives less protection against *Ustilago* spp., *Fusarium* and *Verticillium* spp.



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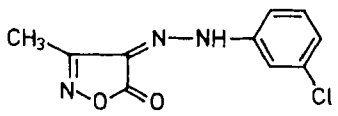
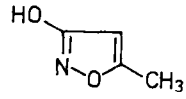


71

Of the 3-hydroxy-isoxazoles, hymexazole **(72)** has proved the most active fungicide. For an antifungal action substitution in position 5 is indispensable. The

highest activity can be attained with the methyl group; an increase in the chain length or substitution of an aryl radical reduces biological activity. Antifungal activity decreases also by methyl, halogen or nitro substitution in position 4 (Takahi, 1973a).

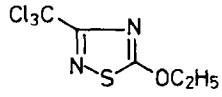


72

Hymexazole (Tomita, 1973) is effective mainly against soil fungi and fungi causing diseases spreading with the seeds, such as *Fusarium, Aphanomyces, Pythium* and *Corticium* spp. Plant roots rapidly absorb the active substance from a nutrient solution or from the soil, the substance then being translocated into the leaves. In the plant tissues hymexazole is detoxicated into two main metabolites, 3-(β-D-glucopyranosyloxy)-5-methylisoxazole and 2-(β-D-glucopyranosyl)-5methyl-4-isoxazolin-3-on, which are still fungitoxic but less toxic to mammals than hymexazole (Kamimura *et al.*, 1974; Murakoshi *et al.*, 1974). A certain growth-stimulating effect on plants has also been observed for hymexazole (Ogawa and Ota, 1973 and 1974). Hymexazole is more efficient in the soil than *in vitro*, which is attributed to the synergistic effect of iron(III) and aluminium ions present in the soil (Takahi, 1973b).

Hymexazole is virtually nontoxic to mammals and aquatic animals. Its acute oral LD_{50} for rats is ~4000 mg/kg (Okudaira, 1973). In tests with ^{14}C-labelled hymexazole it was found that the active substance is rapidly absorbed and distributed in the rat tissues, but within 96 hours 97% of the total active material is excreted in the urine and 0,89% in the feces. Two metabolites have been identified in the urine: 3-(β-D-glucopyranosyloxy)-5-methylisoxazole and 5-methyl-3-isoxazolyl sulfate (Nagakawa and Ando, 1973; Ando *et al.*, 1974). The hymexazole activity persists in the soil for a few weeks. Microorganisms participate in its degradation. The active substance is decomposed first into acetoacetic amide and 5-methyl-2-(3H)-oxazolone, to yield ammonia, acetone and carbon dioxid as end-products (Nakanishi, 1973).

Etridiazole, 5-ethoxy-3-trichloromethyl-1,2,4-thiadiazole **(73)**, is an efficient soil fungicide with systemic action.

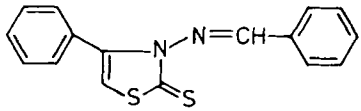


73

It is particularly effective against soil fungi, such as *Pythium* spp. and *Phytophthora* spp., so that it can be used alone or in combination with quintozene as a soil fungicide or for seed dressing (Miller and DeNeve, 1971). Its inhibiting effect is directed with high specificity against *Oomycetes* (Al-Beldawi and Sinclair, 1969).

Its acute oral LD_{50} for mice is 2000 mg/kg. It may cause a certain skin irritation. From studies on the liver microsomes it appeared that etridiazole metabolites may be causing hepatotoxicity by initiating destructive lipid peroxidation of the microsomal membranes (Dalvi and Howell, 1977). Its biological action is manifested by interference with or complete inhibition of hyphal tip growth and by inhibition of sporulation. Etridiazole affects cell membranes, respiration, fermentation and RNA synthesis, but is presumably, also has an effect on syntheses in lipid metabolism (Lyr *et al.*, 1975). Etridiazole inhibits respiration in *Pythium* spp. by blocking electron transfer between cytochromes *b* and *c* in the terminal respiratory chain (Halos and Huisman, 1976a). With increased use of the active substance mutation may occur, giving rise to etridiazole-resistant strains. Sublethal concentrations of the fungicide may also bring about the increased formation of a substance or substances which confer tolerance. Tolerance by *Pythium* spp. probably depends on increased utilization of an alternative pathway of electron transport mediated by ubiquinones (Halos and Huisman, 1976b). According to Gasztonyi (1977) the fungicidal action on the individual fungal species may be attributed to a difference in the uptake of the active substance, with the exception of *Oomycetes* spp., the extraordinary sensitivity of which may be due to a difference in the receptors.

Fentiazon (**74**), 3-benzylidenamino-4-phenyl-1,3-thiazolin-2-thion, developed in Japan (Usui and Yamano, 1969), is a folial fungicide with preventive action against the bacterial leaf blight of rice caused by *Xanthomonas oryzae*. It is not toxic to rice, but is moderately toxic to fish. Its acute oral LD_{50} is 10 000 mg/kg for rats (Anonym, 1967).



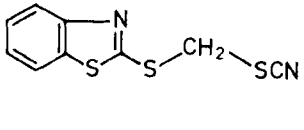
74

Several compounds among the benzothiazole derivatives have a fungicidal action, while the urea derivatives reveal an important herbicidal action.

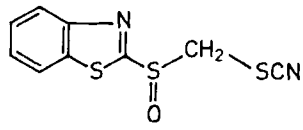
TCMTB, 2-(thiocyanomethylthio)benzothiazole (**75**) is an effective fungicide against soil fungi and for seed dressing (Voets, 1969), being toxic particularly to fungi causing cotton diseases (Pulido, 1969). In the protection of peanut against *Rhizoctonia* causing seedling and pod rot, systemic properties have been observed (Abdou and Khadr, 1974).

TCMTB is moderately toxic to mammals, its acute oral LD_{50} being 1590 mg/kg for rats. It is injurious to the eye and skin, and is toxic to fish. The active substance reduces the ammonifying capacity of the soil and inhibits urease activity in the soil (Voets abd Vandamme, 1970).

TCMTB efficiently replaces mercury-containing seed dressings, mainly on cotton (Pulido *et al.*, 1973; Pulido and Bolton, 1974).



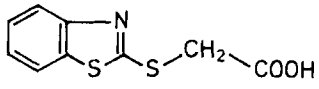
75



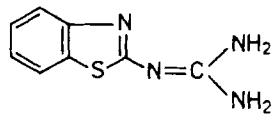
76

TCMTOB, 2-(thiocyanomethylsulfinyl)benzothiazole (**76**), the oxidised derivative of TCMTB, is also used as a seed dressing against the diseases of cereals, maize, rice, cotton, sugar beet and legumes (Hardison, 1972).

2-(Carboxymethylthio)benzothiazole (**77**), besides being a fungicide, is also a growth regulator (Dimond and Davis, 1952; Van der Kerk, 1956). It is slightly soluble in water, but its sodium salt is readily soluble in water.



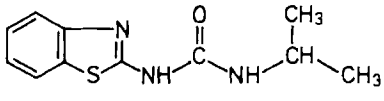
77



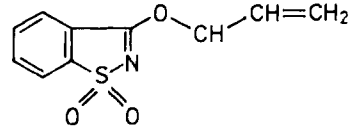
78

Its fungicidal action is moderate *in vitro*, but it has a high chemotherapeutic potency (Dimond and Davis, 1953). It should be mentioned that its parent compound, mercaptobenthiazole, is not a systemic microbiocide, and its activity is partly due to its chelate-forming properties (Horsfall, 1957). It has not become important in agriculture.

2-Benzothiazolyl guanidine (**78**) (Weiss *et al.*, 1975), 1-(benzothiazol-2-yl)-3-isopropylurea (bentaluron, **79**) (Janiak, 1968), and 3-allyloxybenzene-[α]-1,2-thiazole-1,1-thioxide (oryzemate, **80**) (Seki, 1967) are similar experimental fungicides.



79

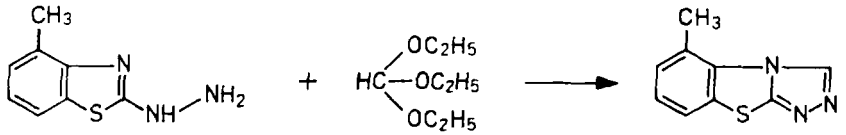


80

Tricyclazol, 5-methyl-1,2,4-triazolo[3,4-b]benzothiazole (**81**) is a fungicide against rice disease caused by *Piricularia oryzae*. Its activity is 25–35 times greater *in vivo* than *in vitro*. It is a systemic fungicide effective over a long period, whether used as a foliage spray or for the treatment of soil, its acute oral LD_{50} is 305 mg/kg for rats, and it is moderately toxic to fish. The advantages of tricyclazol are its long-lasting effect, its systemic action, and the efficiency of its application as a seed dressing or through the roots and the soil (Froyd *et al.*, 1976; Masri and Rafii, 1977). Tricyclazol's blocking of some phases of polyketide metabolism in

Piricularia oryzae may have a role in pathogenicity (Tokousbalides and Sisler, 1978 and 1979).

It is synthesised by the cyclisation of 5-methyl-2-hydrazinobenzothiazole **(82)** with orthoformic acid triethylester **(83)** (Paget, 1971).



82 **83** **81**

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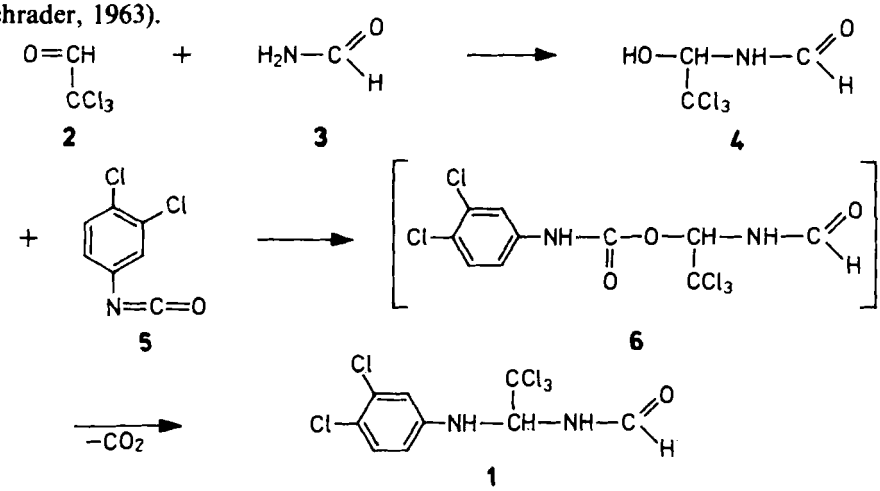
5.8 Fungicides of formamide type

The 40% aqueous solution of formaldehyde, formalin, has been known since 1888 as an excellent disinfectant in medicine. In addition to its good bactericidal properties it is also an excellent fungicide, and was introduced as early as 1895 in agricultural plant protection for seed dressing (Geuther, 1895). It is also used as a soil fumigant. Its protective effect against covered smut is superior to that of copper sulfate. It has the advantage of acting also in the vapour phase, which is very favourable in the treatment of certain diseases (powdery mildew of oat). Nevertheless, it did not gain wide in agriculture because it has no protective effect and is phytotoxic. Seed treatment with more concentrated formalin solutions or over a longer period considerably impairs the germinating power of seeds. It is an important requirement that the seed be sown at the latest 24 hours after treatment, because from the paraformaldehyde which precipitates from the solution during drying, formaldehyde is gradually split off causing an additional reduction in germinating power (Hurd, 1920). On standing at room temperature, formalin polymerises, and white paraformaldehyde powder is formed. To prevent or retard this process, it has been used together with methanol, which itself has been used for seed treatment against loose smut of barley (Ustilgon®) (Wagner, 1959).

The fungicidal action of formeldehyde is based on its reaction with the amino groups of the spore protoplasm, that is, it denatures proteins.

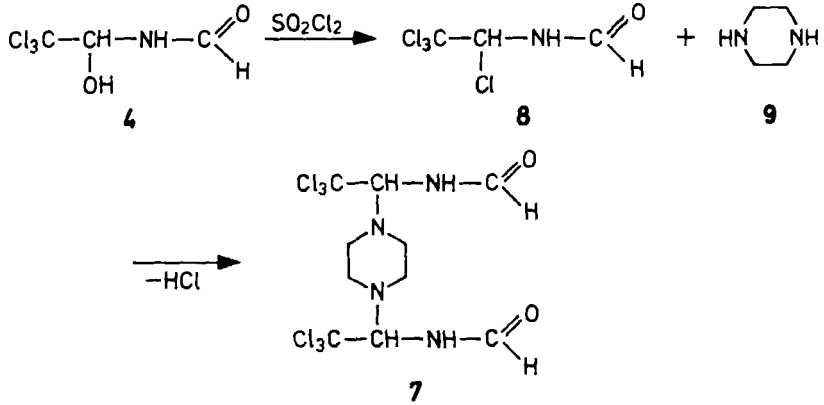
Several fungicides with contact action were also discovered among the derivatives of aldehydes; however, the agricultural use of compounds of this type began only when active substances with systemic action were found among them.

Chloraniformethan (**1**), introduced under the trade name Imugan®, is one of these important fungicides. Its chemical composition is N-[2,2,2-trichloro-1-(3,4-dichloroaniline)ethyl]formamide. Synthesis starts with chloral (**2**), which, in reaction with formamide (**3**) gives chloral-formamide [(2,2,2-trichloro-1-hydroxyethyl) formamide] (**4**). This reacts with 3,4-dichlorophenyl isocyanate (**5**) *via* the formation of the carbamic acid ester (**6**) as intermediate, to yield, after rapid carbon dioxide elminiation, the end-product (**1**) (Malz *et al.*, 1966., Dörker and Schrader, 1963).



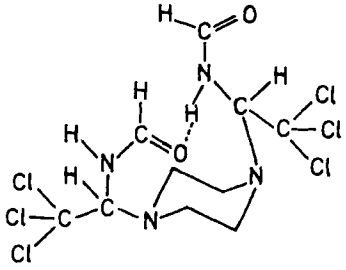
Chloraniformethan is a fungicide with systemic action effective against powdery mildew fungi and particularly to fungi pests of cereals (Davis *et al.*, 1971). It is not toxic to mammals, acute oral LD_{50} for rats being over 2500 mg/kg.

Another powerful active substance of formamide type is triforine 1,1'-piperazine-1,4-diyl-bis[N-(2,2,2-trichloroethyl)formamide] (Cela W524, **7**). By the chlorination of chloral-formamide (**4**) N-(1,2,2,2-tetrachloroethyl)formamide is formed, which forms the active substance with piperazine (**9**) (Ost *et al.*, 1967).

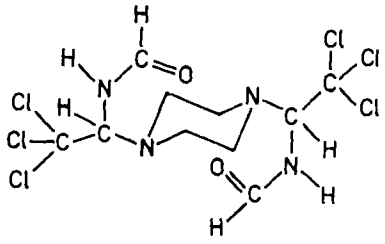


Triforine is rapidly decomposed to chloral or chloral hydrate and piperazine by concentrated sulfuric acid and concentrated hydrochloric acid. With alkalies the decomposition is slower, but it proceeds also in neutral aqueous solution (Josepovits and Gasztonyi, 1976; Darda *et al.*, 1977). Its acute LD_{50} is 6000 mg/kg for rats, thus, it is practically nontoxic. It is not toxic to fish or bees. From the point of view of environmental protection, it is a very promising fungicide (Darda, 1977). Depending on the type of soil, the active substance remains in the top layer (0–10 cm) of the soil, from where it is not leached, so it does not contaminate the ground water. Its degradation in the soil is relatively rapid. Within three weeks of its application half of the active substance is decomposed. The microbiological equilibrium of the soil is not affected by the application of the fungicide, because triforine does not inhibit the nitrification process of the soil and does not depress the vital functions of soil bacteria, *Streptomycetes* or soil fungi (Drandarevski *et al.*, 1975; Drandarevski and Eichler, 1977).

The active substance is absorbed through the roots and is rapidly translocated into the parts of the plant above soil level, where it accumulates in the leaves (Fuchs and Ost, 1974; Fuchs *et al.*, 1976a, 1976b). The relatively small amount of triforine remaining in the roots explains why the active substance does not protect against diseases of the root and stem (Drandarevski and Fuchs, 1973). Its translocation is stimulated by light, and the movement of the active substance in the plant proceeds only at a certain level of photosynthetic activity. Drandarevski and Fuchs (1973) found that triforine is decomposed in the plant and that the half-life depends on the species of the plant. In potato, the half-life is less than 10 days, while in barley, bean and pea it is between 30 and 40 days. The explanation given by Gasztonyi and Josepovits (1976) for the different persistence of triforine in plants is that, depending on the species, triforine forms conjugates with natural components of the plant which change the physical and chemical properties of the active substance. The powerful systemic fungicidal effect of triforine on powdery mildew fungi of wheat can partly be attributed to the higher water solubility and chemical stability of these conjugates, increasing the absorption and translocation rates of triforine and its persistence in the plant. In the plant, triforine is metabolised into several nonphytotoxic compounds. The final residue is presumably piperazine (Fuchs *et al.*, 1972; Rouchaud *et al.*, 1977; 1978a, 1978c; Darda *et al.*, 1977), though recent investigations show that piperazine is certainly not the end-product of the metabolism of triforine in barley (Rouchaud *et al.*, 1978b). Triforine is also rapidly degraded by sunlight; thus, inactivation on the leaves of the plants is considerably more rapid than in the plant tissues (Ost *et al.*, 1971; Buchenauer, 1975). Josepovits and Gasztonyi (1976) found that the water solubility, and because of this the fungitoxicity, of technical triforine is greater than that of the compound of analytical purity. They attributed this phenomenon to the presence of at least two stereoisomers **(10a,b)**, of which the isomer **(10a)** contains an intramolecular hydrogen bond, increasing the polarity and thereby the water solubility of the molecule. The compound of analytical purity is the **(10b)** isomer, from which the isomer of higher solubility has presumably been removed during purification.



10a



10b

The mode of action of triforine, which is similar to that of triarimol (Sherald *et al.*, 1973), has been elucidated by Sherald and Sisler (1975). In the rapidly growing mycelia of *Aspergillus fumigatus*, 10 μg/ml of triforine scarcely inhibited the growth of dry matter within 2 hours. However, between 2.5 and 3 hours, the growth of dry matter was reduced by 85%. Triforine inhibits ergosterol synthesis almost completely. Because of this, the precursors of ergosterol are enriched in the hyphae. Fungitoxicity most likely results from a termination of membrane development due to the lack of ergosterol, but the possibility of inhibition of hormone biosynthesis from sterol is not excluded.

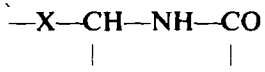
Triforine is particularly effective against powdery mildew fungi on cereals, apple, berries and ornamental plants, but is also gives good protection against apple scab, *Monilia fructicola* and several rust fungi *(Puccinia recondita)* (Fuchs *et al.*, 1971a, 1971b; Schicke *et al.*, 1971; Koestlin, 1972; Ebenebe, 1973). It is used for seed treatment against rust of cereals and powdery mildew diseases (Schicke and Veen, 1969; Rohrbach, 1977). The sensitivity to triforine of various fungi differs considerably (Fuchs and Drandarevski, 1973). Gasztonyi and Josepovits (1975) found in their investigation of seven fungus species a positive correlation between the sensitivity of the fungi to triforine and the quantity of unmetabolised triforine in the mycelia or the spores. In several fungi resistant to triforine, resistance was based on the non-absorption of the active substance, while in other resistant fungi the fungicide was metabolised into inactive compounds very rapidly. This may be the cause of the selectivity of the active substance to the various fungus species (Casperson, 1979).

The structure-activity relationship of compounds of formamide type has been studied by Carter *et al.* (1972 and 1973). This study shows that the 3,4-dichloroaniline group of chloraniformethan and the piperazinyl group of triforine can be exchanged for certain other groups without reducing the effect of the new compound on powdery mildew of cereals. However when the formyl group is replaced by another acyl group, the fungitoxicity of the molecule decreases. It was therefore hypothesised that

$$CCl_3—CH—NH—CHO$$

is the toxophor group in the molecule of the two active substances.

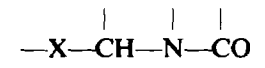
Brown and Woodcock (1975a) synthesised about 70 compounds and investigated their activity on the powdery mildew fungi of barley *(Erysiphe graminis)*. They changed in the molecules the trichloromethyl, the formamido, the 3,4-dichloroaniline and the piperazinyl groups, and continued to develop the hypothesis of Carter *et al.*, (1972 and 1973). They concluded from the inactivity of the compound CCl_3CH_2NHCHO that a substituent attached through a heteroatom to the CH group is essential to the biological activity. Moreover, the trichloromethyl group does not play any specific role because the activity of the molecule was generally preserved by substituting this group for another halogen-containing group. According to these authors, the biologically active centre of the molecule is the



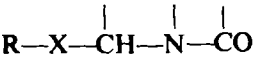
group, in which X is substituted by N, O or S, which are found in each active molecule.

On the other hand, the other parts of the molecule may influence the transfer to the site of action, and steric effects should probably also be considered (Brown and Woodcock, 1975b). Thus, on replacing the trichloromethyl group with tribromo- or dichloromethyl groups, or the formyl group with another keto group, all of the systemic properties of the compound cease. Only the acetyl derivatives of chloraniformethan showed a weak translaminar activity to barley. Substitution of the 3,4-dichloroaniline and piperazino groups gave compounds which showed acropetal translocation, the degree of which increased with the hydrophilicity of the molecule.

For the quantitative characterisation of the structure-activity relationship of formamide-type fungicides, Brown and Woodcock (1975c) also used the method of Hansch and Fujita (1964), which assumes that the concentration of externally applied fungicides at the site of the receptor depends on the hydrophylic–hydrophobic distribution properties of the compound, and that the reaction of the fungicide with the receptor depends primarily on the electron structure of the molecule. They established that in root treatment of barley against powdery mildew the activity of the compound depended on distribution characteristics alone, while in foliage spray tests it was also influenced by the electron structure of the aromatic derivative. Through these recent investigations on triforine and its derivatives, the biologically active centre has been shown to be the



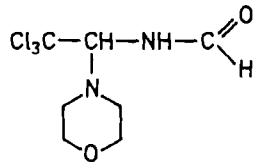
group (X—heteroatom), while that of chloraniformethan and its aryl homologues is the



group where RX is a conjugated system, capable of accepting π-electrons from an electron-donor receptor.

The fungitoxic and systemic properties of other alkoxy, alkylamino and alkylthio trichloroethylformamide (Carter *et al.*, 1975a) and bis[(1-formamido-2,2,2-trichloro)ethylamino]alkane (Carter *et al.*, 1975b) derivatives have also been investigated (Loeffler *et al.*, 1981).

Demečko and Jaras (1977) substituted the formamido radical on the morpholine ring. The synthesis of this N-(1-formamido-2,2,2-trichloroethyl)morpholine, trimorphamide (**11**) proceeds with a good yield by the reaction of N-(1,2,2,2-tetrachloroethyl)formamide with morpholine in the presence of a hydrochloric acid acceptor. The compound is a white crystalline product with a melting point of 116°C. It is readily soluble in organic solvents. The compound is a protective and eradicant fungicide against *Erysiphales* (Demečko and Fandlová, 1977; Hudecová *et al.*, 1978; Vargová, 1981).



11

Trimorphamide is more efficient in emulsifiable form than in the wettable powder form. It is effective against *P. leucotricha* in apple orchards, against *U. necator* of vine and *E. cichoracearum* of tobacco (Gahér and Hudecová, 1978; Swiech, 1981).

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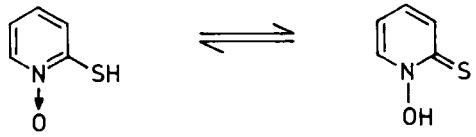
5.9 Various heterocyclic fungicides

5.9.1 Pyridine derivatives

The pyridine group comprises a few compounds, which, due to their mobile halogen atoms, may react with the fungal enzymes containing a mercapto group. Some of these compounds remain experimental, others are used as soil fungicides, but none can be used as foliage fungicides because of their skin irritating effect.

Pyridine-2-thiol-1-oxide (2-mercaptopyridine-N-oxide, **1**), is a fungicide with a

moderate systemic action which has also a bactericidal effect (Szkolnik and Hamilton, 1957; Rombouts and Kaars Sijpesteijn, 1958). An equilibrium exists between its thiol and thion forms. It forms stable chelates with metals, but its metal compounds are not translocated. It can be prepared from 2-bromopyridine-N-oxide with sodium hydrosulfide or with thiourea (Shaw *et al.*, 1950). It is effective against *Fusicladium* in orchards, leaf injury of peach and other fungal diseases. Its application is limited by the fact that in certain cases it also inhibits the development of the plant (Norman, 1957; Kaars Sijpesteijn *et al.*, 1958; Dekker *et al.*, 1958; Ristich and Cohen, 1961).



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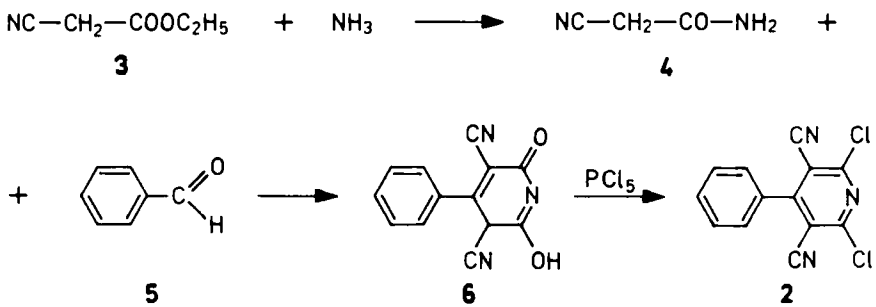
Pyridinitrile, 2,6-dichloro-4-phenylpyridine-3,5-dicarbonitrile (**2**) is a fungicide with a wide range of action against *Venturia inaequalis*, *Aspergillus* spp., *Cladosporium fulvum*, *Botrytis cinerea*, *Plasmopara viticola* and *Phytophthora infestans*. It has a particularly significant effect against *Peronospora* fungi. It is a protective fungicide and is not phytotoxic even at many times the recommended dose. It is not toxic to mammals, the acute oral LD_{50} being 5000 mg/kg for rats. The active substance is rapidly metabolised, and a residue has been found only at the surface of the fruit (Mohr *et al.*, 1968). The product is practically insoluble in water.

Pyridinitrile is prepared by the reaction of cyanoacetic acid ethyl ester (**3**) with ammonia, followed by the coupling of two molecules of the cyanoacetic amide (**4**) formed with benzaldehyde (**5**) and by the chlorination of the product, 3,5-dicyano-4-phenyl-6-hydroxyhydro-2-pyridone (**6**) (Mohr *et al.*, 1963). Pyridinitrile is practically insoluble in water.



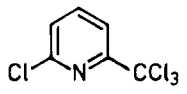
3 **4** **5** **6** **2**

Nitrapyrin (**7**), 2-chloro-6-trichloromethylpyridine, is actually a nitrification inhibitor, slowing down the conversion of ammonium-nitrogen into nitrate. It has a selective bactericidal effect against *Nitrosomonas* spp. (Goring, 1962). However, it has been observed that nitrapyrin reduces the stem rot of maize and cereals. In

particular, infection by *Fusarium moniliforme*, which causes great damage in silty clay loam soils, can be reduced by treatment with nitrapyrin. It is known that stem rot can be reduced with larger quantities of potassium chloride, because the chloride ion inhibits the uptake of nitrate-nitrogen by the plants.

The reduction of stem rot by nitrapyrin may be similar (Anonym, 1975). Nitrapyrin reduces to a greater extent the oxalic acid and nitrate-nitrogen content of plants than inhibitors hitherto known (dicyanodiamine, thiourea, *o*-nitroaniline) (Jurkowska, 1974).

The acute oral LD_{50} of nitrapyrin is 1072 mg/kg for rats. It is converted in the soil into 6-chloropicolinic acid, and it is essentially this that is taken up by the plants (Redemann *et al.*, 1964). In the USA it has been introduced under the trade name N-Serve® for the treatment of maize, cotton and wheat.



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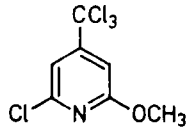

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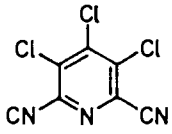
According to Riley and Barber (1970), nitrapyrin and its main metabolite, 6-chloropicolinic acid, are phytotoxic. They cause morphological changes, particularly in young plants, and may reduce yield if their quantity in the soil is $\geqslant$ 50 mg/kg (Mills *et al.*, 1973). Graminae show a higher tolerance to them than dicotyledons, with the exception of rice. Tomato tolerates these substances well even at concentrations as high as 100 mg/kg (Geronimo *et al.*, 1973).

The active substance pyroxychlor 2-chloro-6-methoxy-4-trichloromethylpyridine **(8)**, (Johnston and Tomita, 1964), is particularly active against *Phytophthora* fungus species, but it is also effective against certain *Pythium* spp. *(P. sylvaticum, P. irregulare)* (Richardson, 1976). One of the greatest merits of pyroxychlor it its excellent effect in the protection of tobacco against black shank caused by *Phytophthora parasitica* when applied in transplant water of as a foliage spray (Noeroske, 1975).

The water solubility of pyroxychlor is low (11 μg/ml), and it is a moderately volatile compound. It is rapidly absorbed by the plant, presumably due to its high lipophilicity. It has a systemic and curative effect. It is also translocated basipetally in the plant, so that when sprayed on the foliage it gets into the roots and to the site of infection, (Knauss, 1974). It is scarcely effective *in vitro*, but it provides protection of long duration to the tobacco plant. This is probably due to a bioaccumulation of the active substance in the root system, where the parent compound or its metabolites are persistent. Pyroxychlor is prepared by the chlorination of fused 4-methylpyridine hydrochloride, followed by the reaction of the compound formed with sodium methylate.

The compound Dowco 263, 3,4,5-trichloro-2,6-dicyanopyridine **(9)** was found to be efficient for seed treatment against soil fungi in cereals and cotton (Noeroske and Tobol, 1968). Its acute oral LD_{50} is 562 mg/kg for rats.



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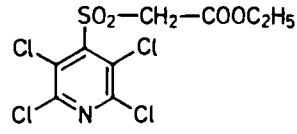

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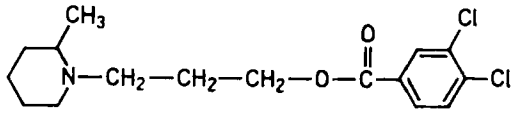
The fungicidal action of 4-pyridine-2,3,5,6-tetrachlorosulfonylacetic acid ethylester **(10)**, used for seed treatment, is similar to that of TMTD (Kuprina *et al.*, 1973).

Pyperalin **(11)**, 3-(2-methylpiperidino)propyl-3,4-dichlorobenzoate, is a protective and eradicant foliage fungicide. It is not toxic to mammals, the oral LD_{50} for rats being 2500 mg/kg. It is a specific fungicide for ornamental plants against powdery mildew fungi. Its agricultural application is of minor importance (Thomson, 1975).



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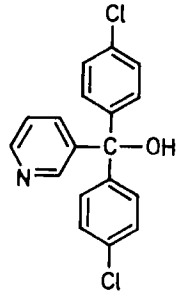
Parinol 3-[hydroxy-bis(4-chlorophenyl)methyl]pyridine **(12)**, is similarly effective against the powdery mildew fungi of ornamental plants. It is a protective



12

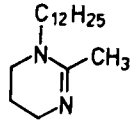
fungicide, persistent on leaves and resistant to rain (Brown *et al.*, 1967; Thayer *et al.*, 1967). It is not tolerated by certain plants (apple and pear trees). The oral LD_{50} is 5000 mg/kg for rats. It caused the stimulation of hepatic microsomal drug-metabolising enzymes in rats (Hoffman *et al.*, 1968 and 1971).

5.9.2 Pyrimidine derivatives

Pyrimidine bases containing a pyrimidine nucleus are important components of the living organism (nucleic acids, vitamins, etc.). This explains why many compounds with pyrimidine nuclei are biologically active, and, particularly in

recent years, have been used as ingredients of well-known drugs and as important pesticides (fungicides and herbicides).

Rader *et al.* (1952) first found active protective fungicides among the tetrahydropyrimidine derivatives; later Nickell *et al.* (1961) also observed a systemic effect in some of the 2-*n*-alkylmercapto-1,4,5,6-tetrahydropyrimidine derivatives used to combat rust. 1-*n*-Dodecyl-2-methyl-1,4,5,6-tetrahydropyrimidine (**13**) has also been applied in practice. It has proved efficient in orchards when used for the control of the disease caused by *Erwinia amylovora* which results in shoot withering and crown gall.



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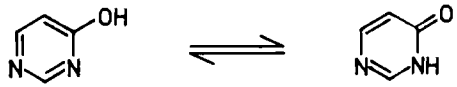
However, of the pyrimidine derivatives, the hydroxypyrimidines proved to be the most active. This important group of active substances has been developed by research workers at the ICI Plant Protection Division Jealott's Hill Research Station. Some of these active substances are widely used and are a valuable contribution to the group of systemic fungicides.

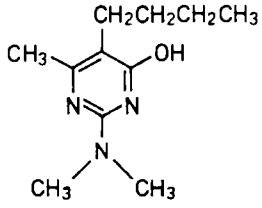
Hydroxypyrimidine and its derivatives exist in tautomeric equilibrium:



Woodcock (1972) summarised the relationships between hydroxypyrimidine derivatives and their biological activity. He established (*1*) that the greatest efficiency is attained by the alkylamino group in position 2, (*2*) the alkyl group influences the biological spectrum, (*3*) substituents in position 5 alter the lipophilic properties of the molecule, (*4*) normal carbon chains containing 2–5 carbon atoms are the most efficient, and finally (*5*) that position 6 is the most advantageous for a methyl or ethyl group. The two most potent active substances of the group are dimethirimol and ethirimol, which differ from each other only with respect to the alkylamino group in position 2.

Dimethirimol 5-*n*-butyl-2-dimethylamino-4-hydroxy-5-methylpyrimidine (**14**), (Elias *et al.*, 1968) is a white crystalline compound. It is stable when heated and in acidic and alkaline solutions. Its solubility in water is 0.12 g/100 at 25°C. It is a weak base, forming stable salts with strong acids which are readily soluble in acidic aqueous solutions.

Ethirimol 5-*n*-butyl-2-ethylamino-4-hydroxy-6-methylpyrimidine (**15**), (Snell, 1968; Bebbington *et al.*, 1969) is a white, crystalline substance, stable when heated and in acidic and alkaline solutions.



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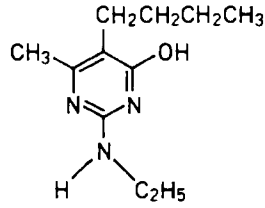

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Both active substances are toxic to powdery mildew fungi, acting specifically against this parasite (Bent, 1970). The fungicidal action of dimethirimol is particularly potent against the powdery mildew of cucurbits, mainly those of cucumber and melon *(Sphaerotheca fuliginea)*, while ethirimol is effective against powdery mildew of cereals, particularly barley *(Erysiphe graminis hordei)*. They are only slightly effective against the powdery mildew of other plants (tobacco, peas, hops) and not at all against other fungus species and vines and roses.

The specificity of ethirimol towards mildews may be related to the presence in mildews of an unusual form of the enzyme adenosine deaminase, which is absent from other organisms. Differences in either the amount of this enzyme present or its sensitivity to ethirimol may explain why fungicide activity differs between mildew species (Hollomon, 1979b, Hollomon and Chamberlain, 1981).

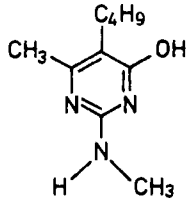
The active substances directly inhibit the germination of spores, the formation of haustoria and the growth of hyphae. Hydroxypyrimidines are translocated in the xylem; thus, being absorbed through the roots, they reach every part of the plant, with the greatest concentration the margins of the leaves. In woody plants the extent of translocation is limited (Sampson, 1969). The two compounds are also absorbed when applied to foliage, but they do not penetrate the phloem; they then move from the site of contact only towards the tips of the leaves or from one surface of a leaf to the other. Therefore, the active substances provide the greatest protection when applied to the root zone, while the foliage spray has a contact or loco-systemic effect, and gives suitable protection only when application is repeated at appropriate intervals.

Studies of the photochemistry of these compounds were carried out by Wells *et al.* (1979) and Cavell (1979).

The active substances are relatively stable in the soil and are generally loosely bound to the soil colloids. The strength of adsorption depends on the pH, exchange capacity and organic matter content of the soil. In acid soils and those with high organic matter content, adsorption is strong, and this hinders the movement of the active substances in the soil. With such soils, it is recommended that the preparation be applied near to the absorbing roots.

The chemicals are not leached immediately from the soil surface into the soil, and must therefore be worked into the soil after their application. The active substance absorbed on the soil particles is slowly released, so that the soil acts as a reservoir from which the roots of the plant slowly and continuously absorb the active substance (Cavell *et al.*, 1971).

Hydroxypyrimidines do not accumulate in large concentrations in the plant tissues, but are immediately metabolised after absorption through the roots. Therefore, to ensure long-term protection the active substances must be continuously absorbed from the soil. The metabolism of the active substances in the plant has been studied with radioactive dimethirimol-2-^{14}C in cucumbers and in barley treated with radioactive ethirimol-2-^{14}C (Slade *et al.*, 1972; Calderbank, 1971). The half-life of degradation of dimethirimol in cucumbers is about 24 hours. The first N-demethylation proceeds very rapidly, forming the N-monomethyl derivative **(16)**, which still has a fungicidal effect. The loss of the second methyl group occurs more slowly to give to inactive 2-amino derivative **(17)**.



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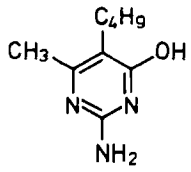
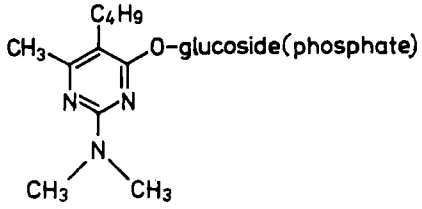


17

The half-life of ethirimol in plants is longer about 3–4 days. The first step in decomposition is the N-deethylation of ethirimol and the formation of the inactive 2-amino derivative. In addition, both active substances are converted into water-soluble metabolites, some of which are also fungitoxic. It has been established that these metabolites are conjugates with glucosides or phosphates **(18)**. Small quantities of hydroxybutyl derivatives **(19)** have also been detected.



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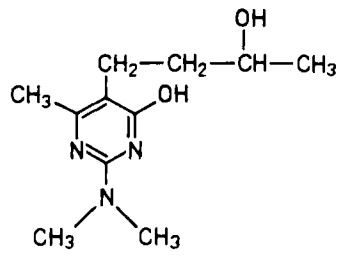
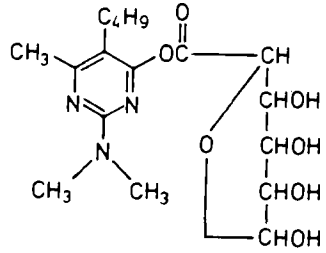


19

The metabolism of the active substances has also been studied in rats. Eighty per cent of the dimethirimol-2-^{14}C fed to the rats was excreted in the urine within 48 hours. The metabolites were isolated from the urine and identified. Metabolism proceeds principally in two ways: the progressive desalkylation of the dimethylamino group; and the oxidation of the *n*-butyl group at the carbon adjacent to the terminal carbon of the chain. In addition to these metabolites, dimethirimol-O-glucuronid **(20)** has been identified in the gall. Similarly, for ethirimol, N-deethylation, hydroxylation of the butyl group and formation of ethirimol-O-glucuronide have been found.



20

The residues of the active substances have been investigated with ^{14}C-labelled active substance. In barley grains a total of 0.05 mg/kg of metabolites originating from ethirimol was detected at harvest, but the ethirimol content was only about 0.002 mg/kg. In barley plant 0.12 mg/kg of metabolites (0.006 mg/kg ethirimol) was found. The residual value of dimethirimol was less than 0.2 mg/kg.

Dimethirimol and ethirimol are effective fungicides at concentrations in the plant of approximately 10^{-7} M. At the sublethal level concentration in the fungi is probably half that in the plant. Hence, it is assumed that these active substances act as noncompetitive enzyme inhibitors (Bent, 1970; Sampson, 1969; Calderbank, 1971). They may act as antagonists in the biosynthesis of purines, thymidine and amino acids. The fungicides may interfere with adenine metabolism at some site subsequent to its synthesis (Hollomon, 1979a).

The decomposition of active substances of the hydroxypyrimidine type in the soil has been investigated by Hill and Arnold (1973). Dimethirimol and ethirimol decompose in the soil in a shorter or longer time, depending on soil conditions. The half-life of ethirimol in nonsterile soils is 1–20 weeks. Decomposition occurs chemically and biologically, and cleavage of the pyrimidine ring was most probably caused by biological action. Microorganisms isolated from the soil and grown on a synthetic nutrient medium at 24°C decomposed 50% of the dimethirimol fed to them at a rate of 10 mg/100 ml in 7 days.

Hydroxypyrimidine derivatives are not harmful from the standpoint of environmental protection. Their toxicity to warm-blooded organisms is low, the acute oral LD_{50} of both compounds for rats being 4000 mg/kg.

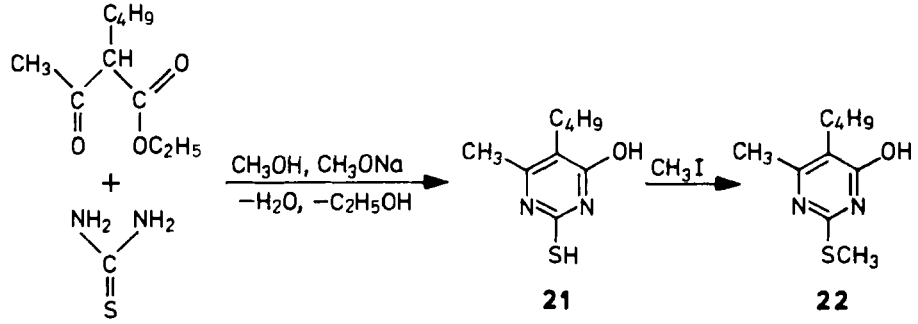
They do not irritate the skin. In 90-day feeding experiments, a dimethirimol level of at least 1000 mg/kg in the diet caused no ill effects in rats or dogs. A dosage of 200 mg/kg of the active substance of ethirimol in rats, and 1500 mg/kg in dogs also had no effect. In the concentrations used, the compounds are not toxic to bees the peroral LD_{50} of which is higher than 10 000 mg/kg or to birds. Another advantage of these compounds is that they do not affect the natural predator of the red spider mite, *Phytoseiulus riegeli*.

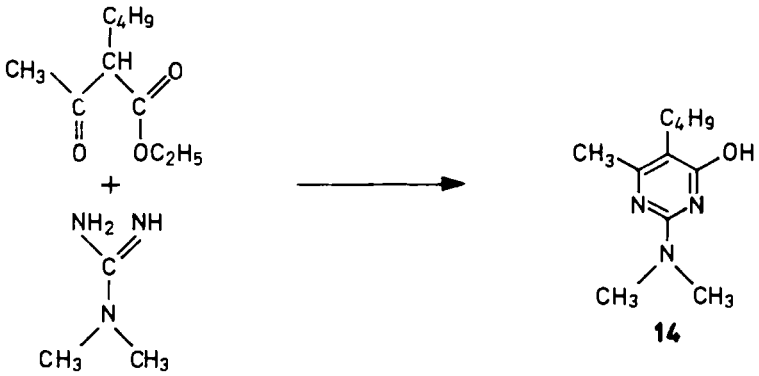
No noticeable effects of these compounds were observed on the microorganisms and microfauna of soil, even after 18 months. For brown trout fingerlings the mean toxic levels were 45 mg/kg for 24 hours exposure, 29 mg/kg for 48 hours and 20 mg/kg for 96 hours. The compounds are not phytotoxic.

After 2–3 years of dimethirimol application, resistant powdery mildew fungi strains were observed (Bent *et al.*, 1971). Investigations seeking to identify the cause and mechanism of the development of resistance are in progress (Hollomon, 1979b).

Pyrimidine derivatives can be prepared in two ways. The first is the condensation of ethyl α-*n*-butylacetoacetate with thiourea in methanol in the presence of sodium methylate, and the reaction of the intermediate product **(21)** with methyl iodide. The compound 5-*n*-butyl-2-methylthio-4-hydroxy-6-methylpyrimidine **(22)** is formed, the reaction of which with dimethylamine acetate gives dimethirimol, and with ethylamine acetate, ethirimol, with a yield of 80%.

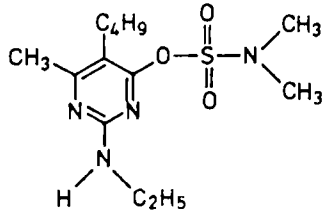
In the second method, dimethirimol can be prepared in a single step with a yield of 50% by condensation of ethyl α-*n*-butylacetoacetate with N,N-dimethylguanidine sulfate in a methanol-containing medium, in the presence of sodium methoxide (Elias *et al.*, 1968; Calderbank, 1971).





The most recent member of the family of hydroxypyrimidines is bupirimate **(23)**, 5-*n*-butyl-2-ethylamino-6-methylpyrimidine-4-yl-dimethylsulfamate (Finney, 1975; Finney *et al.*, 1975).

Bupirimate is a pale brown, waxy solid. It decomposes on heating and is unstable in long-term storage at temperatures above 37°C. At room temperature its solubility in water is 22 mg/kg.



23

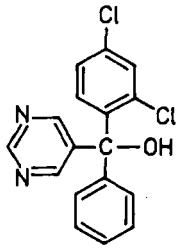
This active substance is also specifically effective only against powdery mildews, but its range of action is much wider than that of the other known members of the hydroxypyrimidine group. It is most effective against apple powdery mildew *(Podosphera leucotricha)*, cucurbit *(Erysiphe cichoracearum)* and rose *(Sphaerotheca pannosa)* powdery mildews.

Bupirimate is a foliage fungicide. Its action as a root fungicide is unsatisfactory, because it is not absorbed from the soil by the roots. As a foliage fungicide it has a protective and eradicant action. It is absorbed when sprayed on the foliage, but does not translocate in the phloem, moving only towards the leaf margins, where it concentrates. It is also absorbed to a certain extent through the green stem of the plant, so that it reaches the new or the nonsprayed leaves. The half-life of decomposition on the leaves of apple trees is about 5 days. Thus, its period of fungicidal activity is greater than that of other powdery mildew fungicides, for example, dinocap, and provides efficient protection even at spraying intervals of 10–14 days. It is nontoxic, its peroral LD_{50} being about 4000 mg/kg for rats. In its decomposition mechanism in plants and animals and in other properties it is similar to ethirimol, the first metabolite of bupirimate being 5-*n*-butyl-2-ethylamino-4-hydroxy-6-methylpyrimidine, that is, ethirimol.

The biological investigation of the substituted derivatives of pyrimidin-5-yl-methanol resulted in systemic fungicides of novel type with a wide range of action (Davenport *et al.*, 1967; Brown *et al.*, 1970; Brown and Hall, 1971).

The first of the series is triarimol **(24)**, 2,4-dichloro-α-(pyrimidin-5-yl)benzhydryl-alcohol, which will not be released as a commercial fungicide (Gramlich *et al.*, 1969). Triarimol is particularly effective against barley and apple powdery mildew, cherry leaf spot and blight of cereals (Rea and Brown, 1971; Thayer *et al.*, 1972). It has a greater fungicidal efficiency against apple powdery mildew than dinocap or benomyl (Bryant and Hitchman, 1971). It is a loco-systemic foliage fungicide with some curative action. It is absorbed through the root and is acropetally translocated, but most of it is lost during translocation through bonding to proteins (Wallenstein *et al.*, 1976). According to Ragsdale and Sisler (1972, 1973), triarimol affects steroid synthesis in *Ustilago maydis* spp. Triarimol protects plants from the injurious effects of atmospheric ozone contamination (Seem *et al.*, 1972).

Recent additions to the series are nuarimol, 2-chloro-4′-fluoro-α-(pyrimidin-5-yl)-benzhydryl alcohol **(25)** (Casanova *et al.*, 1977) and fenarimol, 2,4′-dichloro-α-(pyrimidin-5-yl)benzhydryl alcohol **(26)** (Brown *et al.*, 1975, Buendia *et al.*, 1979).



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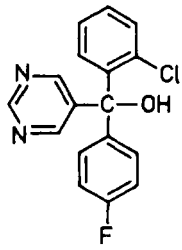

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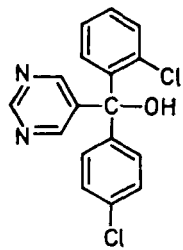


26

Both are colourless crystalline compounds rapidly decomposed by sunlight into much smaller degradation products.

Nuarimol has a systemic action and protects against several phytopathogenous fungi. As a foliage fungicide it is particularly effective against barley powdery mildew, and as a seed dressing it protects wheat and barley against powdery mildew, *Fusarium* and *Ustilago* fungi (Casavona *et al.*, 1977).

Even at small concentrations fenarimol has a protective, curative and eradicant effect against powdery mildew fungi of apple trees, vine, *Cucurbitae* and roses. It gives also efficient protection against *Typhula incarnata* fungi causing snow mould in winter barley (Ebenebe and Fehrmann, 1976).

Results from acute and subacute toxicological studies indicate that these fungicides have a low order of toxicity. The oral acute LD_{50} is 1500–2500 mg/kg for rats.

These compounds can be prepared by the condensation of pyrimidin-5-yl lithium and the respective substituted benzophenon (Davenport, 1967).

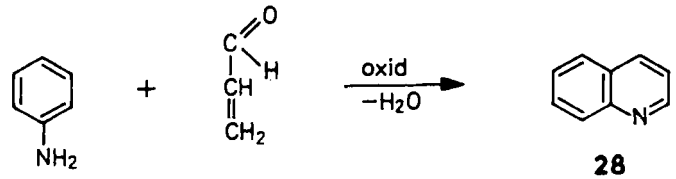
Fenarimol and nuarimol seriously inhibited ergosterol biosynthesis in sporidia of *U. avenae* (Buchenauer, 1977; Döhler and Lempke, 1979). Fenarimol interfers at several synthesis sites, resulting in incomplete membrane structure and thus disturbed membrane function. Fenarimol is thus a multisite inhibitor, so that the development of resistance is not expected from present information. Pyrimidin-5-yl methanols, as a group, are of interest not only because of their antifungal activity, but also because of their growth regulatory activity in higher plants (Sisler *et al.*, 1984).

5.9.3 Quinoline derivatives

A quinoline derivative, 8-hydroxyquinoline (**27**) was the first fungicide with systemic properties, but it did not find a wide application. It is a white crystalline substance, slightly soluble in water but readily soluble in alkalies and acids, with the formation of salts. It is of medium toxicity, its acute oral LD_{50} being 1000 mg/kg for rats.

The preparation of 8-hydroxyquinoline has long been known. The basis of the preparation is Skraup's synthesis, which essentially involves the reaction of primary aromatic amines with unsaturated carbonyl compounds and the oxidation of the

cyclic compound formed into quinoline derivatives. Thus, quinoline (**28**) can be obtained from aniline and acrolein according to the following reaction scheme:



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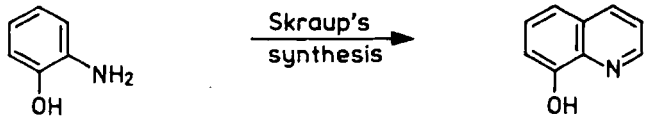
With fuming sulfuric acid quinoline gives quinoline-8-sulfonic acid, from which 8-hydoxyquinoline can be prepared by decomposition with sodium hydroxide (Magidson and Rubtzov, 1935). 8-Hydroxyquinoline can be obtained in a single step from *o*-aminophenol by Skraup's synthesis (Das and Mukherjee, 1951; Kanevskaya and Melenteva, 1953).



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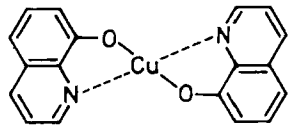
The sulfuric acid salt of 8-hydroxyquinoline, a fungicide known by the trivial name Chinosol® (Fron, 1936), has been used sporadically since the beginning of the 1940s against certain seedling diseases and wilting diseases. The active substance is used even today as a steeping agent for the protection of vine cuttings against *Botrytis*.

The fungicidal action of 8-hydroxyquinoline was initially attributed to its strong chelating ability and to the formation of 1 : 1 and 1 : 2 complexes with heavy metal ions present in fungal organisms in a manner similar to that of the active substances of dithiocarbamate type (Zentmeyer, 1943). Since then the mode of action of 8-hydroxyquinoline has been investigated by several workers (Albert *et al.*, 1947; Rubbo *et al.*, 1950), who have established that of the hydroxyquinolines only 8-hydroxyquinoline has fungicidal properties. The fact that several chelate-forming organic compounds have no fungicidal action promoted the researchers to develop another hypothesis.

Powell (1946) and Mason (1948) found that the 2 : 1 complex of 8-hydroxyquinoline with copper, oxine-copper, has a stronger fungicidal action than 8-hydroxyquinoline. Albert *et al.* (1953) attributed this to the fact that the organic part of the compound makes copper lipoid-soluble and thus accelerates its penetration into the cell. Inside the cell the 2 : 1 complex dissociates into a 1 : 1 complex and free 8-hydroxyquinoline. The active toxic agent is the ionised 1 : 1 complex of nonlipoid properties, which reacts with the enzymes in the fungus and blocks their function. This theory is also supported by the research work of McNew and Gershon (1969).

Oxine-copper, bis(8-quinolinolato)copper **(29)** is an olive-green crystalline substance, insoluble in water, alcohols and most of the organic solvents. Oxine-copper, can be prepared from the aqueous solution of a copper(II) salt by precipitation with 8-hydroxyquinoline.



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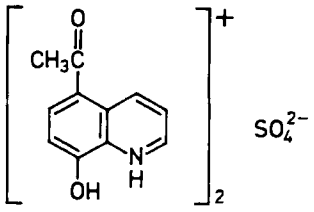
This active substance is known in agriculture as a seed-dressing agent (Mason, 1948) and can be used alone or in mixtures. Particularly in combination with active substances of the oxatiin type it is an excellent seed-treating agent for protection against loose smut of wheat *(Ustilago tritici)* and barley *(Ustilago nuda)*, as well as various *Fusarium, Septoria* and *Helminthosporium* spp. A synergistic action has been found between the two active substances (Richard and Vallier, 1969). This combined seed-treating agent with a wide range of action is important also with regard to environmental protection, because it is virtually nonhazardous to human and to the environment, and can replace mercury seed-dressing for many uses. The LC_{50} (48h) for brown and rainbow trout is 0.2–0.3 mg/l (Alabaster, 1958).

In 8-hydroxyquinoline the OH group has a phenolic, or naphtholic character, and the molecule can therefore be easily halogenated or nitrated in positions 5 and 7. Of the substituted derivatives of 8-hydroxyquinoline, those with a chlorine, bromine, iodine or nitro group in position 5 have a substantially increased fungicidal effect similarly to those with chlorine or bromine disubstituted in positions 5,7. On the other hand, the activity of the molecule is not considerably changed when fluorine is substituted in position 5, or iodine and nitro groups in positions 5,7, and the fungicidal effect is considerably decreased by the substitution of nitroso or amino groups in positions 5 or 5,7 (McNew and Gershon, 1969; Gershon *et al.*, 1972). In the case of these latter derivatives, the lack of activity is presumably due to the steric and electrostatic properties of the molecule. Of all the 7- and 5,7-substituted derivatives 7-iodo-8-hydroxyquinoline is the most active, having an excellent fungicidal effect *in vitro* against the fungi *Trichoderma viride, Trichophyton mentagrophytes* and *Myrothecium verrucaria* at concentrations lower than 0.0037 mg/kg.

Of the substituted derivatives of 8-hydroxyquinoline, quinacetol sulfate, bis-(5-acetyl-8-hydroxyquinolinium) sulfate **(30)**, has attained greater importance so far. The pure active substance is a yellow crystalline compound, soluble to 1 : 100 in water at 20°C, and very slightly soluble in organic solvents. Its acure oral LD_{50} for rats is 2200 mg/kg. It is available commercially in combination with other active substances as a mercury-free seed-dressing agent, and has the same range of action as organic mercury compounds. It is recommended primarily for the seed-treatment of wheat, barley and oats (Hocombe *et al.*, 1973).



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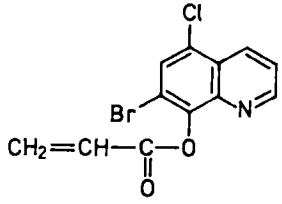
According to Boyland and Watson (1956) and to Clayston *et al.*, (1958), 8-hydroxyquinoline and its 5-nitro derivative may cause, in very high doses, bladder tumour in rats, although Innes *et al.*, (1969), testing 8-hydroxyquinoline in mice, found no carcinogenic effect.



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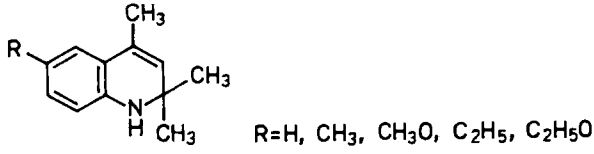
The active substance halacrinate, 7-bromo-5-chloroquinolin-8-yl-acrylate (**31**) can be prepared by the reaction of 5-chloro-7-bromo-8-hydroxyquinoline with acrylic chloride in benzene solution, in the presence of triethanolamine (Huber-Emden *et al.*, 1971). It has a protective and curative effect against *Erysiphe graminis*, both on leaf and ear, moreover, as side-effect, it is efficient also against *Fusarium* and *Puccinia* spp. The combination of halacrinate with captafol gives good protection against *Septorium nodorum* of wheat. The preparation is toxic to bees, but not to mammals. Its acute oral LD_{50} is 6400 mg/kg for rats (Fleming *et al.*, 1975; Smith *et al.*, 1975).

The dihydroquinolines (**32**)



32

were prepared by the condensation of $4\text{-}RC_6H_4NH_2$ with acetone in the presence of iodine of sulfanilic acid. The effectiveness of hydroquinolines in inhibiting the oxidation of carotene increased in the following order (Serdechnaya, 1974):

$$R = C_2H_5 < CH_3 < H < CH_3O < C_2H_5O.$$

Thus ethoxyquin, 1,2-dihydro-6-ethoxy-2,2,4-trimethylquinoline, is the most important active substance practically. It is used for the control of scald in apples (Stop Scald®) and to a lesser extent in pears, as both preharvest treatment and postharvest dips and spray (Porrith and Meheriuk, 1968). It is also used as an antioxidant in spices and fish meal, and in poultry, swine and other animal feed (Danilenko *et al.*, 1968).

5.9.4 Quinoxaline derivatives

Of this biologically very effective group, the carbonic acid derivatives of 2,3-dithioquinoxaline have proved to be the most active (Sasse *et al.*, 1960). The active compounds first became known as excellent acaricides (Unterstenhöfer, 1960; Sasse, 1960) because they were also effective against acarus species resistant to phosphoric compounds. At the same time, they have the valuable property of being toxic to powdery mildew fungi.

Thioquinox **(33)**, 1,3-dithiolo[4,5-b]quinoxaline-2-thione, is primarily an acaricide with mainly ovicidal properties. The compound is practically insoluble in water and is stable to the action of light and heat. It is also resistant to hydrolysis, and although sulfur is oxidised in the molecule, the biological action is not reduced.

It is used as a contact fungicide on cucumber in greenhouse and in orchards against powdery mildew.

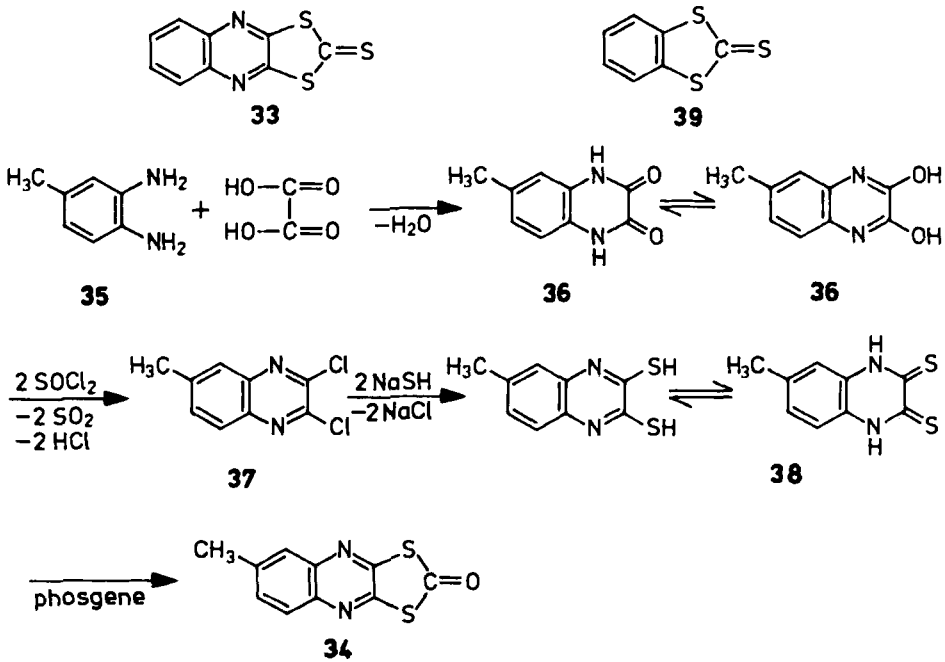
Quinomethionate, 6-methyl-1,3-dithiolo[4,5-b]quinoxaline-2-one **(34)**, has gained wider use in agriculture. It is a more active fungicide than thioquinox, which is partly due to the 6-methyl substituent and partly to the greater activity of dithiocarbonates compared to that ot trithiocarbonates (at least against powdery mildew of cucumber). It is a contact fungicide specific to powdery mildews (*Erysiphe* and *Podosphaera* spp.), and it also has an acaricidal effect (Grewe and Kaspers, 1965). In combination with other fungicides ineffective against powdery mildew fungi (captan, dithiocarbamates) it has synergistic properties.

The synthesis of quinomethionate starts with 4-methyl-1,2-phenylenediamine **(35)**, which, reacting with oxalic acid, gives 6-methyl-dioxyquinoxaline **(36)**, from which 6-methyl-2,3-dichloroquinoxaline **(37)** is obtained by chlorination. The 2,3-dithio derivative **(38)** obtained from it with sodium sulfide is converted with phosgene into the end-product.

Their acute toxicity to mammals is low, but the two active substances may cause dermatitis. In rats fed daily on a diet containing quinomethionate a high cumulative toxicity was observed. A dietary level of 500 mg/kg for 90 days reduced body-weight, caused hypertrophy of the liver, and inhibited acetoacetate synthesis and the microsomal enzymes. It primarily inhibited the function of the HS-enzymes (pyruvate dehydrogenase, succinate dehydrogenase, malate dehydrogenase and α-ketoglutarate oxidase) (Carlson and DuBois, 1970).

2,3-Disubstituted quinoxalines are not toxic to bees, so that, with the exception of a few more sensitive apple species, preparations can also be used in the blossoming period.

The trithiocarbonate group alone cannot be responsible for the biological activity of the active substance, because trithiocarbonates, among them compound **(39)**, are completely inactive. Sasse *et al.* (1960) attribute the biological action to the high reactivity of the acyl derivatives of 2,3-dithioquinoxaline towards amino



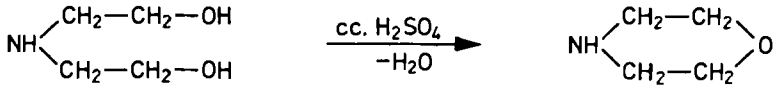
groups, playing a role also in the living organism. However, the metal–ion binding ability of thioquinoxaline liberated by hydrolysis from the derivatives may also be of importance. The possible metabolite of quinomethionate, 6-methyl-2,3-quinoxaline dithiol **(38)**, is twice as toxic to rats and mice as the original compound (Carlson and DuBois, 1970).

5.9.5 Morpholine-type fungicides

The N-cycloaliphatic derivatives of tetrahydro-1,4-oxazine (morpholine) or those with a long-chain alkyl groups are good specific fungicides against powdery mildew fungi (cereals, cucumbers, apples, roses, etc.) (Pommer and Kradel, 1967).

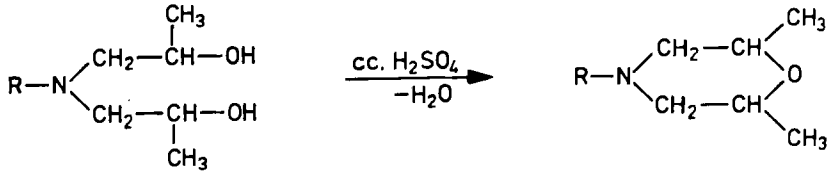
Roots and leaves of the plants both take up these active substances. They are distributed in the plants by translocation from the root, and protect the plants for 3–4 weeks against infection by phytopathogenic fungi. Morpholine-type fungicides also have an eradicant action when applied on the leaves.

Morpholine **(40)** can be obtained in a satisfactory yield by the cyclisation of bis-(2-hydroxyethyl)amine **(41)** with the elimination of water:



41 **40**

Cyclisation can be performed more simply and with a better yield if the amine-hydrogen is substituted for an alkyl radical (R) and the OH groups are located at a secondary carbon atom **(43)**:



42 **43**

An investigation of several hundred N-substituted tetrahydro-1,4-oxazine derivatives with respect to the relationship between structure and biological action showed that the optimum chain length of the N-substituent is in the range of 12–18 carbon atoms. Aromatic substituents make the compound almost inactive as fungicides, but very phytotoxic. In the compounds with cycloaliphatic rings, rings with 12 members are optimal. Alkyl substitution in the cycloaliphatic ring reduces the fungitoxic effect, but small alkyl substitutions in the morpholine ring are favourable. 2,6-Dimethyl substitution proved to be the best, because, in addition to increasing fungitoxicity, it also reduced phytotoxicity. The fungicidal effect of the molecule is scarcely changed by the binding of the free electron pair of the morpholine nitrogen atom (König *et al.*, 1965; Pommer and Kradel, 1967; Pommer, 1984).

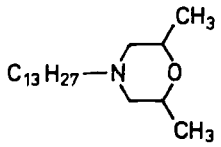
On the basis of these relationships, two active substances are of importance at present.

Tridemorph **(44)**, 2,6-dimethyl-4-tridecylmorpholine, is obtained by the reaction of 2,6-dimethylmorpholine with tridecyl chloride. The base is liberated with alkali from the hydrochloride to give with acetic acid the active substance applied in practice. It is a colourless oily liquid, miscible with water. Tridemorph is an eradicant fungicide with systemic action. Absorbed through foliage and roots, it also has a limited protective action, particularly against the powdery mildew fungi of cereals (Kradel *et al.*, 1968; Pommer *et al.*, 1969). The fungicide is strongly absorbed by the soil and is not leached by ground water. Tridemorph is nonpersistent, being completely degraded biologically in the soil. First, tridemorph-N-oxide is formed, which is then decomposed into 2,6-dimethylmor-

pholine and carbon dioxide (Otto and Drescher, 1973). Tridemorph has little effect on spore germination but inhibits mycelial growth. The fungicide does not affect oxygen uptake by fungal protoplasts. However, incorporation of labelled histidine was reduced, suggesting that tridemorph may inhibit the formation of proteins essential for mycelia growth (Fisher, 1974). According to Müller and Schewe (1975), tridemorph interacts with the mitochondrial electron transport system at at least three sites. According to Bergman *et al.* (1975) tridemorph inhibits respiration and the primary effect should be in the respiratory chain.

Recently Kerkenaar and Kaars Sijpesteijn (1979) demonstrated that inhibition of respiration cannot be the primary cause of growth inhibition, and that the action of tridemorph is similar to that of known sterol biosynthesis inhibitors. Their study seems to favour in lipid biosynthesis, possibly ergosterol biosynthesis, as a primary mode of action of tridemorph, and would agree with the rather late interference of this compound with protein and RNA synthesis (Kerkenaar *et al.*, 1979, 1981).

Dodemorph, 4-cyclododecyl-2,6-dimethylmorpholine, **(45)** is a compound with cyclic substituent.



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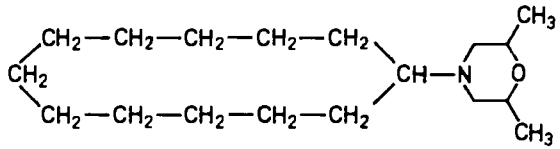
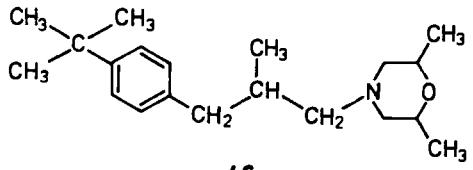


45

It is a yellow liquid, miscible with water. The active substance is its acetate, which is a stable compound. Dodemorph is an eradicant fungicide, which is absorbed through foliage and roots, having a systemic action in the latter case. It is used mainly against the powdery mildew fungi of ornamental plants such as *Sphaerotheca pannosa* and the powdery mildew of roses, but it is also efficient against powdery mildew of cucumbers (Kradel and Pommer, 1967). It is pyhtotoxic to *Cinerarias* and *Begonias*.

A recent addition to this group of active substance is fenpropimorph **(46)** the *cis* isomer of 4-[3-*p*-*t*-butylphenyl)-2-methylpropyl]-2,6-dimethylmorpholine.



46

It has both protective and curative properties and is acropetally transported, protecting the treated crop, including newly developed leaves, for 3–4 weeks. It exhibits strong fumigant activity. Fenpropimorph controls *Erysiphe graminis* and *Puccina* spp. on wheat, barley, oats and rye, and *Rhizoctonia* spp. on cotton (Goebel, 1983).

It has a low mammal toxicity. The acute oral LD_{50} is 3515 mg/kg for rats. Fenpropimorph causes no unwanted side-effects in cereals. The first results indicate that the active substance interfers with the sterol synthesis.

As a seed dressing the best results were obtained against *Tilletia, Ustilago* and *Helminthosporium* spp.

Fenpropimorph is well tolerated by plants, particularly by monocotyledons (Bohnen *et al.*, 1979; Bohnen and Pfiffner, 1979; Saur *et al.*, 1979).

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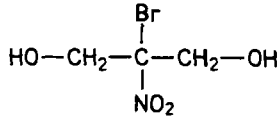
5.10 Other compounds with fungicidal properties

Active substances with fungicidal properties belonging to various groups of compounds are summarised in this chapter. One part of the compounds is only of theoretical importance and has not been used in agriculture for plant protection. The group comprises also new experimental active substances, which are not yet fully known, but seem to be promising.

5.10.1 Alkane derivatives

Of the halogen nitro alkane compound, bronopol (2-bromo-2-nitropropan-1,3-diol, **1**), proved to be also in agricultural use an active substance with good specific bacterostatic action. Bronopol is a compound with wide antimicrobial action, of low toxicity to mammals (Croshaw *et al.*, 1964). This compound was originally used in the cosmetic and pharmaceutical industries. Its acute oral LD_{50} is 180–400 mg/kg for rats. Bronopol is rapidly excreted in the urine (Naito *et al.*, 1974).

Although it inhibits *in vitro* the growth of several phytopathogenic bacteria even at low concentrations, the practical range of action of bronopol is very narrow. From the viewpoint of plant protection it is active only against *Xanthomonas malvacearum*, causing blackarm disease of cotton (Spooner and Wakerley, 1971). However, in this respect it surpasses the effect of mercury-containing seed protectants, which cause environmental pollution problems (Dransfield, 1971). Bronopol inhibits the activity of glyceraldehyde-3-phosphate dehydrogenase, the primary action of the active substance being oxidation of the SH groups into disulfides (Stretton and Manson, 1973). Bronopol is prepared by the bromination of 2-nitropropan-1,3-diol.



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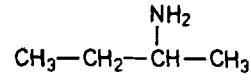


2

In the investigation of the biological activity of *n*-alkylamines and their salts several compounds with fungitoxic properties have been found, but of these only *s*-butylamine (**2**) and its salts are actually used in agriculture (Eckert and Kolbezen, 1962).

s-Butylamine is very effective against *Penicillium digitatum*, which causes citrus rot, but it is also effective against *Penicillium expansum* on pear and apple, *Monilia fructicola* on peach, and *Gloeosporium* on banana. It has the advantageous property of being effective also against *Penicillium* spp. which have become resistant to diphenyl compounds used for similar purposes (Eckert and Kolbezen, 1964). Used as a fumigant, the butyl ammonium salt deposited on the fruit is the carrier of the fungistatic action. However, the best effect is achieved most economically if fruits to

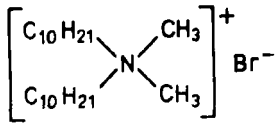
be stored or transported are dipped into a 0.5% aqueous solution of the hydrochloride of *s*-butylamine or if the solution is sprayed on the fruits. The (−) enantiomer of *s*-butylamine is more inhibitory than the (+) enantiomer (Eckert *et al.*, 1972).

s-Butylamine can be also used as a fumigant for the control of gangrene *(Phoma exigua foveate)*, skin spot *(Oospora pustulans)*, and silver scurf *(Helminthosporium solani)*, diseases of potato tubers (Graham *et al.*, 1973).

Conidia of *P. digitatum* germinated in the presence of *s*-butylamine showed enlarged vacuoles and smaller phospholipoprotein inclusions compared to controls. Electronmicrographs indicated that these phospholipoprotein inclusions gave rise to membrane-bound vesicles. *s*-Butylamine may deprive the conidium of materials normally utilised for membrane formation by the developing organelles (Zaki *et al.*, 1973). Recent investigations have shown that the primary site of the fungistatic action of *s*-butylamine is the pyruvate dehydrogenase complex (Yoshikawa and Eckert, 1976; Yoshikawa *et al.*, 1976).

The active substance is not phytotoxic, even at ten times the usual dose, and is moderately toxic to mammals. The acute oral LD_{50} for rats is 380 mg/kg. It is a strong irritant to skin.

A few fungicides have also been developed in the group of quaternary ammonium compounds. Deciquam **(3)**, didecyl-dimethyl ammonium bromide, has a protective and curative effect against apple scab, while allyl-didecyl-methyl ammonium bromide **(4)** is a fungicide with a wide range of action on several cereals, and is also used in the field of hygiene.



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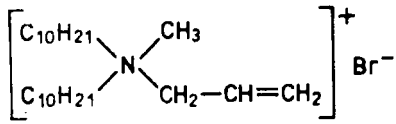
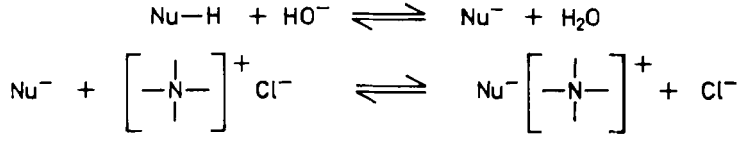


4

Several quaternary ammonium compounds are used in organic chemistry as phase-transfer catalysts. The mechanism of the catalytic process can be represented by a combination of phase-transfer and ion-exchange equilibria. In the case of substitution reactions in two-phase systems, the negatively charged nucleophile is extracted by the positive ammonium ion from the aqueous phase into the organic phase where substitution takes place (Makosza and Serafin, 1965, Makosza, 1969, Dockx, 1973).

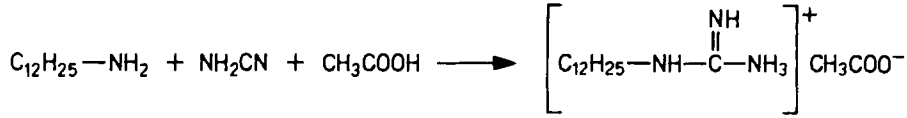


Nu^- nucleophile

In view of the great importance of phenomena proceeding at the phase interfaces and the large number of nucleophilic groups in the living organism available for substitution, this finding may throw a new light on the conceptions of the mechanisms of fungicidal action of quaternary ammonium halides.

The biological activity of guanidine derivatives increases with increasing alkyl chain length (Pressman, 1963). Dodecyl guanidine, the acetate of which is dodine **(5)**, has the greatest fungitoxic activity. It is a specific active substance against scab on apple and pear, but it is effective also for the control of cherry leaf spot (Cation, 1957). Owing to its locosystemic property, which can be attributed to the surface-active behaviour of the active substance, its eradicant effect against *Fusicladium* is at least equal to or surpasses the effect of organic mercury compounds (Jones *et al.*, 1963; Hamilton *et al.*, 1963). Dodine is phytotoxic, during extreme weather conditions however, with the exception of a few sensitive apple species, it can also be used after blossoming.

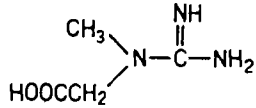
It is synthesised from dodecyl amine **(6)**, cyanamide **(7)** and acetic acid.



6 **7** **5**

The acetate is a water-soluble, white crystalline compound.

Dodine is an advantageous active substance from the standpoint of environmental protection. Its acute oral LD_{50} is 1000 mg/kg for rats. It is not toxic to bees in the concentration range used. The active substance is metabolised in the plant, being converted by the oxidation of the alkyl chain and by biological methylation into creatine **(8)**.



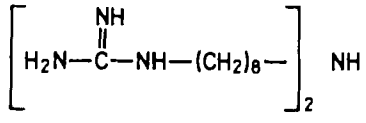
8

Conidia of fungi sensitive to the active substance rapidly absorb dodine (Brown and Sisler, 1960; Somers, 1963). This process is independent of temperature and cell metabolism. Dodine is presumably attached with an ionic bond to the anionic bonding sites of the cell, to the carboxyl groups or to the phosphate groups. This is indicated by the fact that the uptake of dodine by the cell can be reduced with certain metal cations (Ca, Mg) (Miller, 1969). The accumulation of a rather large quantity of the active substance is needed for a sporostatic effect. For *Venturia inaequalis*, the LD_{50} is 2000–2500 μg/g of conidium, while in the case of the less-sensitive *Aspergillus niger* even ten times this quantity is ineffective (Miller, 1969). The fungicide first saturates the cell wall, then reacting with the protoplast membrane and changing its permeability. Because of this, more dodine can

penetrate the cytoplasm, rupturing the intercellular membrane structure (Somers and Pring, 1966). The final cause of fungitoxicity is the competitive inhibition of certain enzymes. According to the research work of Pressman (1963) guanidines affect various sites of the energy transfer process between the electron transfer chain and adenosine triphosphate, and are thus oxidative phosphorylation inhibitors. The guanidine part of the molecule must have a specific effect, because dodine is considerably more active than most of the biologically active alkyl amines.

Guazatine bis(8-guanidine-octyl)amine **(9)**, is used in the form of its water-soluble triacetate or water-insoluble sesquisulfate. The free bases cannot be isolated. This active substance is particularly effective against diseases spreading with cereal seeds, and can therefore replace mercury-containing fungicides. It is moderately toxic to mammals. The oral LD_{50} of the triacetate for rats is 260 mg/kg, and that of the sesquisulfate 550 mg/kg. Guazatine is repellent to chickens.

According to seed dressing experiments (Jackson *et al.*, 1973; Barlett and Ballard, 1975) guazatine used alone does not even approach the results obtained with mercury-containing seed dressers. However, in combination with other fungicidally active substances (carboxin, maneb and imazalil) it replaces mercury-containing seed-dressings even in the protection of barley against *Pyrenophora graminea.*



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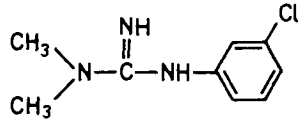


10

An advantageous side effect of guazatine is its action at field dosages as an antifeeding agent against the larve of soybean looper, *Pseudoplusia includens.* Guazatine may be a good candidate for use in integrated pest control programs (Backman *et al.* 1977; Higgins and Pedigo, 1979).

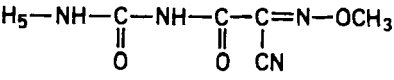
The active substance FDN **(10)**, N,N-dimethyl-N'-(3-chlorophenyl)-guanidine, is a protective and eradicant fungicide of almost the same activity as dinocap against the powdery mildew of cucumber. It is a soil fungicide, the active substance being absorbed by the roots of the plant. It also has a satisfactory effect against *Erysiphe graminis* (Melnikov *et al.*, 1974). Its acute oral LD_{50} is 420 mg/kg for rats.

5.10.2 Alkane carboxylic acid derivatives

Propionic acid (CH_3CH_2COOH) is used mainly in the food industry, but it is also used for limited purposes in agriculture, in particular for the conservation of fodder-maize. At a concentration as low as 0.1% it inhibits the growth of mould fungi.

Cyaniminoacetic acid derivatives with new properties were a valuable contribution to the group of fungicides. Of these compounds 2-cyano-N-[(ethylamino)-

carbonyl]-2-(methoxyimino)acetamide **(11)** proved to be most succesful for agricultural application. The common name of the compound is cymoxanil.



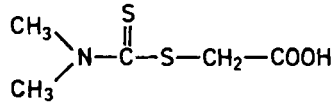
11

Used at low rates against *Peronosporales* it has a distinct curative effect, inhibiting disease development in the incubation period (Serres and Carraro, 1976). It gives good control of *Plasmopara viticola* (Douchet *et al.*, 1977), potato and tomato late blight, and hop downy mildew (Absi, 1979). It is most efficacious against early and severe disease infection.

The compound is rapidly broken down in plant tissues and loses its activity within 3–6 days of application. This short residual life precludes the use of the product alone under practical conditions, but combinations with protectant fungicides (copper oxychloride, dithiocarbamates, folpet, etc.) improve the persistence of control. The fungicide is also rapidly decomposed in soils, over 50% of the initial dose being lost within 2 weeks, with movement limited to the top 5 cm. ^{14}C-labelled cymoxanil is rapidly metabolised by grapes, potatoes and tomatoes, resulting primarily in formation of (^{14}C) glycine with subsequent reincorporation of the radiolabel in other naturally occurring compounds closely associated with the metabolism of glycine (Belasco *et al.*, 1981). The metabolism of cymoxanil in the rat is the same. It is formed glycine which, in turn, is incorporated into polypeptides or conjugated and eliminated as hippuric acid and phenylaceturic acid (Belasco and Baude 1981).

The acute oral LD_{50} is 1425 mg/kg for rats (Klopping and Delp, 1980).

In the investigation of the mode of action of dialkyl dithiocarbamates, tetramethylthiuram monosulfide (TMTM) revealed a systemic action (Pluijgers and Kerk, 1961; Kaslander, 1966). It is thought that the dimethylthiocarbamoyl part of TMTM is the carrier of the protective effect of the molecule. On this basis, several derivatives with systemic action have been synthesised (Carter *et al.*, 1963; Bánki *et al.*, 1966; Matolcsy and Josepovits, 1967), an example of which is N,N-(dimethylthiocarbamoyl)thioacetic acid **(12).**



12

With these compounds the carrrier of fungitoxicity, the dimethylthiocarbamate ion, could be introduced into the plant, but the antifungal activity of the compound *in vitro* is low. On the other hand, the compounds show growth-regulating properties similar to those of phenoxyacetic acid derivatives *in vivo* (Van der Kerk *et*

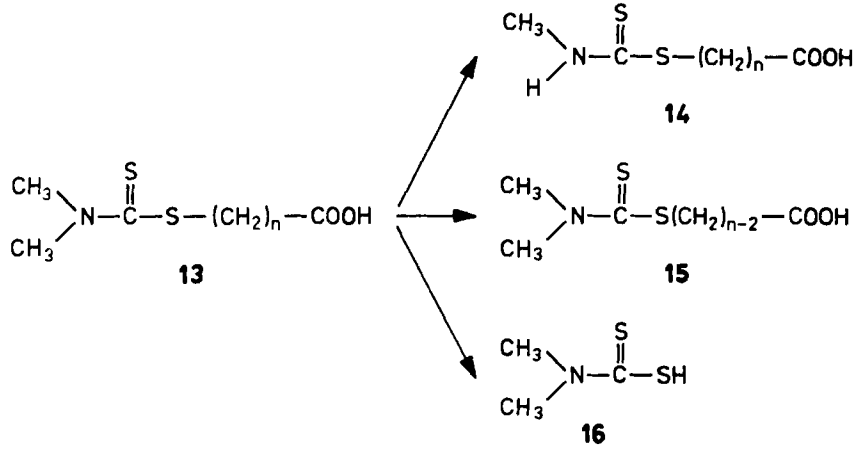
al., 1955), and it should be possible to develop them into products with fungicidal properties *in vivo*.

N,N-(dimethylthiocarbamoyl)thioacetic acid is a white crystalline compound. It is slightly soluble in water, as are its alkali salts. Its protective effect against fungal infections is generally explained by metabolic changes (reduction of sugar level) in conjunction with growth-regulating activity. It seems probable, however, that dimethyldithiocarbamic acid liberated during metabolism in the plant also plays a role in fungicidal activity. The metabolism of N,N-(dimethylthiocarbamoyl)-thioalkanecarboxylic acids **(13)** can proceed *via* three pathways in the plant (Dekhuijzen, 1964; Kaslander, 1966).

(a) the N,N-dimethylamino group is demethylated **(14)**;

(b) the alkanecarboxyl part of the molecule is β-oxidised **(15)**;

(c) the S-alkyl bond is ruptured by hydrolysis **(16)**.



Owing partly to their instability and partly to their phytotoxicity, these derivatives have not been for practical uses.

Of the carbamic acid derivatives two compounds with similar range of action should be mentioned.

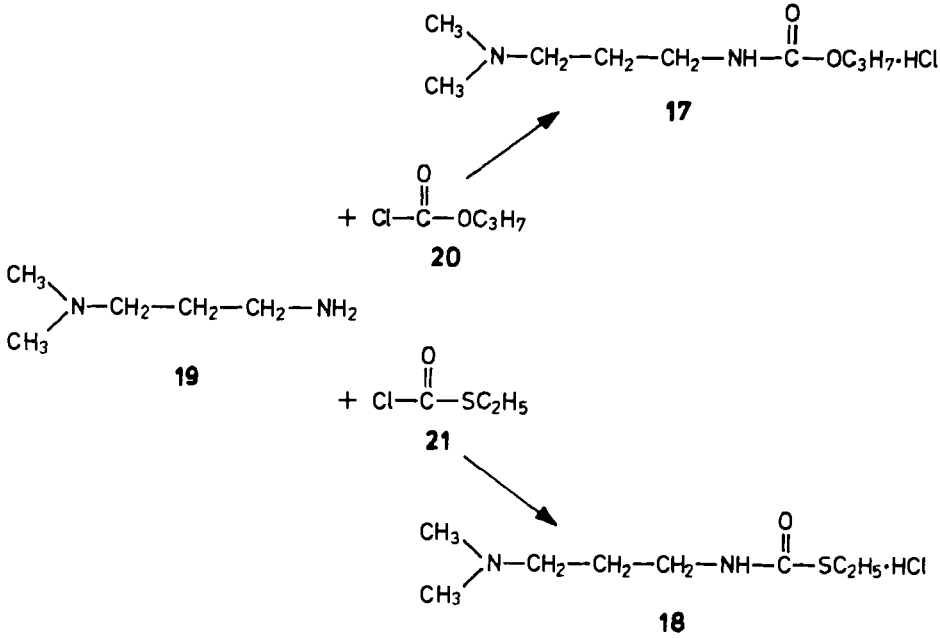
The two compounds, propamocarb propyl-N-(3-dimethylaminopropyl)carbamate **(17)**, (Pieroh *et al.*, 1978), and prothiocarb S-ethyl-N-(3-dimethylaminopropyl)thiolcarbamate **(18)**, (Bastiaansen *et al.*, 1974) are specifically active against *Phycomycetes* spp. fungi. This specific action is attributed to the fact that only those fungi which contain cellulose in their cell walls are sensitive to the active substances *(Oomycetes)* (Rapp and Richter, 1982). Fungi with chitosan or chitin cell walls are not sensitive to these active substances (Kaars Sijpesteijn *et al.*, 1974; Van der Kerk, 1975). These systemic fungicides are absorbed through the roots and have a curative effect.

In agricultural application the water-soluble hydrochlorides are used in the case of both compounds for preventive soil treatment, seed dressing or for the preliminary soaking of the roots.

The possibilities of application include the protection of ornamental plants, strawberry and some vegetables, and the treatment of seeds of sugar beet, cotton, rice and tobacco (Pieroh *et al.*, 1975; Aerts, 1976; Cohen, 1979; Papavizas *et al.*, 1978).

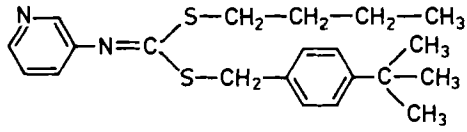
They are moderately toxic to mammals, the acute oral LD_{50} of propamocarb being 7860 mg/kg and that of prothiocarb 1300 mg/kg for rats. In the soil, the compounds are strongly sorbed by the organic soil components and by clay minerals without losing their fungicidal effect. They are broken down microbiologically. Depending on the type of soil, their action lasts for 4–8 weeks. Their activity is lower in acidic soil (Iwan and Goller, 1975).

Their synthesis begins with 3-(dimethylamino)propylamine **(19)**, which is reacted in an inert solvent in the presence of a hydrocloride binding substance with chloroformic acid propyl ester **(20)** and chloroformic acid thiol ester **(21)**, respectively.



Buthiobate (S-1358) is a dithiocarbonic acid derivative which is very toxic to powdery mildew fungi **(22)**. The fungicide, butyl 4-*t*-butylbenzyl-N-(3-pyridyl)-dithiocarbonimidate, has an excellent preventive and curative effect against the powdery mildew fungi of many agricultural and horticultural plants (Kato *et al.*, 1974). Its action is attributed to the inhibition of sterol biosynthesis (Kato *et al.*, 1975), involving the blocking of the demethylation reactions in the conversion of lanosterol to ergosterol. Matolcsy *et al.* (1973) reported that hypocholesteraemic drugs, which inhibit the biosynthesis of cholesterol in mammals, also suppress the

growth of fungi. This inhibiting action on the biosynthesis of sterols has not yet been proved in fungal organisms.



22

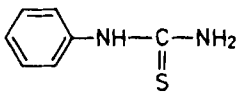
According to studies of structure-activity relationship of buthiobate the activities vary with the change of the S-alkyl group and are maximised at certain numbers of carbon atoms. A different pattern was observed in the activity towards *Sphaerotheca fuliginea* when the carbon atom number was 8 or more. Bulkiness of the S-alkyl group also appears to influence the activities. The steric factor of the *p*-alkyl substituents mainly influences the activity towards *S. fuliginea* up to the *t*-butyl analogue. The activities towards *Coniothyrium diplodiella* and *Sclerotinia sclerotiorum* increase with an increase in the bulkiness and the hydrophilicity of the *p*-substituent (Tanaka *et al.*, 1977a). The 3-piridyl group is essential for the activities (Tanaka *et al.*, 1977b). Finally, the fungicidal activities of buthiobate and its analogues are discussed by Tanaka *et al.*, (1978) in connection with the topomer ratios.

The degradation of the compound proceeds by three primary reactions: oxidation of the sulfur atom, rupture of the dithiocarbonimide bond and oxidation of the methylene group of the benzyl part (Ohkawa *et al.*, 1976).

The active substance is not toxic to mammals, the acute oral LD_{50} for male rats is 4900 mg/kg. The active substance is rapidly absorbed and metabolised in the animal. It is excreted in the urine and feces. The following metabolites have been detected in the urine: *p*-(1,1-dimethyl-2-hydroxyethyl)benzylmethyl sulfide and sulfone, and *p*-(1-methyl-1-carboxyethyl)benzylmethyl sulfide and sulfone and their glucuronide conjugates. In addition to these, butyl-(1,1-dimethyl-2-hydroxyethyl)benzyl-N-(3-pyridyl)dithiocarbonimidate has been detected in the feces (Ohkawa *et al.*, 1975).

One group of systemic fungicides comprises the thiourea derivatives, the action of which is based on increasing the resistance of the host plant against certain fungi. Their action is based on the inhibition of plant polyphenol oxidase, the polyphenols thus accumulated inhibiting the pectolytic enzymes of the pathogenic fungus *(Cladosporium cucumerinum)* (Van der Kerk, 1963 and 1969). Another explanation is that thioureas increase peroxidase activity and lignify the cell walls in the parenchyma around the penetrating hyphae of *Cladosporium*. This blocks further penetration and the spread of the fungi (Kaars Sijpesteijn, 1969). Some members of this group of compounds have also been found effective against *Fusicladium* on apple in addition to the cucumber pest mentioned. The most active members are phenylthiourea (**23**) and its *p*-chloro and *p*-nitro derivatives (Kaars Sijpesteijn and Pluijgers, 1962; Kaars Sijpesteijn and Sisler, 1968).

Thiosemicarbazides are structurally similar to thioureas. In regard to their effect and mode of action, however, they differ sharply, as these active substances also have a powerful fungicidal activity *in vitro*. Of the derivatives investigated so far 1-(*p*-chlorophenyl)thiosemicarbazide **(24)** is the most active, but nonsubstituted 1-phenylthiosemicarbazide is also active (Van der Kerk, 1963). The activity of thiosemicarbazides is very structure-specific. The presence of the phenyl group and the thiocarbonyl group are essential for activity. Certain substituents on the phenyl group increase the activity, but any substitutions at other places are unfavourable (Pluijgers and Kaars Sijpesteijn, 1966; Pandey *et al.* 1977). Phenylthiosemicarbazide is not fungitoxic in itself — actually its dehydrogenation product,



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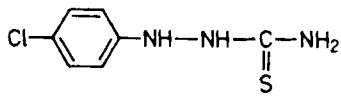

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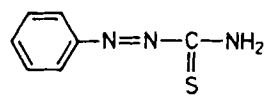


25

phenylazothioformamide **(25)**, is the active molecule. Therefore, substitution of a proton adjacent to nitrogen atoms 1 and 2 results in the inactivation of the molecule (Kaars Sijpesteijn *et al.*, 1968; Van der Kerk, 1969).

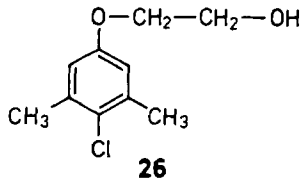
This type of compound is active mainly against *Fusicladium* and some fungal diseases of potato and tomato (Pluijgers and Kaars Sijpesteijn, 1966).

5.10.3 Aromatic compounds

The development of phenoxy alkane carbonic acids, some of which were already known as herbicides, into fungicides with systemic action was of great theoretical interest. This was motivated not only by their good translocating ability, but also by what is known of their biochemical action in plants. The result of one of their diverse actions on the enzymatic processes of the living cell is the reduction of the sugar level in the cell. At the same time, it is known that a high sugar content of cells of the host plant is a precondition of the pathogenicity of certain phytopathogenic fungi (powdery mildew and rust fungi) (Kaars Sijpesteijn, 1961). Thus, growth-regulating substances produce resistance to infection by changing the plant metabolism. The aim then of the research into the development of phenoxy-type compounds was to reduce the phytotoxic effect by the introduction of various substituents while preserving the action of the compound on carbohydrate metabolism and the translocating ability of the compound (Crowdy and Wain, 1950, 1951; Wain, 1951).

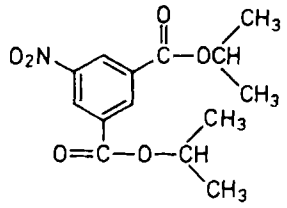
In the experiments, 2,4,6-trichlorophenoxyacetic acid, pentachlorophenoxyacetic acid and pentachlorophenoxyisobutyric acid revealed a systemic action against *Botrytis fabea* and *Alternaria solani*. Fungicides of more favourable action were obtained with such derivatives of phenoxi compounds in which the carbonyl group has also been changed. 4-Chloro-3,5-dimethylphenoxy ethanol **(26)**, effective

against certain fungal diseases (*fusarium* wilt of tomato), proved to be efficient also against the *X* virus of peach. However, it has a formative effect on sensitive plants (Dimond and Chapman, 1951). These compounds did not gain use in agriculture.



26

Nitrothal-isopropyl, diisopropyl-5-nitroisophthalate, (**27**) is not systemic, but is a fungicide of specific activity against apple powdery mildew. It is used in combination (sulfur, zineb). This fungicide is of low toxicity to mammals, bees and earthworms. The acute oral LD_{50} is 6400 mg/kg for rats for the formulated product (50% a. i.) (Phillips *et al.*, 1973; Archer, 1979).



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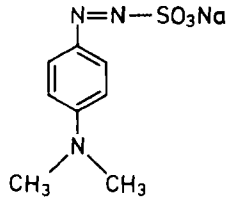


28

Fenaminosulf (**28**) is a diazo compound, the sodium salt of *p*-dimethylamino-benzenediazo sulfonic acid. It is prepared by the reaction of diazotized *p*-dimethyl-aminoaniline with sodium sulfite (Urbschat, 1960).

Fenaminosulf is a promising seed and soil fungicide. It gives protection against diseases originating from the soil and spread by the seeds, thus particularly against *Phycomycetes* fungi (Leach *et al.*, 1960). The active substance is absorbed through the roots and is translocated in the xylem (Hills, 1962), but owing to its low stability its action is of short duration. Fenaminosulf is decomposed by sunlight with evolution of nitrogen; it is then oxidised and the degradation product polymerises (Hills and Leach, 1962). Therefore, the active substance can be used exclusively for seed treatment against *Pythium* (Stahl and Rapp, 1975), *Aphanomyces* and *Phytophthora* spp. (Mitchell and Hagedorn, 1971; Montgomerie and Kennedy, 1977).

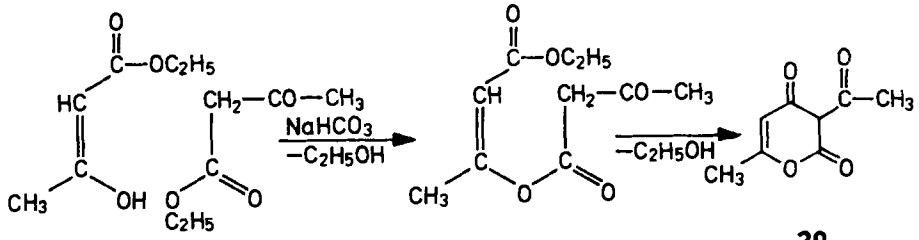
Fenaminosulf is relatively toxic to mammals, its acute oral LD_{50} being 60 mg/kg for rats. Its dermal toxicity is low. Treated seeds are toxic to birds and other wildlife.

Fenaminosulf reduces respiration in sensitive fungi. Thus, it inhibits the mitochondrial oxidation of nicotinamide adenine dinucleotide (NADH) in *Pythium* (Tolmsoff, 1962). On the other hand, in nonsensitive fungi (*Rhizoctonia solani*) a reductase has been identified which decomposes the active substance. But

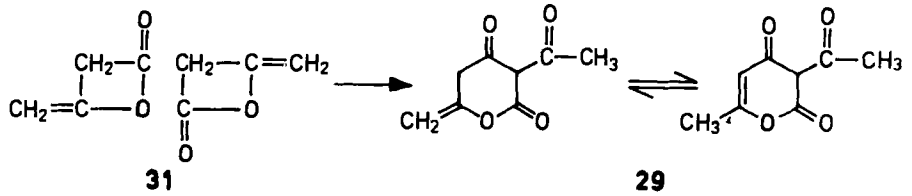
as this reaction is very slow, presumably it does not play a decisive role in the biological specificity of fenaminosulf. The selectivity of the active substance is explained by the different permeability of the mitochondrial membrane (Halangk and Schewe, 1975). Fenaminosulf also blocks other NADH-dependent flavine enzymes. It seems that fenaminosulf is a group reagent of some but not all NADH dehydrogenases of flavine character (Lyr, 1975).

In the soil the active substance is broken down by the soil bacterium *Pseudomonas fragi* into N,N-dimethyl-*p*-phenylene diamine. Like the original active substance, this decomposition product is toxic to *Pythium* app. (Karanth *et al.*, 1974).

Dehydroacetic acid 3-acetyl-6-methyl-2,4-pyrandione **(29)**, can be synthesised by two methods. By the prolonged heating of acetoacetic ester **(30)** two molecules of alcohol are eliminated and crystalline dehydroacetic acid is formed. Sodium bicarbonate accelerates the process.



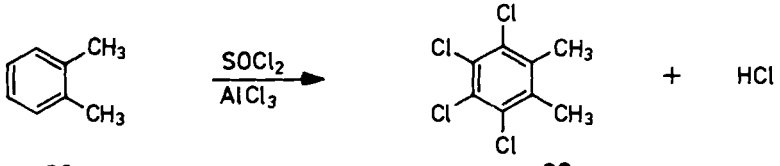
The diketene **(31)** dimerises without loss of alcohol into dehydroacetic acid in the presence of basic electron-donor compounds (tertiary amines) (Meshcheryakova *et al.*, 1970; Polyanskii and Meshcheryakova, 1971).



Dehydroacetic acid forms alkali salts by enolisation. It inhibits mould growth on fresh and dried fruit and vegetables caused by mould fungi and bacteria and is used for the impregnation of wrapping papers for foodstuffs (Wolf, 1950; Gardiner *et al.*, 1971). The effect is somewhat reduced with increasing pH. Dehydroacetic acid is more active against spores than against mycelia (Bomar, 1962). In some cases development of resistance has been observed (Beraha and Garber, 1966). The acute oral LD_{50} of dehydroacetic acid is 1.33 g/kg for rats (Sasaki, 1971).

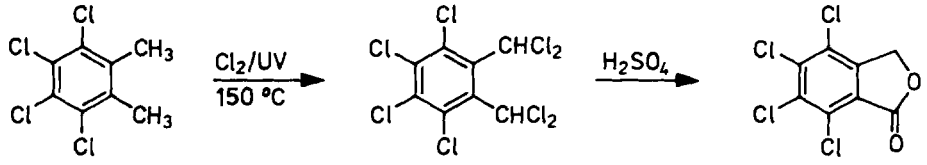
In recent time, phthalide (TCP, **35**), has attained particular importance from the standpoint of environmental protection among the mercury-free protective rice

fungicides (Wagner and Scheinpflug, 1975). Its industrial manufacture starts with the ring-chlorination of *o*-xylene **(32)**.



32 **33**

The second step is the chlorination of the side-chains of tetrachloroxylene **(33)**, which proceeds in 1,2,4-trichlorobenzene solution at 150°C under ultraviolet light with a yield of 80–90%.



33 **34** **35**

By the hydrolysis of 1,2-bis(dichloromethyl)-3,4,5,6-tetrachlorobenzene **(34)** with concentrated sulfuric acid 4,5,6,7-tetrachlorophthalide is formed in the third step in a virtually 100% yield. The active substance has already been prepared in Japan on the industrial scale under the trade name Rabcide®.

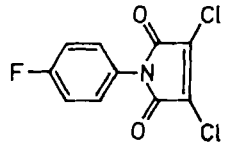
Tetrachlorophthalide is a selective and very effective preventive fungicide against *Piricularia oryzae* fungi which cause rice blast. Although *in vitro* it inhibits spore germination relatively poorly, even under greenhouse conditions it provides complete protection at very low concentrations (0.005%). It can be also used against the fungi of other cultures in addition to rice blast (Nambu, 1972). Its systemic effect is slight, so it has no curative effect. However, its action lasts longer than that of all the fungicides used so far.

Concerning its mode of action, it is thought that the main mechanism in rice blast control by phthalide is the inhibition of hypha penetration (Aoki and Yamada 1979).

To achieve a curative effect, phthalide is combined with edifenphos, which has a systemic action. Additonally, the two active substances have a synergistic action in the preparation. 4,5,6,7-tetrachlorophthalide is very slightly toxic to mammals and fish. The acute oral LD_{50} is > 1000 mg/kg for rats.

Fluoromide (Mk-23) 2,3-dichloro-N-(4-fluorophenyl)maleinimide **(36)**, acts specifically against citrus scab *(Elsinoe fawcetti)*. The acute oral LD_{50} is > 15000 mg/kg for rats. It has also an acaricidal action on citrus red mite on grapefruit (Kawada *et al.*, 1971).

The systemic action of 6-azauracil, 3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine **(37)**, was discovered in 1961. In addition to its cytostatic and antibacterial action, it is effective also against powdery mildew fungi as both a root and foliage fungicide.



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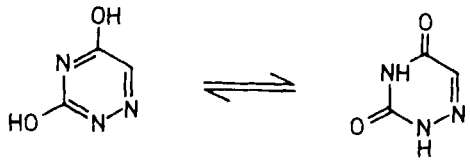
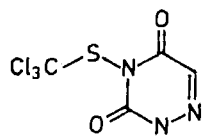


37

In concentrations up to 1000 mg/kg no fungicidal activity of 6-azauracil in preventing the germination of conidia of *Erysiphe cichoracearum* was observed *in vitro*, suggesting that activity takes place exclusively inside the host tissues. On cucumber plants treated with 6-azauracil, germination of powdery mildew conidia appeared to be normal, but growth of the fungus stopped after the formation of the first haustorium. The activity of 6-azauracil on *E. cichoracearum* could be counteracted by uracil. Thus, it has been presumed that this fungicide acts as a competitive antagonist of uracyl, possibly interfering with the synthesis of RNA (Dekker, 1962; Dekker and Oort, 1964).

Contrary to the finding of Dekker and Oort (1964), Matolcsy and Doma (1967) reported contact antifungal action of 6-azauracil, but not of its riboside, 6-azauridine (Matolcsy and Doma, 1969), formed in the initial metabolic step. The activity of 6-azauracil proved to be highly structure-specific, and any alteration in its molecule resulted in a loss in activity.

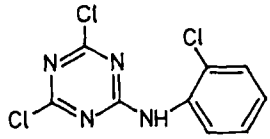
3-Trichloromethylmercapto-6-azauracil **(38)**, a compound related to captan, proved to be more active than captan (Matolcsy and Bordás, 1969).



38

Of the *s*-triazine derivatives, the chloro, methoxy and methylthio dialkylamino derivatives form one of the important groups of herbicides. According to the research work of Wolf *et al.*, (1955) some of the *s*-triazine derivatives have fungicidal properties. In particular, those 2,4-dichloro-*s*-triazines, which contain an arylamino or aryloxy group in position 6 have an important toxic action against phytopatogen fungi. One of these, 2,4-dichloro-6-(2-chloroanilino)-*s*-triazine,

anilazine (**39**), has a wide range of action (Schuldt and Wolf, 1956). However, this active substance did not gain widespread use in agriculture because of the sensitivity of certain cultures. It has a herbicidal effect against Canada thistle (*Cirsium arvense var. mite*), and causes injuries similar to these from bipyridylium herbicides (Marriage, 1973).



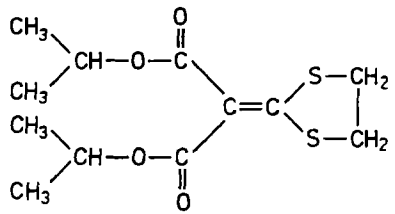
39

The fungitoxic properties of the active substance are attributed to its high reactivity towards amino groups, due to the electron-attracting chlorine substitution in the benzene ring (Matsui *et al.*, 1960). Anilazine is rapidly absorbed by the fungal spores (Burchfield and Storrs, 1957). The active substance penetrates the fungal cells to react there immediately with the amino groups and less rapidly with cell components containing thiol groups, thus inhibiting nonspecifically several cell processes (Lukens, 1969). Its action is thus nonselective. It is a protective fungicide against several phytopathogen fungi (*Helminthosporium, Fusarium, Rhizoctonia, Alternaria, Stemphylium, Cercospora* and *Botrytis* spp.).

Owing to its high chemical reactive and short life, it cannot be used for soil treatment (Burchfield, 1959). The active substance is nontoxic. In chronic feeding tests at a rate of 5000 mg/kg per day rats showed no toxic symptoms (Cohen and Murphy, 1973). However, it may cause skin irritation.

Isoprothiolane (**40**), diisopropyl-1,3-dithiolan-2-ylidene malonate is a selective fungicide with excellent systemic action against the fungus *Piricularia oryzae*, which causes rice blast. From the granules used in the flooding water, the active substance easily gets through the roots into the rice plant and is translocated into the leaves. (Katagiri and Uesugi, 1977; Hirooka *et al.*, 1982).

It is slightly toxic to mammals, its oral LD_{50} for male rats being 1190 mg/kg. Chronic toxicological tests showed no ill effects. It is moderately toxic to fish (Chou *et al.*, 1980). An important property of the active substance is its insectostatic side effect. This is manifested by a thinning of the plant-hopper population living on rice. It has been shown *in vitro* that used in the first larval stage it kills the insect, generally between the third and fifth moulting. Thus, isoprothiolane interfers in the metamorphosis of the insect (Araki *et al.*, 1975).



40

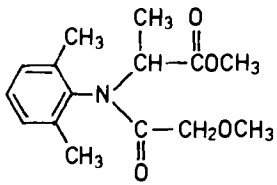
Acylalanines are a new class of fungicides, two members of which metalaxyl (CGA 48 988), methyl N-(2,6-dimethylphenyl)-N-(2-methoxyacetyl)-DL-alaninate, **(41)** and furalaxyl (CGA 38 140), methyl-N-(2,6-dimethylphenyl)-N-(2-furoyl)-DL-alaninate **(42)** (Schwinn *et al.*, 1977a, 1977b; Wiertsema and Wissink, 1977).

Both have high activity at low concentrations in foliar or soil application against diseases caused by air- and soil-borne *Oomycetes* in various agricultural and horticultural crops.

They are protective fungicides with systemic properties. Owing to their acropetal transport, new plant growth can be protected for a period. Furthermore, since the compounds are taken up by the plants, they are not washed off by rain. They have a certain curative activity (Staub *et al.*, 1978; Cohen *et al.*, 1979).

The toxicological properties of metalaxyl and furalaxyl are favourable, with acute oral LD_{50} for rats of approximately 669 mg/kg and 940 mg/kg, respectively. There is no serious skin or eye iriritation in rabbits, and no sensitising effect on guinea pigs. They are slightly toxic to fish.

Their main field of application is against diseases caused by *Phytophthora* infestans on potato and tomato, by *Plasmopara viticola* on vine, and by *Pseudoperonospora humili* on hop. Their range of action can be extended through combination with protective fungicides (Smith *et al.*, 1977; Smith, 1979; Urech *et al.*, 1977).



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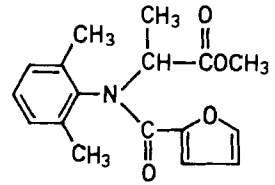
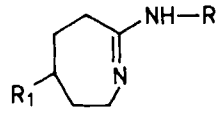


42

As concerning the mode of action of these fungicides, a recent study of Kerkenaar and Kaars Sijpesteijn (1981) describes the *in vitro* selectivity of metalaxyl and furalaxyl for the *Peronosporales* as well as several other effects. Since respiration of *Pythium splendens* was not inhibited it was supposed that the compounds act on biosynthesis or interfere directly with membranes.

The fungicides inhibited protein and nucleic acid synthesis. RNA production was particularly affected. There was some evidence of a reduction in nuclear division. The primary effect of metalaxyl and furalaxyl probably involves impaired biosynthesis of RNA so that mitosis is inhibited (Kerkenaar, 1981; Fischer and Hayes, 1982).

The group of substituted azepine-type compounds comprises fungicides with systemic properties **(43)**, effective mainly against leaf spots, powdery mildew and rust fungi. The tolerance of plants for these compounds is problematic (Gaetzi, 1962; Schwinn, 1969).



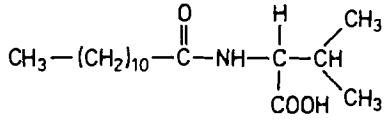
R = alkyl ($C_{10}-C_{12}$)
R_1 = alkyl (*t*-butyl)

43

5.10.4 Biodegradable pesticides

Problems of environmental pollution caused by the use of pesticides necessitated a search for agricultural pesticides which were nonhazardous, being either not toxic or degraded after their application in the environment into biologically inactive metabolites. In this field of research a new approach has been developed in Japan. This was outlined by Misato *et al.* at the seminary "Environmental Toxicology of Pesticides", held in Oiso in 1971, as follows: "DDT, BHC, and plastics have chemichal structures which do not exist in the natural world, and this is the reason why these substances are resistant to degradation by microbes. It is supposed that naturally-occurring compounds, or their derivatives with similar structures, can be degraded by microbes. Thus, their practical use may not carry with the possibility of environmental pollution" (Misato *et al.*, 1972b).

In research work employing this concept, excellent results have been obtained by the use of antibiotics as fungicides. Another approach, developed at the beginning of the 1970s, has been the study of naturally-occurring substances such as amino acids or fatty acids, which are essential constituents of every organism. Several natural amino acids inhibit, even if only weakly, the spore germination of certain fungi (Van Andel, 1966). The first important result of this research work was the demonstration of the fungicidal action of N-lauroyl-L-valine (**44**). This derivative of lauric acid and valine, linked with an N-acyl bond, showed, in a concentration of 2000 mg/kg, an excellent preventive effect against rice blast, powdery mildew of cucumber, cucumber anthracnose, grey mould of tomato, tomato blight and lemon melanosis (Homma *et al.*, 1973a).



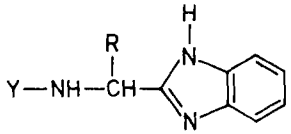
44

Of the salts of N-lauroyl-L-valine only the sodium and the potassium salts were active (Homma *et al.*, 1973b).

The fungicide N-lauroyl-L-valine does not pollute the environment, because the N-acyl bond of the complex is easily ruptured, and the two components are rapidly degraded by microorganisms (Misato *et al.*, 1974).

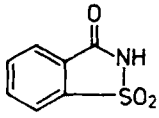
A broad study concerning other derivatives of amino acids and peptides, such as triazine and benzimidazole derivatives, has been started (Maekawa *et al.*, 1975). Of the triazine derivatives, few have shown any decisive fungicidal action. However,

among the benzimidazole derivatives of amino acids and peptides (**45**) several have revealed fungicidal action. The benzimidazole derivatives of isoleucine, valine and glutamic acid have an antifungal effect, and the benzimidazole derivative of phenylalanine even shows an antiviral effect against tobacco mosaic virus at a concentration of 100 mg/kg.



45

A third direction of research for pesticides that are readily degraded in the environment is the investigation of food additives as possible pesticides. These compounds are widely used in the food industry (preservatives, colouring substances, etc.). They are not hazardous to mammals, and their safe use has been checked from several aspects. Japanese workers have studied about 200 food additives including phosphatides such as soybean lecithin, which has proved to be, in a concentration of 2000 mg/kg, a substance with excellent fungicidal action under field conditions against the diseases of several crops, for example the powdery mildew of strawberry and cucumber, cucumber anthracnose and rice blast (Misato *et al.*, 1972a).



46

Other food additives have also shown an antifungal effect, for example oxalic acid, saccharin and its sodium salt, erythorbic acid and its salts, acrylamidated and hydroxyethylated starch. Saccharin (**46**) in an aqueous solution of 2000 mg/kg protects rice from infestation by *Piricularia oryzae* fungi (Misato *et al.*, 1973).

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5.11 Agricultural antibiotics

The introduction of antibiotics into agriculture for the protection of plants began in 1952, when streptomycin, used with excellent results in human therapy, was successfully used in the USA against fire blight of pear (Mitchell *et al.*, 1952). Streptomycin, or a mixture of streptomycin and terramycin, only protected plants against bacterial diseases, but cycloheximide and griseofulvin, which were discovered later, had an antifungal effect. These antibiotics were widely used in stock breeding for the preservation of food and in other fields, but they did not become well established in plant protection because of their high cost and because a wide selection of pesticides with satisfactory action was already available for plant protection.

Meanwhile, with the emphasis on environmental protection, the use of several fungicides was limited or banned and, at the same time, active antibiotics were discovered in increasing numbers, substances with excellent effects against several phytopathogenic fungi but which did not pollute the environment. Thus, the importance of antibiotics in agriculture rapidly increased.

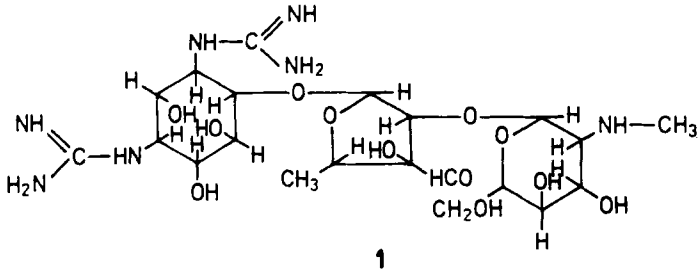
In the last 10 years, particularly in Japan, notable results have been attained in the field of antibiotic research and application. According to the data of Misato (1976), about 50 000 tons of preparations containing antibiotics were used in Japan in 1973, mainly on rice cultures. In 1977 the world production of antibiotic active substance was 360 metric tons.

One of the characteristic properties of antibiotics is their highly selective action. This is reflected by the fact that antibiotics generally have either an antibacterial or an antifungal activity, there being only a few compounds in which these two actions are combined. Most of the antibiotics used in agriculture have a systemic action, thus, besides giving preventive protection to the plants, they also have a curative effect if used immediately after infection. With a few exceptions they are not toxic to mammals.

Most of the antibiotics are unstable compounds — they are rapidly degraded by abiotic and biotic factors into biologically inactive compounds, so that they leave little or no residue. Usually no problems are caused from the point of view of environmental protection and, in any case, they are applied to plants in relatively small concentrations. However, because of their rapid degradation, their effects decrease considerably more rapidly than those of conventional fungicides, thus the checking of their efficiency is very important. In many cases, their phytotoxicity is considerable, which limits their application. Another limiting factor is the relatively rapid development of resistance to antibiotics. Antibiotics have not as yet shown any fundamental effect against viral diseases.

Today, the number of antibiotics already discovered may amount to several hundred, and of these the number of compounds effective against plant diseases is close to fifty. In this chapter only those antibiotics which have already been applied to agricultural practice for plant protection or which are promising as future agricultural antibiotics will be discussed in detail.

Streptomycin is an antibacterial antibiotics although a certain fungicidal action has also been noted (Müller *et al.*, 1954; Horner, 1963; Vörös, 1965). It was isolated in 1944 from cultures of *Streptomyces griseus*, *S. bikiensis* and *S. mashuensis* fungi (Waksman, 1953). It is strongly basic and is therefore marketed in the form of its hydrochloric acid or sulfuric acid salt. Its salts are soluble in water. Its composition is 2,4-diguanidino-3,5,6-trihydroxycyclohexyl-5-deoxy-2-O-(2-deoxy-methylamino-α-L-glucopyranosyl)-3-C-formyl-β-L-lyxopentanofuranoside **(1).**

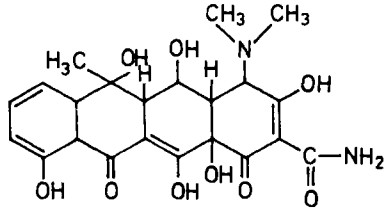


1

Stroptomycin has a systemic action, and is in certain cases phytotoxic at levels required for bacterial action. It was tried with good effect against bacterial diseases of plants (Mitchell *et al.*, 1952). It has since been used in agriculture against bacterial diseases of fruits and vegetables, primarily against fire blight of apple and pear *(Erwinia amylovora)*, and has an important role in the protection of tobacco from wild fire (Ark and Alcorn, 1956). Its general application is limited by the high costs of its preparation and by its phytotoxicity.

The fungicidal action of streptomycin is exerted on *Oomycetes* fungi (*Pythium* and *Phytophthora* spp.) which are able to absorb the antibiotic (Vörös, 1965).

Streptomycin preparations generally contain 1.5% terramycin to prevent the development of resistance to streptomycin. Terramycin (oxytetracycline) belongs to the tetracyclic antibiotics, isolated by Finlay *et al.* (1950) from *Streptomyces rimosus* culture **(2).** It is an antibiotic with contact and systemic fungicidal action, and has been recommended alone for protection against *Puccinia triticina* and *Xanthomonas pruni* (Müller, 1969, Keil and Civerolo, 1979).



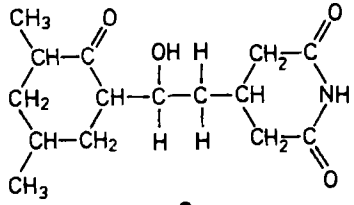
2

The primary effect of streptomycin is presumably the inhibition of protein synthesis (Anand and Davis, 1960; Hahn *et al.*, 1962; Venis, 1969). The antibiotic reduces bonding between aminoacyl-tRNA and the ribosomes, but does not affect

the bonding of messenger RNA. The antibiotic also blocks the normal growth of cells by causing a misreading of the genetic code from messenger RNA. Abnormal enzymes are thereby formed, and this phenomenon leads to the death of the cells (Davies *et al.*, 1965; Modolell and Davis, 1969).

The acute LD_{50} of streptomycin for rats is 9000 mg/kg. Streptomycin is one of the safest systemic bactericides; its wide clinical use has proved its low hazard to man.

The antibiotic cycloheximide was isolated in 1946 from *actinomycetes* fungi producing streptomycin (Leach *et al.*, 1947; Whiffen, 1948), and later was also produced from *Streptomyces noursei* fungi (Brown and Hazen, 1956). Naramycin A, isolated in Japan from *Streptomyces naranensis* fungi, is also cycloheximide (Okuda, 1959). Cycloheximide was first used in agriculture in 1948 under the name Actidione in the USA. Its chemical structure is 4{(2*R*)-2-[(1*S*,3*S*,5*S*)-(3,5-dimethyl-2-oxocyclohexyl)]-2-hydroxyethyl} piperidine-2,6-dion (**3**) (Kornfeld *et al.*, 1949; Johnson *et al.*, 1966).



3

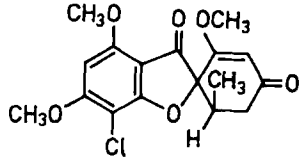
Cycloheximide in an antifungal antibiotic with eradicant properties. It has a very broad range of action, being toxic to yeast fungi, filamentous fungi, algae, even to higher plants and to animals, but it has hardly any effect on bacteria. Its toxicity to animals is rather species-specific; the acute oral LD_{50} for mice is 2.5 mg/kg.

Although it is very effective against many plant-pathogenic fungi, the agricultural use of cycloheximide is limited by its high toxicity to plants and mammals. It is therefore mainly used in those cases where it is effective at very low concentrations. In Japan and in the USA it is a commercial product. In a concentration of 2 mg/l it is used against onion *peronospora* and several diseases of turf and ornamentals (Ford *et al.*, 1985). As a growth regulator it is used for promoting the abscission of citrus fruits. *In vitro*, cycloheximide in a concentration of 1 mg/l inhibits the growth of *Merulius lacrymans* and other wood-damaging fungi (Ubrizsy and Vörös, 1963), which makes it promising as a fungicide in forest cultures.

The mode of action of cycloheximide has been studied for a long time. Past findings indicated that, like streptomycin, this antibiotic intervened in ribosomal protein synthesis, thereby inhibiting the growth of the fungi (Kerridge, 1958). Recent research has shown, however, that protein synthesis is not inhibited by the changes produced by cycloheximide in intermediate metabolic processes, such as the formation of amino acids, organic acids, adenosine triphosphate (ATP) and other nucleotides. Siegel and Sisler (1963) found that the incorporation of

^{14}C-labelled leucine into protein is inhibited at very low cycloheximide concentrations in the cell-free system of *Saccharomyces pastorianus*. According to the mechanism they suggest the antibiotic inhibits the transfer of amino acids from aminoacyl-tRNA to the protein chain (Siegel and Sisler, 1964a, 1964b, 1965). This mode of action of cycloheximide has been unequivocally verified by other workers (Wettstein *et al.*, 1964), not only in fungi but also in animals (Ennis and Lubin, 1964). However, the exact site of action has not yet been determined.

The antibiotic griseofulvin (**4**) was isolated by Oxford *et al.* (1939) from the metabolites of *Penicillium griseofulvum*. Later it was also isolated from the metabolites of many *Penicillium* spp. It had a property called the "curling factor" by Brian *et al.* (1946) because it causes the stunting and distortion of the germ tubes and hyphae of sensitive fungi in concentrations as low as 0.1–10 μg/ml. Its chemical structure is 7-chloro-4,6-dimethoxycoumaran-3-one-2-spiro-1′-(2′-methoxy-6′-methylcyclohex-2′-en-4′-one) (Grove *et al.*, 1951, 1952).



4

More than 300 derivatives of griseofulvin have been prepared and investigated, but none of these has surpassed the activity of the original molecule (Crosse *et al.*, 1964).

Griseofulvin is an antifungal antibiotic. It is fungistatic to *Basidiomycetes*, *Ascomycetes*, *Fungi imperfecti* and certain *Phycomycetes* spp. (Brian, 1949). *Botrytis alii* fungi, on which it has a specific action, are the most sensitive. On the other hand, yeast fungi and bacteria, as well as *Oomycetes* from the class of *Phycomycetes*, are not sensitive to griseofulvin even at concentrations of 100 μg/ml.

Griseofulvin has a systemic action when sprayed (Brian *et al.*, 1951; Crowdy *et al.*, 1956), but the plant absorbs it more rapidly through the roots; thus better results can be obtained through root treatment than through foliage spraying, although this antibiotic is degraded at a much higher rate in the soil than on the leaves. In the low concentration used, griseofulvin is not toxic to plants, but in higher concentrations inhibits chlorophyll formation (Wright, 1951).

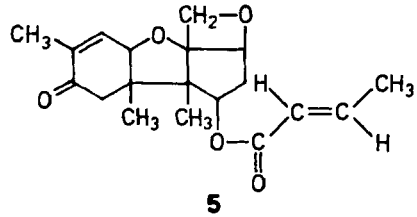
It was first used for plant protection in 1957 against powdery mildew fungi (Dekker and Van der Hoek–Scheuer, 1964) *Botrytis* and *Cercospora* spp. Because of very high manufacturing costs, it has not been widely used, but it is still useful in some specific instances. For example, griseofulvin has been used in Japan since 1959 against the *fusarium* wilt of watermelon and rot diseases of apple blossom (Misato, 1976).

Brian (1949) presumed that griseofulvin affected the morphogenesis of the chitinous cell walls in fungi, and thus explained the nonsensitivity of fungi with cellulose cell walls (*Oomycetes*, yeast fungi) and of bacteria to this antibiotic.

Later, however, more and more data indicated that sensitivity to griseofulvin does not depend on the chitin content, but on the quantity of the antibiotic that the organism can take up (Evelight and Knight, 1965). Nonsensitive yeast fungi and bacteria do not bind a substantial quantity of griseofulvin. Although fungi of lower senstivity *(Neurospora crassa, Aspergillus niger)* take up a considerable quantity of the antibiotic from the surrounding aqueous solution, very sensitive *Dermatophytes (Microsporum gypseum, Trichophyton spp.)* are able to take up and accumulate within the cell concentrations of the antibiotica hundred times that of the medium (El-Nakeeb and Lampen, 1964). It seems that griseofulvin is bound to nucleic acids, preventing their further synthesis (McNall, 1960). The incorporation of the ^{14}C-labelled bases uridine and thymidine into nucleic acids was considerably reduced by griseofulvin (El-Nakeeb and Lampen, 1965a, b; El-Nakeeb *et al.*, 1965). It seems likely that action on cell division and not on chitin synthesis, is the primary action of the antibiotic (Crackower, 1972).

Griseofulvin is not toxic to mammals; the acute oral LD_{50} for rats is 400 mg/kg. Even a daily dose of 2000 mg/kg administered intraperitoneally did not cause patricular ill effects in rats. According to recent results, however, griseofulvin is teratogenic, embryotoxic and carcinogenic (Melnikova, 1971), and since it has a long persistence on fruits treated with it, its application in orchards is not recommended. According to the investigations of Anderson (1966), griseofulvin caused considerable anatomical changes in the cuticle of the larvae of *Aedes atropalpus*.

The antibiotic trichothecin has been isolated from cultures of *Trichothecium roseum*, which belongs to the group of *Fungi inperfecti* (Freeman and Morrison, 1948). It has a very potent antifungal action, but is biologically inactive against bacteria (Freeman and Morrison, 1949). This compound is the isocrotonyl ester of trichothecolone (2a,3,4,4a,4b,8a-hexahydro-4-hydroxy-4a,4b,7-trimethyl-1H-oxetho-[3',2',1,5]-cyclopenta-[1,2b]-benzofuran-6-[5H]-one) **(5)** (Freeman *et al.*, 1959; Fishman *et al.*, 1959).

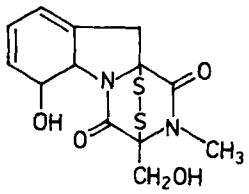


5

Trichothecin is effective against several fungi, for example root rot of cereals *(Helminthosporium sativum)*, loose smut of wheat *(Ustilago tritici)*, diseases of sour cherry and cherry (Vörös, 1955), fusarium wilt of *Pinaceae* (Belimova and Lopatin, 1963) and powdery mildew of tobacco (Manucharjan, 1964). Its most promising practical applications are the control *Verticillium* wilt of cotton and of the fusarium diseases of field crops (Askarova and Joffe, 1962; Bunina, 1960; 1963).

Fungi maintained on media containing sublethal concentrations of trichothecin developed resistance to this fungicide. It is assumed that a trichothecinase enzyme is formed, which inactivates the antibiotic (Sidorova, 1967). From the point of view of environmental protection, trichothecin has no deleterious effect on predator mites (*Phytoseiulus persimilis*). In a concentration of 0.0001%, it enhances photosynthesis, but at 0.001% it has an inhibiting effect. It has no residual effect (Petrukhina *et al.* 1975).

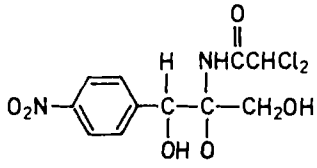
Gliotoxin (**6**) is present in the metabolites of many fungi, such as *Trichoderma viride*, *Gliocladium fibriatum*, *Aspergillus fumigatus* an several *Penicillium* spp. (Brian and Hemming, 1946). It is a fairly stable compound of composition, 2,3,5a,6-tetrahydro-6-hydroxy-3-hydroxymethyl-2-methyl-10H-3,10a-epidithiopyrazino-[1,2-a]-indol-1,4-dion (Bell *et al.*, 1958).



6

The compound is susceptible to oxidation and is rapidly inactivated by heat. This instability and biological activity of gliotoxin are associated with the disulfide bridge. Although it has a strong antifungal action, inhibiting the growth of *Fusarium caeruleum* spores at a concentration as low 2 mg/kg because of its instability gliotoxin is only of theoretical importance. Its mechanism of action is based on its complex-forming property.

The antibacterial antibiotic chloramphenicol (**7**), 2-dichloroacetamido-1-*p*-nitrophenylpropanediol-(1,3), has been used in agriculture since 1964. It has been isolated from *Streptomyces venezuelae* culture, and is of great importance in human therapy. Today it is manufactured on an industrial scale. The active *l*-form, isolated from the mixture of *l* and *d*-isomers, is used as a drug while the mixture is used in agriculture. The antibiotic is taken up by the roots of the plant and translocated into the leaves (Crowdy *et al.*, 1955). Its agricultural use is of minor importance, although in Japan it is used against the bacterial leaf blight of rice in a concentration of 200 mg/kg.

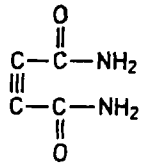


7

Chloramphenicol inhibits the formation of peptide bonds in bacteria and mitochondria (Hahn and Wolfe, 1962).

The antibiotic cellocidin was discovered by Japanese researchers. It was isolated by Suzuki *et al.*, (1958) from *Streptomyces chibaensis* culture.

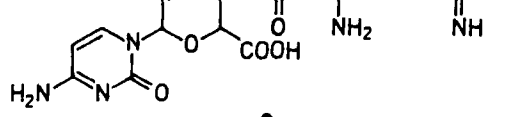
Compared to other anibiotics its composition is very simple — acetylene dicarbonic acid diamide (**8**) (Suzuki and Okuma, 1958), and it can be easily synthesised from fumaric acid or from butene diol.



8

Cellocidin is an antibacterial antibiotic. In concentrations of 100–200 mg/kg it has a preventive action against bacterial rice disease caused by *Hypochnus sasakii*, which causes high losses at the high atmospheric humidity prevailing in Japan and in Asia in general. Administered intravenously, cellocidin is very toxic to animals (LD_{50} for mice: 11 mg/kg), but it is less toxic when administered orally or through the skin; oral LD_{50} is about 100 mg/kg, dermal LD_{50} 667 mg/kg. It is moderately toxic to fish. Cellocidin inhibits the function the α-ketoglutarate-succinate system (Okimoto and Misato, 1963a, 1963b). Cellocidin has been used in Japan in rice paddies, but it is scarcely used today, presumably because of its toxic effect.

Blasticidin S is an antibiotic of pyrimidine type, discovered in 1955 in the metabolites of *Streptomyces griseochromogenes* (Fukunaga *et al.*, 1955). Blasticidin S, soluble in water, appears in the form of white needles. Its structure was elucidated by Yonehara and Otake (1966): S-[4-[3-amino-5-[(amino-imino-methyl)-methyl-amino]-1-oxopentyl]-amino]-1-[4-amino-2-oxo-1(2H)-pyrimidinyl]-1,2,3,4-tetradeoxy-β-D-*eritro*hex-2-ene pyranuronic acid (**9**).



9

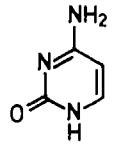
Blasticidin S is a contact fungicide and bactericide with a highly selective action (Takeuchi *et al.*, 1958; Huang *et al.*, 1964b). Absorbed through the roots, it is translocated into the leaves, but when sprayed on the foliage, it has at the most a locosystemic effect. Its highest efficiency was shown against rice blast, being effective in doses as low as 10–20 mg/l. The growth-inhibiting preventive and eradicant action of blasticidin S on the mycelium of *Piricularia oryzae* is 10–100 times stronger than that of organic mercury compounds.

The activity of blasticidin S involves primarily the inhibition of fungal protein synthesis. In the presence of blasticidin S, the incorporation of amino acids into protein is reduced by 80–90% (Gottlieb *et al.*, 1955: Misato *et al.*, 1961; Huang *et al.*, 1964a). It was found that blasticidin S reduces the formation of aminoacyl-tRNA. Hence the next step, the incorporation of the amino acid, is also blocked. The site of primary action is not yet known.

High concentrations of the active substance or frequent treatment cause necrotic spots on leaves of the rice plant, particularly at high temperatures and high humidity (Hashimoto *et al.*, 1963). Tomato, tobacco and bean are also sensitive to blasticidin treatment. Thus, its use is somewhat limited by its phytotoxicity. Of its salts, the monobenzyl aminobenzene sulfonate is the least phytotoxic (Asakawa *et al.*, 1963). In commercial preparations this salt is the active substance. The phytotoxicity of blasticidin S can be reduced with detoxin. Detoxin, the selective antagonist of blasticidin S, stops the inhibitive action of the antibiotic on *Bacillus cereus* but not on *Piricularia oryzae*. Thus a combination of blasticidin S and detoxin remains an excellent fungicide against rice blast, while its toxicity is considerably to other organisms (Yonehara *et al.*, 1968).

Blasticidin S is rather toxic to mammals, the oral LD_{50} for mice being 39.5 mg/kg. It is toxic to fish in concentrations as low as 0.5 mg/kg. It irritates the eye. When used as a dust, it can produce conjunctivitis, but this can be avoided by using it as an aqueous spray. The eye-irritating effect of blasticidin preparations can be reduced by the addition of calcium salts of aromatic carboxylic acids or inorganic calcium salts (Sugimoto *et al.*, 1970a,b).

Blasticidin S is a fairly stable compound, but when applied on the plants it is rapidly decomposed or inactivated by sunlight and microorganisms. The main photodecomposition product is cytosin **(10)**. Cytomycin **(11)** and other unidentified products were found. Within the plant enzymatic metabolism occurs, the products of which are cytomycin and deaminohydroxy blasticidin S **(12)**, while microorganisms decompose the antibiotic to cytomycin, deaminohydroxy blasticidin S and deaminohydroxy cytomicin **(13)**.



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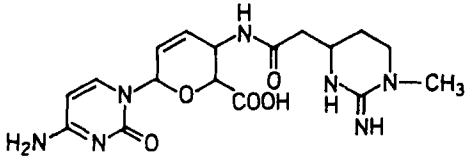

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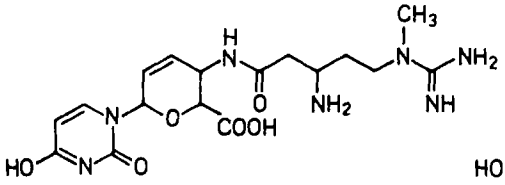

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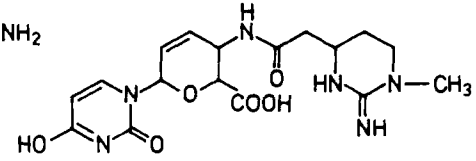


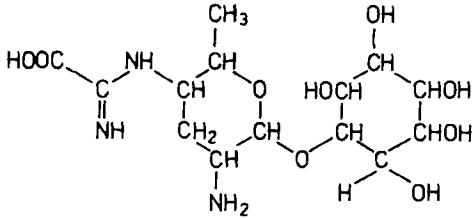
13

Blasticidin S was the first antibiotic used in large quantities for agricultural purposes. Although it is beginning to lose its importance today, there being another antibiotic, kasugamycin, with better properties, in 1973 almost 5000 tons were used for the protection of rice (Misato, 1976).

Several fungi are resistant to blasticidin S, but *Piricularia oryzae* can be made resistant only *in vitro*. By gradual culturing in a medium containing blasticidin S, clones have been prepared which tolerate concentrations as high as 1000–4000 mg/kg of the antibiotic (Nakamura and Sakurai, 1968). At the same time, no strains resistant or tolerant to blasticidine S have yet been found in nature, although it has already been used for ten years in rice plantations. With regard to the cause of resistance, it has been established that in cell-free systems of *Piricularia oryzae*, in both sensitive and resistant clones, blasticidin S inhibits the incorporation of ^{14}C-labelled amino acids into protein, while the effect was different in intact cell systems. In this case, resistance can presumably attributed to a reduced permeability of tolerant clones (Huang *et al.*, 1964b). In experiments carried out in a greenhouse on rice plants infected with tolerant and sensitive clones, the tolerant clones showed the same sensitivity to the antibiotic as the sensitive clones. The sensitivity of *Piricularia oryzae* is thus completely different *in vitro* and *in vivo* (Uesugi *et al.*, 1969). The nonsensitivity to blasticidin S of other fungus species (e.g. *Pellicularia sasakii*) can be explained by different pathways for their protein synthesis.

Blasticidin S inhibits the multiplication of tobacco mosaic virus (Hirai *et al.*, 1966), and reduces the rice stripe virus-transferring ability of *Laodelphax striatellus* vector (Hirai *et al.*, 1968), thus showing also a certain antiviral effect.

The antibiotic presently used in the largest quantity in agriculture is kasugamycin **(14)**. According to data for 1973, nearly 40 000 tons of kasugamycin were used in Japan against rice blast. This antibiotic was discovered by Umezawa in the metabolites of *Streptomyces kasugaensis* culture (Umezawa *et al.*, 1965). Its structure was found to be 5-amino-2-methyl-6-(2,3,4,5,6-pentahydroxycyclohexyloxy)-pyran-3-yl-amino-α-iminoacetic acid (Suhara *et al.*, 1966; Idekawa *et al.*, 1966).



14

The biological action of kasugamycin is very selective. In a concentration of 20 mg/kg it has an antifungal effect against *Piricularia oryzae*, which causes rice blast (Ishiyama *et al.*, 1965). It is also effective against halo blight of bean, and several bacteria such as *Pseudomonas* spp. Kasugamycin is active against *Piricularia oryzae* only in acidic media (pH = 5), being almost ineffective in neutral media. The leaves

of rice are slightly acidic, and this explains the high selectivity against rice blast. Against bacteria, the antibiotic is more effective in neutral than in acidic media (Hamada *et al.*, 1965).

In its other properties, kasugamycin is far superior to blasticidin S. It is not toxic to rice, but slight injuries have been observed on other plants (bean, soybean, vine, lemon, etc.). It is not toxic to mammals, the acute oral LD_{50} for rats is 40 000 mg/kg. A daily dose of 1000 mg for three months caused no abnormalities in rats. It is not toxic to fish. All of these favourable properties from the standpoint of environmental protection make possible its safe use for the protection of rice, even when sprayed by airplane. Treatment of rice seed with kasugamycin protects against rice blast for about a month after showing.

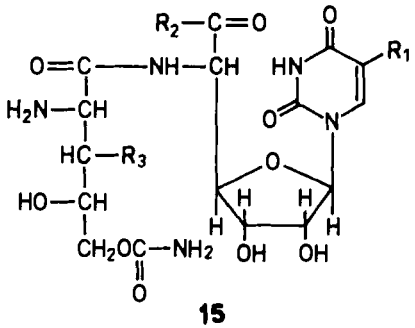
The mode of action of kasugamycin is similar to that of blasticidin S. It inhibits protein synthesis in fungi and bacteria. It inhibits binding of the aminoacyl-tRNA complex to the ribosome (Tanaka *et al.*, 1966), but does not disturb the synthesis of nucleic acids. The inhibitory effect is considerably lower in the liver tissue of rats. The selectivity of toxicity may be due to the particular sensitivity to kasugamycin of the ribosomes of each type of organism. This may also explain the relatively rapid development of resistance to kasugamycin.

Resistant pathogens tolerant to even 10 000 mg/kg of the antibiotic are easily isolated from a medium containing kasugamycin (Ohmuri, 1967). These tolerant clones were compared to sensitive clones on rice plants with respect to pathogenicity and drug sensitivity. Infection occurred with both clones, but the efficiency of kasugamycin against the resistant clones was considerably lower. When the ribosome fraction was extracted from clones sensitive to *Piricularia oryzae*, the reaction system was always inhibited by 20 mg/kg of kasugamycin, whether it contained sensitive or resistant aminoacyl-tRNA.

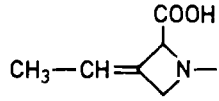
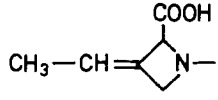
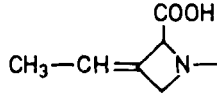
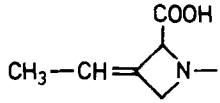
Since 1968, the development of resistant *Piricularia oryzae* strains has increased in Japan with the increasing use of kasugamycin in rice plantations. In one of the territories, 97% of the pathogens became resistant in 1972, so that in 1973 no kasugamycin was used for protection. Since that time the number of resistant strains has diminished considerably (Misato, 1976).

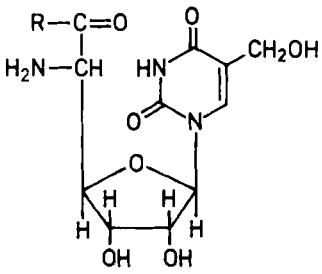
Polyoxin antibiotics were discovered in Japan in cultures of *Streptomyces cacaoi var. asoensis* (Suzuki *et al.*, 1965). They are a mixture of related components with similar physical and chemical properties. The structure of polyoxins **(15, 16)** was elucidated by Isono *et al.* (1969). That, for example, of polyoxin B was found to be 5-(2-amino-5-O-carbamoyl-2-deoxy-L-xyloamido)-5-deoxy-l-(1,2,3,4-tetrahydro-5-hydroxymethyl-2,4-dioxopyrimidinyl)-β-D-allofuranuronic acid.

Up to the present, 12 components have been isolated which differ substantially with respect to the various pathogens affected (Isono *et al.*, 1967). Of the derivatives A-L, polyoxins C and I **(16)**, with structures differing from the others, are less active against sheath blight of rice *(Pellicularia sasakii)*, while polyoxins B and L are effective against pathogens causing apple and pear scab, in addition to sheath blight. Polyoxin A protects against brown spot of rice *(Helminthosporium oryzae)*. Recently an excellent prophylactic and curative effect of polyoxins B and D has

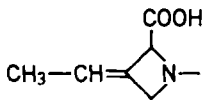


15

	R_1	R_2	R_3
Polyoxin A	$-CH_2OH$		$-OH$
Polyoxin B	$-CH_2OH$	$-OH$	$-OH$
Polyoxin D	$-COOH$	$-OH$	$-OH$
Polyoxin E	$-COOH$	$-OH$	$-H$
Polyoxin F	$-COOH$		$-OH$
Polyoxin G	$-CH_2OH$	$-OH$	$-H$
Polyoxin H	$-CH_3$		$-OH$
Polyoxin J	$-CH_3$	$-OH$	$-OH$
Polyoxin K	$-H$		$-OH$
Polyoxin L	$-H$	$-OH$	$-OH$



16

	R
Polyoxin C	$-OH$
Polyoxin I	

been observed in the protection against blackspot caused by *Alternaria brassicae* (Tewari and Skoropad, 1979). Their effective concentration is 50–100 mg/kg.

Polyoxins have a systemic action (Sasaki *et al.*, 1968a). Their mode of action has been elucidated by Japanese researcher by extensive, systematic work. Sasaki *et al.* (1968b), investigating the derivative polyoxin D, established that the antibiotic does not inhibit endogenous or exogenous respiration, the incorporation of ^{14}C-labelled amino acids into protein, or the incorporation of [^{32}P] phosphate into nucleic acids, but inhibits the incorporation of ^{14}C-labelled glucosamine into the insoluble fractions. Endo and Misato (1969) showed that polyoxin D is the antimetabolite of UDP-N-acetyl glucosamine, inhibiting competitively N-acetyl glucosamine transfer from UDP-N-acetyl glucosamine into the chitin of cell walls. As a result, UDP-N-acetyl glucosamine in the treated fungal mycelia accumulates to 60–150% over the level in the control. Chitin synthetase isolated from *Piricularia oryzae* fungi was completely inhibited by the addition of as low a concentration as 0.1 mg/kg of the antibiotic (Ohata *et al.*, 1970; Endo *et al.*, 1970). This action of polyoxin antibiotics is also indicated by the structural similarity of polyoxins and the uridine part of UDP-N-acetyl glucosamine (Hori *et al.*, 1974). Polyoxin B inhibits chitin synthetase, that is, it blocks the polymerisation of amino sugars.

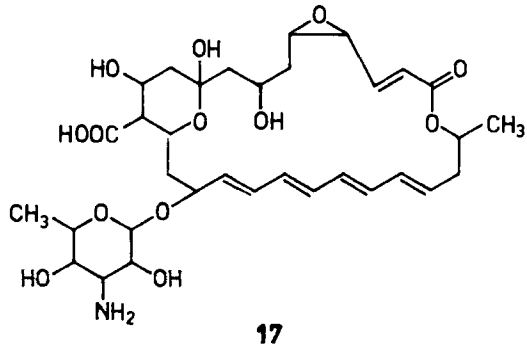
Polyoxins have a low toxicity to mammals. In oral doses of 15 g/kg, or by intravenous administration of 800 mg/kg, they are not hazardous to mice, nor are they toxic to fish. They are not phytotoxic—rice plants are unaffected even by treatment with 800 mg/l of polyoxin. In Japan, polyoxin D is a commercial product for the control of sheath blight of rice.

Several antibiotics belong to the group of polyene macrolides, the members of which are characterised by a polyene chromophore group in the macrocyclic lactone ring. The single members are thus closely related compounds with respect to both chemical structure and physiological properties. All of the antibiotics of this group are metabolic products of *Streptomycetes* spp. Their antifungal effect is particularly strong against mycelial fungi and yeasts, but they also inhibit certain processes in algae, protozoa, insects and mammals. On the other hand, they are ineffective against blue-green algae and several fungi. Their action is fungistatic rather than fungicidal. Antibiotics belonging into this group are classified according to the number of conjugated double bonds they contain in four subgroups: tetraenes, pentaenes, hexaenes and heptaenes. Their growth-depressing effect increases from tetraenes to heptaenes (Egorenkova, 1964).

About 70 polyene macrolide antibiotics are known at present.

The best known of these, also used in agriculture, is pimaricin, isolated from *Streptomyces natalensis* culture. The chemical composition of pimaricin is (8*E*, 14*E*, 16*E*, 18*E*, 20*E*)-(1*S*, 3*R*, 5*S*, 7*S*, 12*R*, 24*R*, 25*S*, 26*R*)-22-(3-amino-3,6-dideoxy-β-D-mannopyranosyloxy)-1,3,26-trihydroxy-12-methyl-10-oxo-6,11,28-trioxatricyclo [22.3.1.$0^{5,7}$]octacosa-8,14,16,18,20-pentaene-25-carboxylic acid (**17**) (Golding *et al.*, 1966; Meyer, 1968). Pimaricin is prepared by the fermentation of *S. natalensis* and *S. chattanoogensis*, and is used in the form of its water-soluble salt. Pimaricin is used as a fungicide to control diseases of bulbs, particularly basal rot of daffodils,

preferably combined with hot-water treatment of the bulbs. The acute oral LD_{50} is 2.73 to 4.67 g/kg for rats (Levinskas *et al.*, 1966).



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Aureofungin belongs to the group of polyene antibiotics. It is a wide-spectrum fungicide with systemic action, and is translocated both in the xylem and the phloem. Although it is relatively stable in ultraviolet light compared to other polyene antibiotics, its use is limited by its phytotoxicity (Kluge *et al.*, 1975; Jacob and Schluttig, 1975). These antibiotics suppress the growth of organisms, cause morphological changes in fungal cells and inhibit exogenous aerobic and anaerobic respiration (Gottlieb *et al.*, 1961). Observations indicate that polyene macrolides change the permeability of the cell membrane (Shockman and Lampen, 1962), and that reactions in conjunction with sterols play the main part in the changes of the protoplasmic membranes. Gottlieb *et al.* (1958, 1960, 1961) and other authors found that the mode of action of polyene macrolides involves the binding of these antibiotics to sterol-containing membranes, forming a sterol-polyene complex, which changes the permeability of the cell membranes such that essential cell metabolites can permeate the membrane out of the cell, thereby inhibiting respiration and the synthesis of cell components so that growth stops. Thus, sensitivity to polyene macrolides depends on the sterol content of the organism. Bacteria are not sensitive to polyenes because their membranes generally do not contain sterols, while the membranes of most of the fungi and other organisms such as algae and protozoa do contain sterols, making them sensitive these antibiotics (Lampen and Arnow, 1961; Ghosh and Chatterjee, 1962).

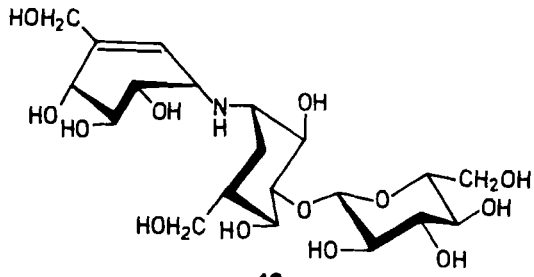
Polyene antibiotics are not phytotoxic. In spite of this they are not widely used, mainly because of their instability. After application they are rapidly degraded by oxidation on the plant surfaces. Although these antibiotics have a systemic action, when absorbed through the roots they lose their antifungal activity in the plant, probably because they are bound by certain plant components and are thus inactivated (Oort and Dekker 1960).

Basidiomycetes fungi form polyenes and polyines, which have an antibacterial effect in addition to an antifungal effect. These antibiotics are only of theoretical importance, however, since their high instability makes them unsuitable for

practical purposes. The crystalline substance mycomycin **(18)**, an example of this group, has a half-life of only three hours at 22°C.

$$HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2{-}COOH$$

The antibitotic validamycin A has been used in Japan since 1972 in rice cultures. Validamycins, glucose-containing basic compounds with closely related structures, have been isolated from the metabolites of the fungus *Streptomyces hygroscopicus var. Limoneous* (Iwasa *et al.*, 1971a, 1971b). So far, six members, validamycins A, B, C, D, E and F, have been identified. The composition of validamycin A **(19)** is L-(1,3,4/2,6)-2,3-dihydroxy-6-hydroxymethyl-4-[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-hydroxymethylcyclohex-2-enylamino]cyclohexylβ-D-glucopyranoside (Horii and Kameda, 1972). The other validamycins differ from A with respect to the type of glucoside and to the location of the bond (Horii *et al.*, 1972).



19

All of these compounds are readily soluble in water.

Validamycins have a very selective fungistatic action. *Basidiomycetes* spp. are most sensitive to them. Their main field of application is the control of sheath blight of rice and of the damping-off of vegetable seedlings caused by *Rhizoctonia solani* (Bakkeren *et al.*, 1977). These antibiotics do not actually inhibit the growth of *Pellicullaria sasakii* fungi, but they cause abnormal branching at the hyphal tips (Nish and Nizushima, 1974).

Validamycins are not phytotoxic, nor are they toxic to mammals; the acute LD_{50} for rats is higher than 20 000 mg/kg. In three-moth toxicity tests no pathological effects were produced in any of the organs of mice or rats (Onishi and Miyaji, 1973). These antibiotics are not hazardous to fish or to bees or other beneficial insects. In 1973, 2 500 tons of validamycin A antibiotic preparations were used in rice cultures.

Meanwhile, further antibiotics have been isolated, among them some potential fungicides are worth mentioning.

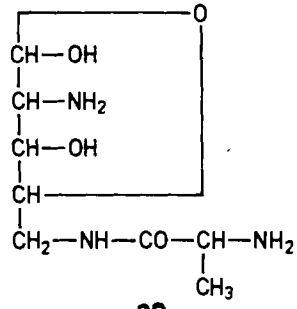
The antifungal antibiotics mucidine was discovered in 1969 (Musilek *et al.*, 1969) in the metabolites of the fungus *Oudemansiella mucide*, which belongs to the class of *Basidiomycetes*. Mucidine inhibits the growth of fungi, producing characteristic morphological changes, while it has no effect on bacteria (Šašek and Musilek, 1974a, 1974b). The primary site of action of the antibiotic is the specific inhibition of mitochondrial electron transport between cytochromes b and c (Šubik *et. al.*,

1974a). A similar mechanism has been found in the hepar mithochodria of rat livers (Šubik *et al.*, 1974b). Mucidine is a potential fungicide. It is effective in a concentration of 200–500 μg/ml primarily against filamentous fungi, *Mucor* and *Rhisopus* spp. being most sensitive.

Aabomycin, isolated from Streptomyces 325–17 strain in Japan (Aizawa *et al.*, 1969), forms white needle-like crystals. It is effective against several fungi, primarily *Piricularia oryzae* and *Trichophyton* spp. It has no antibacterial effect. *Piricularia oryzae* is sensitive to concentrations as low as 20 mg/kg. Aabomycin is effective also against *Piricularia oryzae* strains that are resistant to blasticidin and kasugamycin. It is not phytotoxic even in a concentration of 1000 mg/kg and is therefore a promising selective fungicide against rice blast. It is almost nontoxic to mammals (Yamaguchi *et al.*, 1969).

Ezomycin, effective against *Sclerotinia* and *Botrytis* spp., is obtained from *Streptomyces* cultures. In Japan it has been used against the stem rot of kidney bean (Sakata *et al.*, 1974).

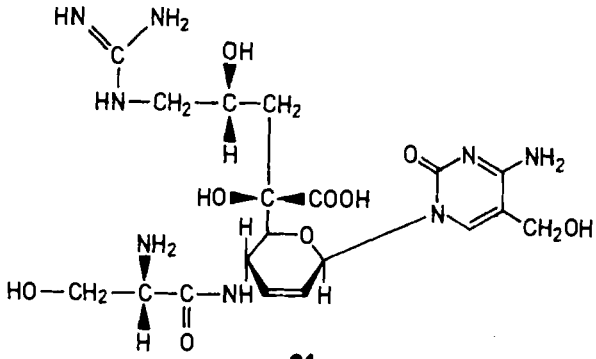
The antibiotic prumycin, a metabolic of *Streptomyces* strain No. F-1028, is also a potential fungicide, its main range of action involving *Botrytis*, *Sclerotinia* and *Sphaerotheca* spp. It is not toxic to mammals (Hata *et al.*, 1971). The structure of prumycin has been determined by Omura *et al.* (1972) to be a 2,5-diamino-2,5-dideoxypentose-5D-alanyl derivative **(20)**.



20

A new antibiotic has been reported by Kusaka *et al.* (1979): TF-138. Its chemical composition is: (2*R*,4*R*)-2-[(2*R*,5*S*,6*S*)-2-(4-amino-1,2-dihydro-5-hydroxymethyl-2-oxopyrimidin-1-yl)-5,6-dihydro-5-L-serylamino-2H-pyran-6-yl]-5-guanidino-2,4-dihydroxyvaleric acid **(21)**.

TF-138 is obtained from the cultured broth of *Streptoverticillium rimofaciens*, and is a new nucleoside antibiotic, which has 5-(hydroxymethyl) cytosine as its chromophore. The acute and subacute toxicities to rats and fish are low. TF-138 shows weak antimicrobial properties against phytopathogenic fungi, yeasts and bacteria on agar plates. However, it is toxic to 8 genera of powdery mildew fungi at



21

40–80 mg/l when applied to the foliage of cucumber, rose, apple, grape, barley, tobacco, green peppers, oak and mulberry. No phytotoxicity was observed in any plants. It is also effective against benomyl-resistant strains of *Sphaerotheca fulgina*.

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6. Herbicides

6.1 Inorganic herbicides

Chemical weed control in agriculture began in the 1880s. The first preparations used were exclusively inorganic compounds. The applicability of nitrophenols, organic active substances, as herbicides was first reported in 1935 (Truffaut and Pastac). Since that time inorganic herbicides have gradually lost their importance, although some are still widely used, mainly for total weed control.

The first successful weed control with chemicals was reported by Bonnet in 1896, who used 6% copper sulfate solution to kill charlock *(Sinapis arvensis)* selectively in cereals. The process was developed further by Bolley (1908) and Schultz (1909).

Researchers experimented with other salts of caustic action, such as iron(II) sulfate and copper nitrate, and with sulfuric acid, and reported successful weed control.

It was already recognised by the turn of the century that high doses of fertilisers, such as Chile salpetre ($NaNO_3$), ammonium sulfate, calcium cyanamide and kainite (KCl, $MgSO_4 \cdot 3H_2O$) exhibit herbicidal action. Remy and Vasters (1914) were the first to observe the phenomenon of synergism in combined preparations. They established that 10% of kainite mixed with calcium cyanamide was more active than double doses of the single components used alone. A similar enhancement of action was observed by Bolley (1901) in the case of mixtures of copper sulfate and sodium arsenite.

The use of sulfuric acid began similarly in the 1900s in France, and shortly afterwards in Germany (Rabaté, 1911; Gelpke, 1914). The selective application of sulfuric acid and sulfates has been described by Morettini (1915) and Korsmo (1930).

The phytotoxic action of boron compounds was recognised as early as the end of the last century (Peligot, 1876), but they were not applied as total and selective herbicides until the 1920s (Crafts and Raynor, 1936).

The phytotoxic action of chlorates was also recognised at the turn of the century. Chlorates were introduced into agriculture on the basis of the experiments of Aslander (1926, 1928) and later Crafts (1935). A review on the application of chlorates and borates can be found in the reports of Robbins *et al.* (1952) and of Long (1934).

The herbicidal effect of high concentrations of ammonium thiocyanate was first described by Harvey (1931a), and its selective applicability to cereals by Singh and Das (1939).

The herbicidal properties of ammonium sulfamate were described by Cupery and Tanberg (1942).

6.1.1 Sulfuric acid and its derivatives

Sulfuric acid is used even today for weed killing in the USA, UK and The Netherlands because of its low price. Concentrated sulfuric acid is a total weed killer, while dilute (3–4%) sulfuric acid can be applied selectively in vegetables (onion, cabbage). Sulfuric acid has the disadvantage of being highly corrosive. It is a contact herbicide, rapidly penetrating the leaf tissues and destroying the protoplasm and the chloroplast of cells (Aslander, 1927). According to Korsmo (1930) the primary action of sulfuric acid is its dehydrating effect, irreversibly disturbing the water-retaining capacity of the cells.

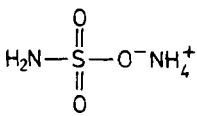
Ammonium sulfate is a compound with weak herbicidal action. Applied at high rates on the leaves of dicotyledons it has a contact action. Its phytotoxic action can be attributed mainly to the ammonium ions. Ammonia rapidly penetrates to the acid-buffered cell sap, making it alkaline, thus rapidly destroying the cells (Harvey, 1911). Bokorny (1915) assumed that ammonia formed complexes with cell proteins.

Ferrosulfate heptahydrate ($FeSO_4 \cdot 7H_2O$) is another compound with weak herbicidal action. Applied as an aqueous solution at rates of 6–12 kg/ha, it has been used for the postemergence control of dicotyledonous weeds in cereals. At rates of 100 kg/ha (in the form of a 10% aqueous solution) it can be used for the control of moss in turf.

The salts of heavy metals, namely iron and copper salts, are general enzyme poisons and protein coagulants. Iron sulfate causes plasmolysis, though Aberg (1948), on killing *Sinapis* plants with 5% iron sulfate solution, found no plasmolysis in the plants or damage to the chloroplasts.

Copper sulfate pentahydrate ($CuSO_4 \cdot 7H_2O$) is used today only as an algicide in fish ponds and in industrial water basins at 1 ppm concentration.

Of the sulfuric acid derivatives the most efficient herbicide is ammonium sulfamate, AMS, introduced in 1945 in the USA.



Ammonium sulfamate may be prepared by the reaction of sulfur trioxide with liquid ammonia, or by the neutralisation of sulfamic acid (made by the reaction of fuming sulfuric acid with urea) with ammonia (Cupery and Tanberg, 1942; Sasaki *et al.*, 1968).

Crystalline ammonium sulfamate is a stable, water-soluble compound. Its aqueous solution is slowly hydrolysed into ammonium hydrogen sulfate.

Ammonium sulfamate is a contact herbicide with systemic action. It is used particularly for the control of woody weeds as a 6–7.5% aqueous solution, and for the treatment of basal bark and cut stump in the form of a 40% aqueous solution (Crafts, 1945).

Its acute oral LD_{50} for rats is 3900 mg/kg (Ambrose, 1943; Lehman, 1951). It is not toxic to forest game (deer), and is thus not hazardous for the clearing of forest brush (Haugen, 1953).

Applied at a rate of 1.5 kg/100 m^2, ammonium sulfamate disappears in 6–8 weeks from the soil under humid conditions. Degradation proceeds by the microbial route (De France, 1943; Jensen, 1963).

Ammonium sulfamate prolongs the dormant stage of plants to the extent that the starch and sugar reserves of the woody plants are exhausted and the plants wilt (Robbins *et al.*, 1952). Regrettably, the biochemical process producing dormancy is not yet known.

6.1.2 Cyanates, thiocyanates and cyanamides

Potassium cyanate (KOCN) is a herbicidal compound for the selective control of broad-leaved weeds in monocotyledonous crops, such as onion (Hedlin, 1948). It is readily soluble in water (65 g/100 ml at 10°C). Its usual rate of application is 6–14 kg/ha in the form of a 1–3% aqueous solution. Potassium cyanate is rapidly degraded in the soil. Its acute oral LD_{50} for rats is 850 mg/kg.

All of the water-soluble thiocyanates are very phytotoxic compounds, ammonium thiocyanate (NH_4SCN) being the most active. According to Harvey (1931b) and Landen (1934) ammonium thiocyanate is a protoplasm poison, paralysing certain enzymes of the plant, (e.g. catalase) and coagulating cell proteins.

Ranjau and Kaur (1954) found that a 2% aqueous solution of ammonium thiocyanate reduces the sprouting and respiration of potato tubers.

Ammonium thiocyanate by itself is not used as a herbicide, although at a rate of 80–100 kg/ha it is suitable for total weed killing. At the same rates, it can be used for defoliation and for temporary soil sterilisation. It is rapidly absorbed both by the roots and the leaves of plants and is translocated.

In agriculture ammonium thiocyanate is used in combination with aminotriazole (see triazoles), because it synergises the herbicidal action of aminotriazole.

Calcium cyanamide (CaNCN) has been used in agriculture since the beginning of the century as a fertiliser and herbicide (Remy and Vasters, 1914). In preemergence application at rates of 140–150 kg/ha it is effective for the control of mono- and dicotyledonous weeds. It is also absorbed through the leaves and can thus be used as a foliage herbicide. It is generally used in the form of granules for the preemergence treatment of cereals, potato and sugar beet. In onions it is used postemergence (Hedlin, 1948), and it has also been recommended for postemergence weed control in maize (Gould *et al.*, 1950).

Calcium cyanamide is slightly soluble in water; precipitation or irrigation is needed for the exertion of its action. It can also be used for the defoliation of cotton and other plants, alone or mixed with Na_2SiF_6.

In the soil calcium cyanamide slowly decomposes into calcium carbonate and ammonia:

$$CaNCN + 3H_2O = CaCO_3 + 2NH_3.$$

The biochemical mode of action of calcium cyanamide is unknown. After treatment with calcium cyanamide the cell substance becomes granulated, which indicates the precipitation of proteins.

The acute oral LD_{50} of calcium cyanamide for rats is 1000 mg/kg.

Sodium cyanamide is hygroscopic and is hence used as a defoliant and herbicide in arid regions (Hedlin, 1948).

6.1.3 Chlorides and chlorates

Kainite ($KCl \cdot MgSO_4$) previously used occasionally for the control of cruciferous weeds, is no longer used because of its weak action.

In the USA sodium chloride is used in a restricted measure for postemergence treatment in table beet, and ammonium chloride (NH_4Cl) is included as a component of cotton desiccation formulations.

Calcium chloride ($CaCl_2$) and magnesium chloride ($MgCl_2 \cdot 6H_2O$) are sporadically used in the USA at rates of several hundred kg/ha as total weed killers for the sterilisation of soil on industrial sites, on the banks of highways and other non-crop areas.

Two salts of chloric acid, sodium chlorate ($NaClO_3$) and magnesium chlorate ($Mg(ClO_3)_2 \cdot 6H_2O$), have gained use in agriculture.

Sodium chlorate is readily soluble in water (790 g/l at 0°C) and is therefore applied as an aqueous solution. It is a strong oxidant. It reacts with organic materials in the presence of sunlight, creating a serious fire hazard when spray splashed on clothing forms deposits. Residual compound on wilted weeds has a tendency to self-ignite. To reduce the fire hazard, calcium chloride, sodium sulfite or trisodium phosphate is mixed with the sodium chlorate.

Sodium chlorate is strongly phytotoxic to all green plant tissues, hence it is used as a total contact herbicide on soil and foliage. It is also absorbed through the roots and is rapidly translocated into the parts of the plant above the soil.

It is generally applied on established weeds at rates of 200–600 kg/ha in the form of a 1–2% aqueous solution. At rates over 300 kg/ha it provides persistent control for 6 months if there is no heavy rainfall, because sodium chlorate is not adsorbed by the soil and is washed by precipitation into the deeper soil layers.

The mode of action of sodium chlorate is not yet fully known. Yamasaki (1929) established that sodium chlorate becomes phytotoxic on reduction to sodium hypochlorite in the plant. This finding seemed to be supported by the observation that higher quantities of reducing substances were found in sensitive plants than in those less sensitive, and the sensitivity of the latter could be increased by subsequent absorption of formaldehyde. Aberg (1948) established antagonism between sodium chlorate and nitrate. Chlorate taken up by the plants is reduced by those enzymes, the role of which were to be the reduction of nitrate. Goksir (1951) concluded from his experiments that chlorate blocks the nitrate-reducing enzyme system of the plants.

Neller (1931) found that chlorate reduced catalase activity by 50% in the roots of *Convolvulus,* but Brian (1964) considers it doubtful that this decrease in activity would materially reduce the peroxide equilibrium of the cell, since catalase is very efficient in decomposing hydrogen peroxide.

Offord and Urbal (1931) observed a vigorous plasmolytic effect on filamentous algae *(Nitella clavata)* at chlorate concentrations as low as 0.01 mole/dm^3. According to Cove (1972), the chlorate ion acts by mimicking the nitrate ion, thus interfering with the degradation of nitrogen compounds needed as a source of nitrogen.

The acute oral LD_{50} of sodium chlorate for rats is 286–632 mg/kg. It is toxic to fish, the LC_{50} (96 hours at 22°C) for *Lebistes reticulatus* being 2.5 mg/l, and for carp *(Cyprinus carpio)* 15 mg/l. Up to a concentration of 1 g/l it is not toxic to bees.

Magnesium chlorate (Margon®, Ortho MC®) is used as a defoliant in cotton 2–3 weeks before harvest. Owing to its hygroscopicity, it is less of a fire hazard than sodium chlorate.

6.1.4 Boron compounds

Borates, primarily sodium tetraborate, borax ($N_2B_4O_7$) are used as micronutrients in agriculture. Borax affects the movement of sugars in the plant, sugar carbohydrate equilibrium, protein synthesis, respiration and auxin transport.

Three borates are used as herbicides: sodium metaborate tetrahydrate ($Na_2B_2O_4 \cdot 4H_2O$), borate (meta), disodium octaborate tetrahydrate ($Na_2B_8O_{13} \cdot 4H_2O$), borate (octa) and sodium tetraborate ($Na_2B_4O_7$) in anhydrous form and as penta- and decahydrate. The name borax refers to the decahydrate form (Anonym, 1974).

At high rates of 1.2–3.5 tons of B_2O_3/ha, all three borates are used pre-and postemergence as total herbicides for soil sterilisation on non-crop sites. At these rates they are suitable also for the eradication of St. John's wort (Litzenberger *et al.*, 1945) and poison ivy (Stodard, 1944). At lower rates of 40–100 kg B_2O_3/ha they can also be used for selective weed control in sugar beet and fodder beet (Crafts and Raynor, 1936; Wang and Klotz, 1938; Crafts *et al.*, 1941).

High doses of borates persist for 2–5 years in the soil, depending on precipitation and the clay content of the soil. Owing to their good solubility in water, borates diffuse into the deeper layers of the soil and can kill deep-rooted weeds. Borates are combined with urea herbicides (e.g. diuron), 2,4-D, chlorates and uracyls.

In plants treated with borates phytotoxic symptoms develop slowly, the main symptoms being withering and scorching. The biochemical mode of action of borates is unknown. According to the investigations of Brebion *et al.* (1954), sodium tetraborate considerably inhibits chlorophyll synthesis in young wheat plants, indicating one possible cause of its herbicidal activity.

Boven and Gauch (1966) attribute the fungicidal action of boron compounds to the inhibition of the glycolytic enzyme aldolase. It is conceivable that this inhibition also has a role in the herbicidal activity. On the other hand, the decreased water

uptake by the roots of the plants treated with borate undoubtedly contributes to the herbicidal action.

A good review has been published by Gauch and Dugger (1954) on the physiological effects of boron compounds on higher plants, and the interpretation of these effects.

Borates are not toxic to mammals but are slightly toxic to fish, the acute oral LD_{50} values for rats are borate (meta), 2330 mg/kg, borate (octa), 2000 mg/kg, and borax, 556 mg/kg. For infant rats the lethal dose is 5–6 g.

6.1.5 Arsenic compounds

The anhydride of arsenous acid, arsenic trioxide (As_2O_3), sodium metaarsenite ($NaAsO_2$; the anhydride of arsenic acid, arsenic pentoxide (As_2O_5), arsenic acid ($H_3AsO_4 \cdot 1/2\,H_2O$); and calcium arsenate ($Ca_3(AsO_4)_2$) are all total action contact herbicides of persistent action. Arsenic trioxide is used on non-crop sites for long-acting soil sterilisation; arsenic acid is used for the desiccation of cotton; sodium arsenite is used for soil sterilisation, aquatic weed control and the chemical debarking of trees; and calcium arsenate is used preemergence as a selective herbicide for the control of *Digitaria sanguinalis* on lawns. These compounds are used mainly in the USA. Their strong toxicity to mammals and their accumulation in animal and plant organisms, and, thus, the food-chain led to their gradual replacement by other herbicides in agriculture and in weed control for industrial sites. Inorganic arsenic compounds have recently been replaced to a certain extent by organic arsenic compounds (see Section 6.22).

6.1.6 Azides

In the last few decades a single group of inorganic compounds, the azides, has attained practical importance as agricultural herbicides. Though the biological action of sodium azide on germinating plants was studied as early as 1891, sodium and potassium azide were not introduced until about 80 years later by PPG Industries (USA) for agricultural use.

Azides are the salts of the very unstable and poisonous hydrazoic acid (HN_3):

$$Na—N{=}N{\equiv}N \qquad K—N{=}N{\equiv}N$$

Sodium azide is prepared by introducing dinitrogen oxide into a sodium amide melt at 200°C

$$NaNH_2 + N_2O \rightarrow NaN_3 + H_2O$$

Sodium amide is prepared by the reaction of sodium and ammonia in the presence of ferric chloride as catalyst.

Sodium azide is a white crystalline compound decomposing explosively at 300°C. It is easily decomposed by radiation. It is readily soluble in water (at 10°C 40 g/100 g, at 17°C 42.7 g/100 g).

Sodium azide and potassium azide have a broad range of biocidal action, possessing, besides herbicidal activity, fungicidal, bactericidal, nematocidal and insecticidal activity.

Azides are used for weed control by preplanting incorporation or postemergence treatment in the form of 8% or 16 % granules on an attapulgite of montmorillonite support, or as an aqueous solution. At a rate of 40–120 kg/ha sodium azide is a nonselective, broad-spectrum herbicide effective against annual and perennial weeds. At this high rate of application it is used for general soil sterilisation 2–4 weeks before the planting of the crop, the chemical being incorporated into the soil after its application.

In postemergence application in the form of an aqueous solution it is used at a rate of 2–5 kg active ingredient/ha for the desiccation of cotton and as a direct treatment for selective weed control. The granulated formulation can be used at a rate of 2–10 kg/ha for postemergence selective weed control in peanut, soybean, maize and rice. The rate of application depends on the temperature and the pH of the soil. Below 16°C and above pH 7.0 higher rates are needed.

Azides are easily absorbed by seeds and by the roots of sprouting plants, and to a lesser degree by the epicotyls of the plant. The herbicide absorbed is easily translocated acropetally to the xylem, where it is rapidly metabolised.

According to Bradbury *et al.* (1957) metabolic degradation proceeds by two pathways. One of these is oxidation, during which azide ions are oxidised by the oxidants of the plant cell, for example by nitrates. The other pathway involves first the formation of hydrazoic acid by ion exchange, which then forms acid azides with the organic acids of the plant. Acid azides are degraded by Curtius rearrangement into isocyanate and nitrogen. By reacting with water, isocyanate yields substituted urea and carbon dioxide.

The latter pathway can be described by the following reaction scheme:

$$R-COOH + NH_3 \rightarrow RCON_3 + H_2O$$
$$RCON_3 \rightarrow RNCO + N_2$$
$$2RNCO + H_2O \rightarrow RNHCONHR + CO_2$$

In the soil, azides are not degraded microbiologically but purely chemically, according to the two different mechanisms shown above. In acid soil and with adequate humidity, the main route of decomposition is the formation of hydrazoic acid. The highly volatile acid rapidly volatilises from the soil (Ketchersid and Merkle, 1976). Alkalinity of soil and the admixture of cyanamide to the azide increase the herbicidal efficiency and persistence (Danielson, 1965; Colby and Freemy, 1967).

In rice, sodium azide at recommended rates of 2.5–3.2 kg/ha is decomposed in 7–10 days; at rates of 40–120 kg/ha this takes 3–5 weeks.

The biological action of azides is caused by HN_3 formed by hydrolysis (Bradbury *et al.*, 1957; Parochetti and Warren, 1970). The biochemical mode of action is based, according to Keilin (1936), on the paralysis of cell respiration and on the inhibition of the oxidative enzyme system of the cell.

Sodium azide is strongly toxic to mammals and fish, its acute oral LD_{50} for rats being 27 mg/kg, and for rabbits 10 mg/kg. Ninety-five hour LC_{50} for fish is 0.68–0.8 ppm.

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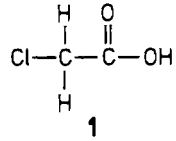
6.2 Halogenated-alkanoic acid derivatives

Unsubstituted aliphatic acids have no herbicidal activity. Several of the halogenated acetic acid and propionic acid derivatives, however, reveal important herbicidal properties. Today, two compounds, trichloroacetic acid and 2,2-dichloropropionic acid are of commercial importance.

Halogenated-alkanoic acid derivatives are efficient mainly for the control of grass weeds. In agriculture they are always used in the form of their sodium salts, which are readily soluble in water.

Monochloroacetic acid (MCA, **1**) is a halogenated-alkanoic acid derivative, the herbicidal properties of which were first described by Zimmermann and Hitchcock (1950, 1951).



1

The sodium salt of monochloroacetic acid, prepared by the hydratation of trichloroethylene or by the chlorination of acetic acid, is used for the selective control of grass weeds in maize, potato and onion crops.

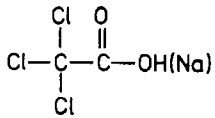
The disadvantages of monochloroacetic acid are its weak activity, requiring its application at rates of 50–100 kg/ha, and the brief duration — a few days — of its effectiveness. Monochloroacetic acid is hydrolysed in the soil to glycolic acid.

The diethylamide (CDEA) and the diallylamide (CDAA) of monochloroacetic acid are also selective herbicides which kill grassy weeds (see Section 6.5). The herbicidal properties of the methylol and alkoxy-alkyl derivatives of monochloroacetic acid amide have also been described (Chupp, 1964a, 1964b; Hamm

and Speziale, 1965), but these derivatives have not gained commercial importance to date.

Dichloroacetic acid has no herbicidal activity, but the N,N-diallylamide of dichloroacetic acid is an important commercial product as the antidote of thiol carbamate herbicides (see Section 6.10).

The herbicidal properties of trichloroacetic acid (TCA, **2**) were discovered in the USA simultaneously in the research laboratories of the E. I. du Pont and the Dow Chemical Co. (Dow, 1947; Barrons and Watson, 1949).



2

The free acid is a hygroscopic crystalline substance hence, it is always used in the form of its less hygroscopic sodium salt. Both the acid and its sodium salt are readily soluble in water and both are stable compounds in the absence of moisture. In the presence of water, particularly under alkaline conditions, the acid is decomposed by heating into chloroform and carbon dioxide.

$$CCl_3COOH \rightarrow CCl_3H + CO_2$$

Heated above its boiling point, the anhydrous acid is decomposed into hydrochloric acid, carbon monoxide, carbon dioxide, phosgene and other products.

Trichloroacetic acid is prepared by the catalytic chlorination of acetic acid. Iodine, sulfur, phosphorus trichloride or their mixtures are used as catalyst:

$$CH_3COOH + 3\ Cl_2 \rightarrow CCl_3COOH + 3\ HCl$$

A simpler method giving trichloroacetic acid at a good yield is the oxidation of chloral with nitric acid:

$$CCl_3CHO \xrightarrow{ox.} CCl_3COOH$$

The sodium salt of trichloroacetic acid is obtained from the acid by neutralisation with sodium hydroxide. To avoid the decomposition just described, neutralisation is carried out at low temperature.

TCA is a preemergence herbicide used for the selective control of grass weeds in sugar beet, sugar cane, alfalfa, peas and some other crops at a rate of 15–30 kg active ingredient/ha.

TCA is absorbed only by the roots of the plants and then translocated in the transpiration stream. (Blanchard, 1954).

Phytotoxic symptoms caused by TCA are wilting of the leaves and inhibition of root and stem growth (Mayer, 1957). The foliage temporarily becomes dark green, then chlorosis is manifested. The weeds treated die in 3–4 weeks. Treatment with

TCA changes the permeability of the cell membranes (Mayer, 1957) and reduces the wax secretion of the leaves (Dewey *et al.*, 1956).

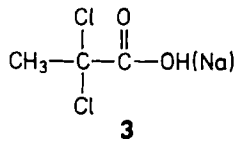
Though numerous investigations show that TCA affects several biochemical processes of the plants—metabolism of sugars, lipids, nitrogen and enzyme reactions—this does not occur to an extent sufficient to explain the mode of action of a molecular level. As the protein-precipitating action of halogenated-alkanoic acids, hence of trichloroacetic acid, is well known, it is possible that the main biochemical action of TCA is the structural modification of proteins (Ashton and Crafts, 1973).

TCA is not metabolised in the plants. The selective action may be the result of different extents of accumulation and elimination in susceptible and tolerant plants.

TCA is decomposed in the soil mainly by the microbial pathway (Gemmel and Jensen, 1964). Its persistence is 1–3 months (Jensen, 1960).

TCA is slightly toxic to mammals. Its acute oral LD_{50} is 5000 mg/kg for rats. The free acid is very corrosive, and on longer contact the sodium salt also causes burns. TCA-Na powder is a strong irritant of the mucous membranes and is irritating to the eye. TCA is not toxic to fish and bees.

The herbicidal activity of 2,2-dichloropropionic acid was described by Barrons (1963). Its approved common name is dalapon **(3)**.



3

The free acid is an odourless, colourless liquid, the commercial product (Na-salt) is a slightly hygroscopic powder readily soluble in water. The aqueous solution cannot be kept for a long time, because it hydrolyses, slowly at room temperature but relatively rapidly at 50°C. During hydrolysis pyruvic acid is formed:

$$CH_3—CCl_2—COONa \rightarrow CH_3—CO—COOH + NaCl + HCl$$

Dalapon is produced by the chlorination of propionic acid. Chlorination is carried out at high temperature in the presence of a catalyst, phosphorus trichloride or light, for example, to suppress the formation of 2,3-dichloropropionic acid. The technical acid is contamined by small quantities of 2-chloropropionic acid and 2,3-dichloropropionic acid.

Owing to the tendency of the acid to hydrolyse, the preparation of the sodium salt is a delicate operation. The neutralisation of the acid with sodium hydroxide is therefore undertaken under intensive cooling and the salt solution is evaporated under vacuum. Maylott and Meyer (1964) recommended anhydrous reaction conditions for the formation of the salt. The reacting anhydrous acid and dry alkali compound are dispersed in liquid hydrocarbon. At the end of the reaction the sodium salt is filtered off from the reaction medium.

Dalapon, like TCA, is a contact selective herbicide for the control of grassy weeds. It is used for selective weed killing at a rate of 0.8–10 kg acid equivalent/ha, and for total weed control on non-crop areas at a rate of 10–25 kg/ha.

Unlike TCA, dalapon is also absorbed through the leaves. Its effect can be enhanced by the addition of surfactants. It is used for selective weed control in sugar cane, sugar beet, maize, potato and in orchards.

Dalapon absorbed by the plants is translocated *via* phloem and xylem, freely penetrating plant tissues, and is even able to pass from the phloem to the xylem and *vice versa*, thus circulating throughout the assimilation and transpiration streams of the plant. Dalapon temporarily cumulates in young plant tissues and is not metabolised (Sagar, 1960; Saidak, 1961; Andersen *et al.*, 1962; Foy, 1961, 1962).

The uptake and translocation of dalapon is similar in sensitive and tolerant plants, so the toxicity of the compound to weeds must have another basis. Despite rapid absorption the phytotoxic action is manifested slowly. The leaves of sensitive plants curl and, starting from the margins, become yellow. The development of the plants stops, buds and roots cease to grow, and finally, the plants wither in 3–4 weeks. Seed germination of dicotyledonous weeds is barely inhibited by dalapon, and even that of monocotyledons only at a high concentration.

As does TCA, dalapon reduces the leaf wax synthesis of peas and cabbages, thereby increasing the sensitivity of the plants to contact herbicides (Pfeiffer *et al.*, 1960).

The biochemical mode of action of dalapon has not been unequivocally elucidated. The protein precipitating action of chlorinated aliphatic acids, hence of dalapon, is known (Redemann and Hamaker, 1954), and it has also been proved by the investigations of Kemp *et al.* (1969) that the acid form of dalapon is able to form a hydrogen bond with the amide group of the protein molecule, so that this mechanism, in blocking enzyme activity, may be the cause of the phytotoxic action. Hilton *et al.* (1959) proved that dalapon inhibits the pantothenic acid synthesis of plants.

It has been observed that by the action of dalapon phosphate uptake in maize is changed, and the protein content of sugar beet is reduced (Ingle and Rogers, 1961).

Dalapon is only slightly toxic to mammals. The acute oral LD_{50} for male rats is 9330 mg/kg, for female rats, 7570 mg/kg. In rats, the no-effect level is 15 mg/kg/day (Dalgaard-Mikkelsen and Poulsen, 1962).

Dalapon is practically nontoxic to fish and bees.

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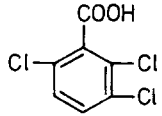
6.3 Benzoic acids

Although Zimmermann and Hitchcock reported on the growth regulating properties of the substituted benzoic acids in 1942, the herbicidal properties of these compounds were evaluated only in 1948 in England and a little later in the United States (Bentley, 1950; Zimmermann and Hitchcock, 1951; Miller, 1952).

Of the many compounds investigated only the 2,3,6-trichlorobenzoic acid and two substituted dichlorobenzoic acids have gained commercial interest.

2,3,6-Trichlorobenzoic acid (TBA, **1**) was introduced in the United States in 1956 under the trade mark Trysben®.



1

It may be synthesised by several methods. The industrial synthesis starts with 2-chlorotoluene, which is chlorinated to a mixture of 2,3,6- and 2,4,6-trichlorotoluenes. The resulting intermediate is then oxidised to the corresponding trichlorobenzoic acids, containing about 60% TBA and 40% 2,4,5-trichlorobenzoic acid.

It forms alkali metal and amine salts, which are readily soluble in water and are compatible with other hormone-type weed killers.

TBA is an auxin-type growth regulator herbicide. It is used in postemergence application against broad-leaved annual and perennial weeds, including deep-rooted weeds resistent to MCPA and 2,4-D, primarily on non-crop land. It is also used in combination with dicamba + mecoprop + MCPA (Cambilene®) in cereals and grass seed crops to control *Anthemis* spp., *Galium aparine, Polygonum* spp., *Stellaria media, Solanum nigrum, Sonchus arvensis, S. oleraceus, Spergula arvensis.*

TBA is readily absorbed and translocated by plants. It moves both acropetally and basipetally and causes typical auxin effects in sensitive plants. It strongly inhibits apical growth and leaf formation (Zimmermann and Hitchcock, 1951). It does not cause epinasty in the MCPA-tolerant weeds but stops their growth so that they cannot compete with the crop at the later growth stages.

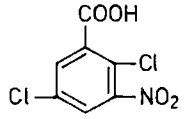
Several studies show that TBA is not readily metabolised in plants or in soil. In larger doses it persists in the soil for several years. TBA residues are lost from the soil by leaching, adsorption and microbial degradation (Crafts and Drever, 1960; Burnside 1965; Phillips, 1968; Sheets *et al.*, 1968).

TBA is not metabolised in warm-blooded animals. Orally administered TBA is rapidly excreted either in unchanged form or as a conjugate in the urine. Its acute oral LD_{50} for rats is 1500 mg/kg.

The iodine anologue of TBA, 2,3,5-triiodobenzoic acid (TIBA), is of similar activity but is no longer manufactured or marketed.

Amchem workers synthesised a number of nitrosubstituted and aminsubstituted chlorobenzoic acids. Their herbicide screening revealed several compounds of selective activity. Two have been developed into commercial products: Dinoben® and Amiben® (Amchem, 1959; Sterry, 1961).

The active ingredient of Dinoben® **(2)** is 2,5-dichloro-3-nitrobenzoic acid.



2

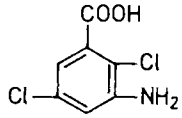
This compound is produced by the nitration of 2,5-dichlorobenzoic acid and the fractionation of the resulting isomeric nitration product.

Its water-soluble sodium and triethylamine salts are preemergence selective weed killers effective against annual grasses and broad-leaved weeds in maize, soybeans and horticultural crops.

At the time of its commercial development, extensive tests showed that the reduction product of 2,5-dichloro-3-nitrobenzoic acid, 3-amino-2,5-dichlorobenzoic acid (chloramben, **3**) is a compound of similar selectivity but greater activity and better tolerated by a number of crops.

Leeper and Cooke (1972) investigated the sixteen possible isomers of 3-amino-5,6-dichlorobenzoic acid, and found that the chloramben was the most outstanding among them. They concluded that its unique molecular configuration was responsible for the exceptional biological activity.

Chloramben in the form of its ammonium salt (Amiben®) or its methyl ester (Vegiben®) is a preemergence selective herbicide used primarily for the selective control of annual grasses and broad-leaved weeds in soybeans. It is also used in dry beans, sunflowers, carrots, maize, peanuts, transplanted tomatoes and various ornamentals.



3

Chloramben is rapidly decomposed by light to compounds which are not phytotoxic. It is therefore advisable to incorporate it into the soil under some conditions (Sheets, 1963; Plimmer and Hummer, 1969).

Dinoben® and chloramben are effective growth regulators. Both herbicides inhibit elongation and growth of roots and stems of many susceptible plants and also inhibit several enzymatic functions (Colby, 1965; 1968; Stoller and Wax, 1968).

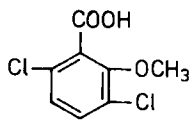
Chloramben is metabolised in the plants partly to insoluble, bound complexes and to immobilised N-glucoside conjugate (Stoller, 1969). Its selectivity is based on the different detoxifying capacity of the sensitive and tolerant plants.

Chloramben is degraded by microbes in the soil (Sheets *et al.*, 1968). Its average half-life is 6–8 weeks (Sheets, 1963). Leaching may also account for losses from soil surface layers.

Chloramben is slightly toxic to warm-blooded animals. Its acute oral LD_{50} for rats is 5620 mg/kg. It does not accumulate in the animal organism (St. John and Lisk, 1970).

The most selective member of the benzoic acid herbicides is 3,6-dichloro-2-methoxy-benzoic acid (dicamba, **4**), (Sterry, 1961; Velsicol Chemical Co., 1974).

Dicamba is synthesised in the following way (Richter, 1961):



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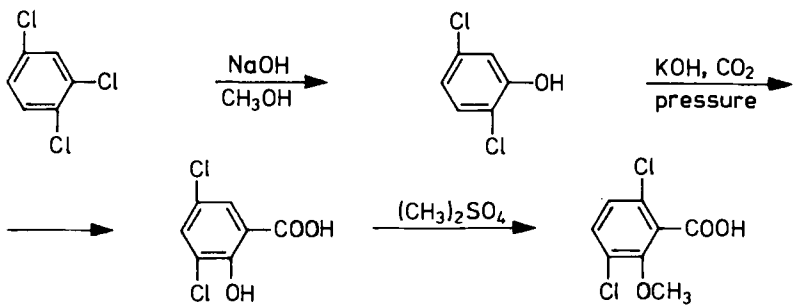

Dicamba in the form of its dimethylamine salt is a translocatable auxin-type herbicide, which by pre- or postemergence treatment, usually combined with one or more phenoxyalkanoic acids, is used for the control of grasses, broad-leaved weeds and several shrubs. In combinations mainly 2,4-D, MCPA, and mecoprop are used. Its recommended rate is 80–130 g a.e./ha.

As mentioned before, dicamba has much greater selectivity than the other benzoic acid herbicides. It is also active against phenoxy-resistent weeds. It is selective in small grains, maize, sugar cane, perennial seed grasses, turf and non-crop land. Its oil-soluble ester is used as a brush-killer.

Dicamba is readily absorbed by leaves and roots and is translocated apoplastically and synplastically (Binning *et al.*, 1971; Ashton and Crafts, 1973).

In the sensitive plants dicamba shows very distinctive morphological symptoms similar to the well-known overgrown symptoms caused by the phenoxy acids. Its mode of action is still unknown.

Loss and detoxification of dicamba from treated plants occur by exudation through the roots and leaves and by metabolism in the plant. The main metabolite of dicamba is 5-hydroxy-2-methoxy-3,6-dichlorobenzoic acid, which forms conjugates (Broadhurst *et al.*, 1966; Chang and Van den Born, 1971). Dicamba is mobile in the soil, so its leaching depends on seasonal precipitation. It is readily metabolised by microorganisms in the soil. The major metabolite is 3,6-dichlorosalicylic acid (Harris, 1967).

Dicamba is a not persistent herbicide. Its half-life is 14 days–12 weeks, depending on precipitation and other climatic conditions.

It is moderately toxic, the acute oral LD_{50} for rats, as for dimethylamine salt, being 1028 mg/kg. It is also only moderately toxic to wildlife and fish.

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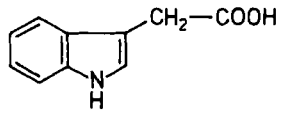
6.4 Phenoxyalkanoic acids and their derivatives (Phenoxy herbicides)

During World War II plant physiological research, which began almost a century ago, led to the discovery of substances of immense practical importance — the hormone-type phenoxy herbicides.

Phenoxyalkanoic acids, introduced in the middle of the 1940s, are even today the most important selective herbicides, manufactured and used in the largest quantity. Owing to their particular selectivity, their wide field of applicability and their economy, demand for this type of herbicide continues to increase. In 1974 and 1975, 200 000 to 300 000 tons, yearly about 55–60% of the world herbicide production, was phenoxy acid compounds.

Sachs (1880) established at the end of the last century that plants themselves produce those substances which regulate their growth. Went (1928) pointed out that there is no growth without growth substances, and elaborated a practical method for their extraction and investigation. Two of these regulating substances, auxin A and auxin B, have been isolated by Kögl *et al.* (1934). Kögl and Kostermans (1935a, 1935b) later isolated heteroauxin (auxin C) from human urine, and proved it to be 4-(indol-3-yl)acetic acid (**1**). The current abbreviation of this compound in the literature is IAA. Its first synthesis is linked with the name of Fischer (1886).



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Following the discovery of heteroauxin, Zimmermann and Wilcoxon (1935) synthesised several related compounds of 4-(indol-3-yl)acetic acid and studied their physiological and morphological effects. They studied the growth-regulating action of 1-naphthylacetic acid (NAA), 2-naphthoxyacetic acid (NOXA) and 4-(indol-3-yl)butyric acid (IBA) on various plants. These substances had already been used in garden cultures as rooting compounds, but their herbicidal action had not been recognised. The application of the closely related compounds 1-naphthylacetic

acid, phenylacetic acid, and their nitriles and amides as growth promoters was protected with a patent in 1938 by the American Chemical Paint Co. (D.R.P. 716 342).

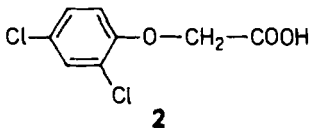
Nutman and coworkers (1945) established the selective herbicidal action of 1-naphthylacetic acid. Charlock *(Sinapsis arvensis)* and sugar beet were killed by NAA, while cereals (oat) were not injured. Later investigations showed that 4-chloro-2-methylphenoxyacetic acid (MCPA) and 2,4-dichlorophenoxyacetic acid (2,4-D) are considerably more potent than naphthylacetic acid.

From the point of view of chemical structure, the common characteristic of hormone-type phenoxyalkanoic acids is a substituted phenoxy radical, to which a low carbon number fatty acid is attached.

6.4.1 Phenoxyacetic acids

The derivatives of substituted phenoxyacetic acids are in practice the most important and most widely used of the hormone-type herbicides.

Three herbicides, 2,4-dichlorophenoxyacetic acid (2,4-D, **2**), 4-chloro-2-methylphenoxyacetic acid (MCPA, **3**) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T, **4**), are of particular importance.



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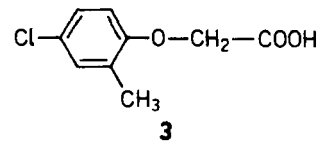

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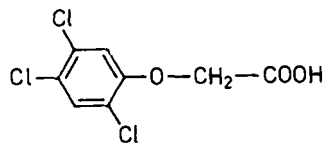


4

The free acids are not used as herbicides, but are processed to the alkali, ammonium or amine salts, which are readily soluble in water, or to alkyl esters soluble in organic solvents, and are marketed in these forms.

Phenoxyacetic acids are weak acids, their dissociation constant being $5.2–20 \cdot 10^{-4}$.

The free acid 2,4-D (**2**) is a stable, white crystalline compound with a corrosive effect on metals and well soluble in water and in organic solvents. The ammonium salt and the metal salts of 2,4-D are very slightly soluble or virtually insoluble in water (Melnikov, 1971).

Amine and alkanolamine salts are available as aqueous solutions (WSC), generally with methanol added, to prevent crystallisation during storage.

Those esters of 2,4-D formed with alcohols of low carbon number are not used because of their high volatility. The dispersal of the vapours of volatile esters is a grave hazard for the dicotyledonous cultured plants of neighbouring plots, particularly for vineyards, which may be completely destroyed. Most often, the

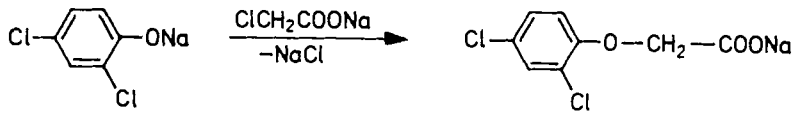
isopropyl, butyl, *sec*-butyl, amyl, octyl and isooctyl, and the ethyleneglycol esters are used. These esters are readily soluble in alcohols, oils and kerosene, and are formulated as emulsifiable concentrates (EC).

The salts and esters of 2,4-D are systemic foliage herbicides, with moderate soil herbicidal action. They are applied postemergence mainly in cereals, maize, rice, sugar cane and on pastures at a rate of 0.280–2.3 kg/ha active ingredient for the selective control of dicotyledonous weeds. At an application rate of 2.3 kg/ha, it is decomposed in about a month in the soil.

The acute oral LD_{50} of 2,4-D (acid) for rats is 375 mg/kg, that of 2,4-D-Na 666–805 mg/kg, of the mixed butyl esters 620 mg/kg, and of the isopropyl ester 700 mg/kg. The MAK value in air is 10 mg/m^3.

The effect of 2,4-D on humans, domestic animals and wild-life has been summarised by Way (1969) and Maier-Bode (1970). This latter work also gives a summary of the literature on the toxicological and residue problems of all the important aryloxy acid derivatives.

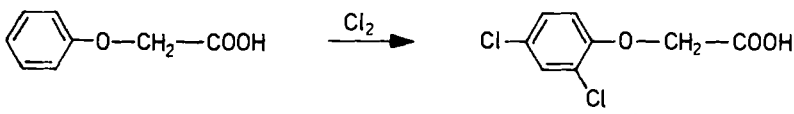
Several processes are described in the technical literature for the preparation of 2,4-D. On a large scale it is prepared mainly by the condensation of 2,4-dichlorophenol with the sodium or ammonium salt of monochloroacetic acid in aqueous or nonaqueous medium:



2

2,4-D prepared in this way always contains 2,4-dichlorophenol.

Chlorination of phenoxyacetic acid in aqueous medium or in organic solvent yields a purer product but is a more expensive process:



2

This product does not contain dichlorophenol of disagreeable odour.

The esters are prepared from 2,4-D acid by heating with the respective acids in the presence of catalyst. Water formed is removed by azeotropic distillation. Isopropyl ester is most widely used.

The Imperial Chemical Industries introduced MCPA, 4-chloro-2-methylphenoxyacetic acid (**3**) in 1945, under the name Agroxone®.

It is prepared by the condensation of 4-chloro-*o*-cresol with sodium monochloroacetate in alkaline aqueous solution. As the isomeric 6-chloro-*o*-cresol is always present as an impurity in 4-chloro-*o*-cresol, the crude MCPA also contains isomeric 6-chloro-3-methylphenoxyacetic acid.

In technical MCPA the ratio of the 4-chloro and 6-chloro isomers is 60–65 : 35–40%.

Like to 2,4-D, MCPA is slightly soluble in water depending on the isomer ratio. It is readily soluble in ethyl alcohol and in diethyl ether, and it forms readily soluble salts with alkali metals and organic bases. Alkali metal salt solutions are alkaline in reaction and corrode aluminium and zinc. The salts are precipitated by hard water. The esters are soluble in organic solvents and oils.

Commercially the sodium salt of MCPA is formulated as a water-soluble powder (75–80% MCPA), or as an aqueous concentrate, while its esters are formulated as emulsifiable concentrates.

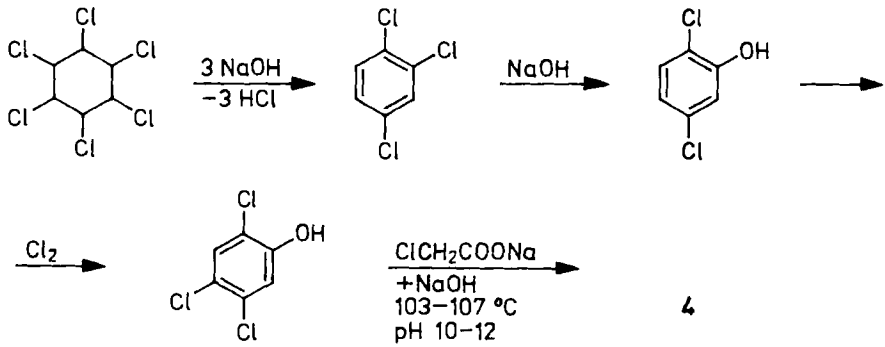
The acute oral LD_{50} for rats is 700 mg/kg, for mice 550 mg/kg. In a concentration of 10 ppm MCPA is not hazardous to fish.

Its field of application is similar to that of 2,4-D. It is used as a postemergence foliage herbicide in cereals, flax and on pasture land at a rate of 280 g–2.25 kg active ingredient/ha. It is effective mainly for the control of dicotyledonous weeds, killing both annual and perennial weeds. Its herbicidal spectrum differs somewhat from that of 2,4-D. Cereals are more resistant to MCPA than to 2,4-D, while the reverse is true for maize.

The herbicidal properties of 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid **(4)** were first reported by Hammer and Tukey (1944). It was introduced in the same year in the USA under the trade name Weedone 2,4,5-T (Amchem Products Inc.).

The last step in its synthesis is the condensation of sodium monochloroacetate with 2,4,5-trichlorophenol. The preparation of the latter from the inactive hexachlorocyclohexane (BHC) isomers has been described by Galat (1952).

The synthesis method starting from BHC is the following:



4

A further technical manufacturing process from sodium-2,4,5-trichlorophenolate and monochloroacetic acid in solvent medium has been developed too. 2,4,5-T acid is a white crystalline compound soluble in water, ether, ethanol and acetone. The acid is stable and non-corrosive. Its sodium and aliphatic amine salts are readily soluble in water.

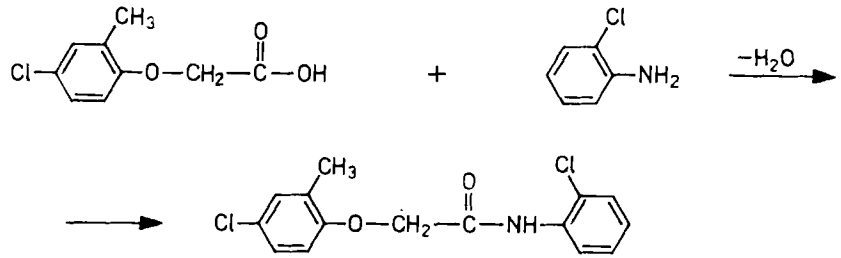
The aliphatic esters of 2,4,5-T are insoluble in water but are soluble in aliphatic petroleum oils (kerosene, diesel oil).

The acute oral LD_{50} of 2,4,5-T for rats is 500 mg/kg, for dogs 100 mg/kg. The acute oral LD_{50} of 2,4,5-T isopropyl ester for rats is 495 mg/kg, that of the mixed butyl ester 481 mg/kg.

2,4,5-T is a hormone-type systemic foliage herbicide applied postemergence. Its herbicidal properties are similar to those of 2,4-D, but it is more effective against woody weeds. The rate of application is 0.25–3 kg/ha.

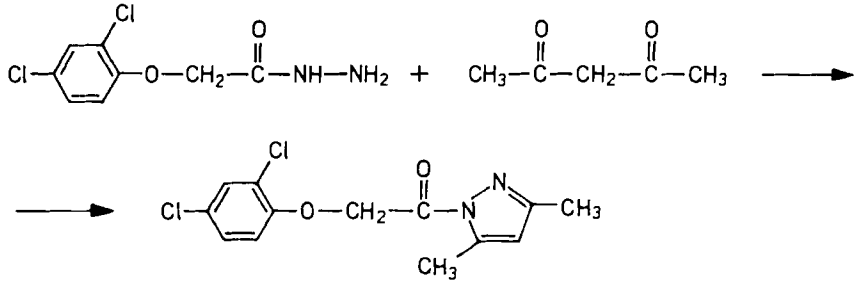
Three recent derivatives of α-phenoxyacetic acid homologues are MCPCA (**5**), Tomacol® (**6**) and OCS 21 799 (**7**).

The synthesis of MCPCA, 4-chloro-2-methylphenoxyacetyl-2-chloroanilide (**5**), proceeds by the following route:



5

Tomacol has been developed by the Takeda Chemical Industries (1964). Tomacol®, 1-(2,4-dichlorophenoxyacetyl)-3,5-dimethyl pyrazole (**6**), is prepared from 2,4-dichlorophenylacetyl hydrazine and acetyl acetone according to the following reaction scheme:



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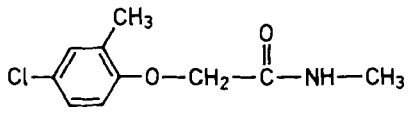
Tomacol® differs with respect to selectivity from the phenoxyacetic acid derivatives discussed in the foregoing. It is recommended for selective weed control in vegetable crops, particularly in tomatoes.

The compound of code number OCS 21 799 of the Velsicol Co. is 4-chloro-2-methylphenoxy-N-methyl acetamide (**7**).



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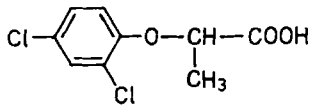
6.4.2 Phenoxypropionic acids

The other group of auxin-type phenoxyalkanoic acids comprises the α-methyl homologues of substituted phenoxyacetic acids.

Only the D(+) form of this group of compounds is active; the L(−) form is not (Burström *et al.*, 1955). Technical products contain the two isomers in equal quantity.

The range of action of α-phenoxypropionic acids differs from that of phenoxyacetic acids, as was established by Luckwill and Lloyd-Jones (1960). They assumed that decarboxylation causing the detoxication of the molecule is inhibited in certain plant species because of the α-methyl substitution, and that this kills the weeds resistant to phenoxyacetic acids (Fawcett *et al.*, 1953; Lush and Leafe, 1956). Leafe (1962) found that *Galium aparine* (cleavers), resistant to MCPA, is killed by 2-(4-chloro-2-methylphenoxy)propionic acid, because it cannot metabolise the latter.

The three most important members of this group of compounds are 2-(2,4-dichlorophenoxy)propionic acid (dichlorprop, 2,4-DP, **8**), 2-(4-chloro-2-methylphenoxy)propionic acid (MCPP, CMPP, mecoprop, **9**) and 2-(2,4,5-trichlorophenoxy)propionic acid (2,4,5-TP, fenoprop, silvex, **10**).



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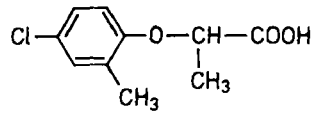

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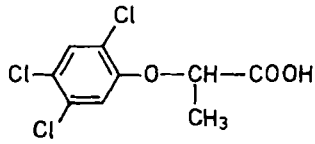


10

Dichlorprop **(8)**, a white crystalline substance, is slightly soluble in water but readily soluble in organic solvents. It is not sensitive to heat and is resistant to oxidation, reduction and hydrolysis.

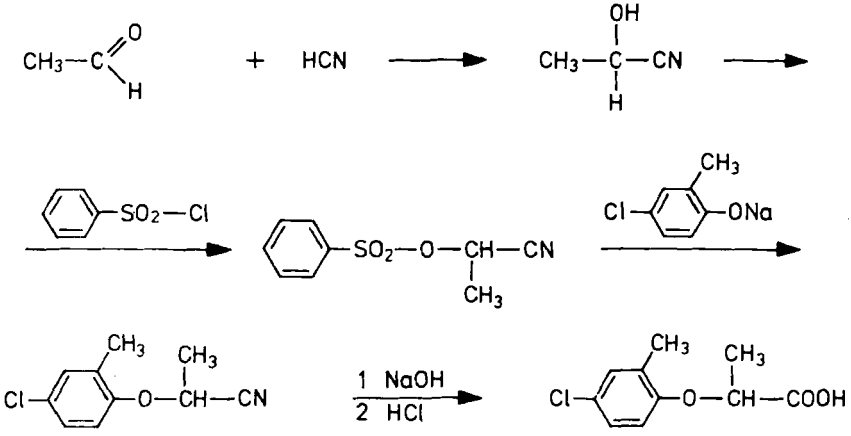
The alkali and diethanolamine salts of dichlorprop are readily soluble in water; its esters are soluble in organic solvents.

The acute oral LD_{50} for rats is 800 mg/kg, for mice 400 mg/kg. Dermal LD_{50} for mice is 1400 mg/kg. A 1% solution does not irritate the eye nor the 2.4% solution the skin. Daily doses of 12.4 mg fed to rats for 14 weeks did not produce toxic symptoms. Daily doses of 50 mg fed over the same period caused mild hypertrophy of the liver.

Dichlorprop is prepared by the condensation of 2,4-dichlorophenol and α-chloropropionic acid, or by the chlorination of α-phenoxypropionic acid. The technical product is a 1 : 1 mixture of the biologically active dextrorotatory (+) isomer and the biologically inactive levorotatory (−) isomer. Its biological action was first reported by Zimmermann and Hitchcock (1944), but it was only introduced in 1961.

It is a postemergence systemic herbicide, recommended for the control of some *Poligonum* spp., *Galium aparine, Stellaria media,* and *Tussilago farfara* weeds in cereal crops at a rate of 2.5 kg active ingredient/ha. It is generally used in combination with other herbicides (2,4-D; MCPA; 2,4,5-T; mecoprop; ioxynil; bromoxynil, bentazon).

The acid mecoprop **(9)** is prepared by the condensation of *p*-chloro-*o*-cresol with α-chloropropionic acid. Stevenson and Brooks recommended the following alternative route of synthesis (1959):



Its acute oral LD_{50} for rats is 930 mg/kg, for mice 650 mg/kg. Three-week feeding tests on rats at 65 mg produced no symptoms, and seven-month feeding tests of 100 mg daily produced only slight renal hypertrophy.

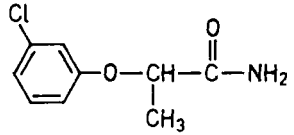
Its herbicidal range of action and its application rates are largely the same as those of dichlorprop.

Fenoprop **(10)** is a white crystalline compound, it is marketed in the form of its propylene glycol ether ester.

The acute oral LD_{50} of the acid for rats is 650 mg/kg, that of the butyl and propylene glycol butyl ether esters 500–1000 mg/kg. The acid and its undiluted esters are painful to the eyes.

Fenoprop is absorbed both by leaves and roots and is translocated. At higher rates of 2–4 kg active ingredient/ha it is recommended for the control of woody weeds (*Genista* spp., *Crataegus* spp., etc.) and aquatic weeds; at lower rates of 0.75–1.5 kg active ingredient/ha, combined with mecoprop, and chlorfenprop-methyl, it is used for selective weed control in rice and cereals.

Of the derivatives of α-phenoxypropionic acid, 2-(3-chlorophenoxy)propion-amide (3-CPA, **11**), described by Synerholm and Zimmermann (1947) and recommended for selective weed control in orchards should be mentioned.



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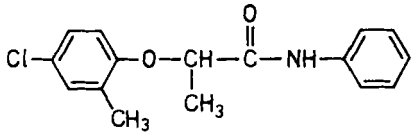
Buchanan (1967) reported on the herbicidal action of 2-(4-chloro-2-methyl-phenoxy)propionanilide **(12)**.



12

This anilide derivative can be used in dicotyledonous cultures, such as soybean, for the control of mono- and dicotyledonous annual weeds.

The phenylhydrazides of α-phenoxypropionic acids are also effective against monocotyledonous weeds.

6.4.3 Phenoxybutyric acids

Three γ-phenoxybutyric acids are used as herbicides in agriculture.

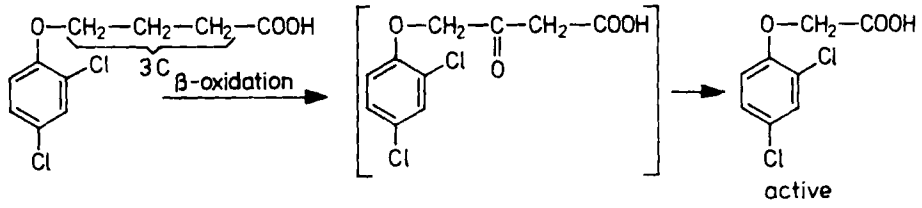
Their discovery can be traced to the classical investigations of Knoop (1904). By feeding phenoxyalkanoic acids to dogs, he established that the degradation of fatty acids in the animal organism begins with oxidation at the carbon atom in the β-position with respect to the carboxy radical, and terminates with decomposition

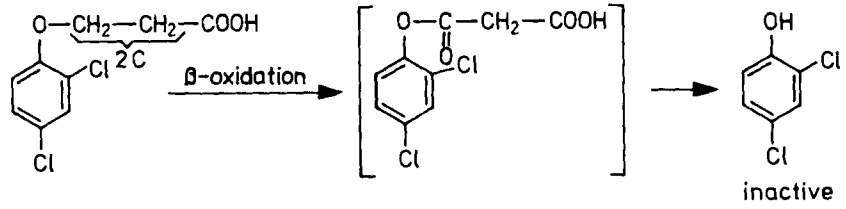
into the fatty acid two carbon atoms shorter (β-oxidation) according to the following reaction scheme:

$$R\text{—}\overset{\beta}{C}H_2\text{—}\overset{\alpha}{C}H_2\text{—}COOH \rightarrow R\text{—}CO\text{—}CH_2\text{—}COOH \rightarrow R\text{—}COOH$$

Grace (1939) investigated the effect of ω-(1-naphthyl)alkanoic acids on the rooting of cuttings, and established that homologues containing an uneven number of methylene groups were active, while homologues containing an even number of methylene groups were inactive.

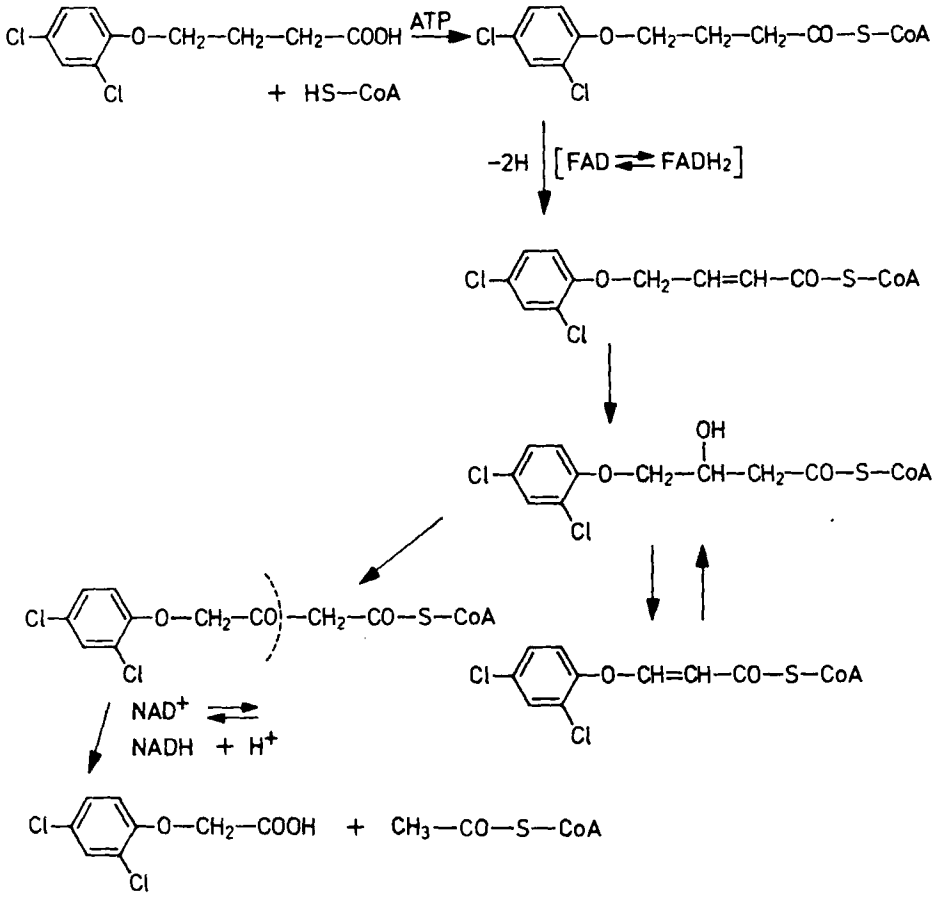
Synerholm and Zimmermann (1947) investigated the homologous series of ω-(2,4-dichlorophenoxy)alkanoic acids on tomato leaf in epinasty tests. Of the seven derivatives investigated only fatty acid derivatives containing an uneven number of methylene groups (acetic acid, butyric acid, caproic acid and caprylic acid) were active. Owing to enzymatic β-oxidation, phenoxyalkanoic acids are decomposed in the plant either to the active phenoxyacetic acid derivative or to inactive phenol. Biologically active 2,4-dichlorophenoxybutyric acid is decomposed to 2,4-dichlorophenoxyacetic acid, and inactive 2,4-dichlorophenoxypropionic acid to inactive dichlorophenol:





In addition to aryl oxycarboxylic acids, aryl oxycarboxylic acid amides, aryl oxycarboxylic acid nitriles and, after oxidation, aryl oxyalkanoles can undergo β-oxidation.

In the following example of enzymatic β-oxidation, 4-(2,4-dichlorophenoxy)-acetic acid is formed from 4-(2,4-dichlorophenoxy)butyric acid, 4-(2,4-DB):



4-(2,4-Dichlorophenoxy)butyric acid is converted in the presence of ATP into dichlorophenoxybutyryl coenzyme A. This acyl-CoA is converted by the electron acceptor flavine adenine dinucleotide (FAD) into dichlorophenoxycrotonyl-CoA. One carbon atom of the unsaturated bond is hydroxilated and dichlorophenoxy-β-hydroxybutyric acid-CoA is formed. In certain plants possessing specific β-oxidase enzyme systems, β-ketobutyric acid-CoA is formed from this intermediate compound by the mediation of NAD and NADH in a reaction catalysed by β-hydroxyacyl-CoA dehydrogenase. This compound is decomposed by hydrolysis into 2,4-D and acetyl-CoA.

Wain, Fawcett, Taylor and their coworkers investigated the effect of several ω-phenoxy acid homologues on wheat, tomato, pea, flax, nettle *(Urtica urens)* and on other weeds (Wain, 1954; 1955a; 1955b; Wain and Wightman, 1955; Wain, 1957; Fawcett *et al.*, 1958; Fawcett *et al.*, 1959; 1960; Taylor and Wain, 1962). They established as a result of their exemplary systematic fundamental research

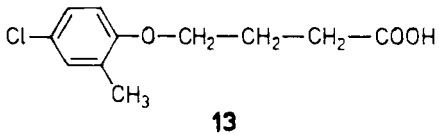
that ω-phenoxyalkanoic acids are converted by β-oxidation in plants, and that the active homologues exert their action in the form of phenoxyacetic acid formed during oxidation. Not all plants possess specific β-oxidase enzymes. Plants possessing β-oxidase systems "lethally" decompose ω-phenoxyalkanoic acids and are killed. This phenomenon opened the way for the "superselective" application of γ-phenoxybutyric acid derivatives.

Of the cultured plants, the papilionaceae, clover, alfalfa and pea among others — have no β-oxidative activity (Table 6.1).

Table 6.1
Susceptibility of several plants to phenoxybutyric acids

Plants tolerant to		Susceptible plants
2,4-DB and MCPB	2,4,5-TB	
Alfalfa	Flax	Annual nettle (*Urtica urens*)
Carrot	Rape	Creeping thistle (*Cirsiun arvense*)
Celery	Soybeans	Charlock (*Sinapis arvensis*)
Clover	Sweet clover	Fathen (*Chenopodium album*)
Flax		Fumitory (*Fumaria* spp.)
Parnsip		Pigweed (*Amaranthus* spp.)

Three phenoxybutyric acid derivatives have been developed for agricultural use: 3-(4-chloro-2-methylphenoxy)butyric acid (MCPB, **13**), 3-(2,4-dichlorophenoxy)-butyric acid (2,4-DB, **14**) and 3-(2,4,5-trichlorophenoxy)butyric acid (2,4,5-TB, **15**).



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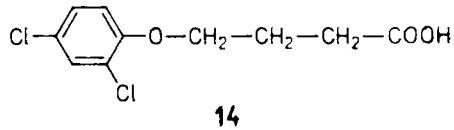

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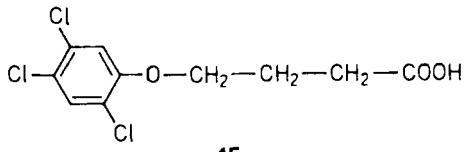

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In addition to the common name MCPB (**13**), approved by the ISO and WSSA, the common name 2,4-MCPB is used in France, and 2M-4Kh in the USSR.

The acute oral LD_{50} for rats is 680 mg/kg for the acid, 690 mg/kg for the sodium salt.

It is used postemergence in papilionaceae, cereals, clover and established grassland at a rate of 2–3 kg active ingredient/ha. It is also effective for the control of *Rumex* spp., *Ranunculus* spp. and *Equisetum* spp.

The technical 2,4-DB **(14)** is slightly soluble in water and readily soluble in organic solvents; its alkali metal salts are water-soluble. It is marketed in the form of the aqueous solution of its mixed potassium and sodium salts.

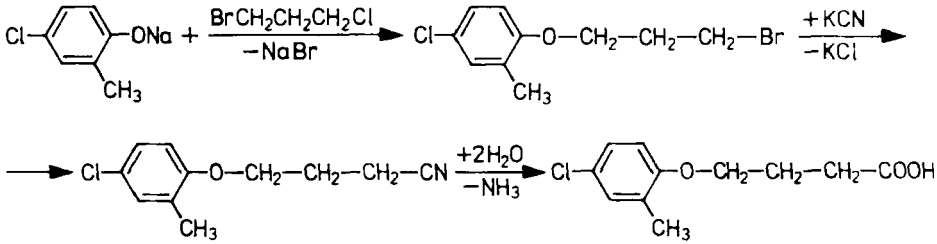
The acute oral LD_{50} for rats is 700 mg/kg (acid) and 1500 mg/kg (Na salt).

It is used postemergence at a rate of 1.5–3.0 kg active ingredient/ha in alfalfa, soybean, cereals and pastureland. It is also effective for the control of *Juncus* spp. and *Anthiriscus campestris*.

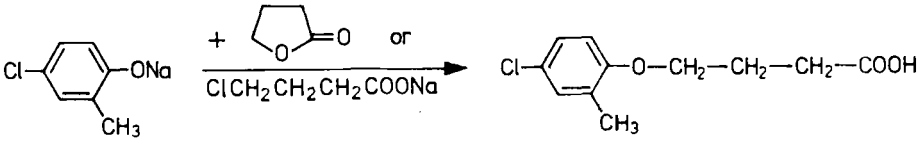
2,4,5-TB **(15)** is a contact herbicide, used postemergence in cereals and quince berry at a rate of 2.5–4 kg active ingredient/ha, mainly for the control of *Convolvulus* spp. and *Calystegia sepium*.

Three synthesis routes are known for the preparation of phenoxybutyric acid derivatives (Melnikov, 1971).

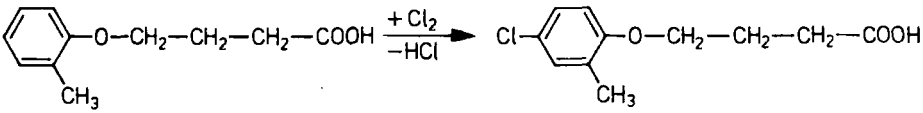
(1) Reaction of the sodium salt of the substituted phenol with 1,3-bromo-chloropropane, conversion of the intermediate formed into nitrile and the saponification of the latter:



(2) Reaction of the sodium salt of the substituted phenol with γ-butyrolactone or with sodium monochlorobutyrate:



(3) Chlorination of 3-(2-methylphenoxy)butyric acid in aqueous medium or in organic solvent:



3-(2,4,5-Trichlorophenoxy)butyric acid can be prepared by methods *(1)* and *(2)*.

6.4.4 Structure–activity relationships

Since the recognition of the auxin action of phenoxy acids extensive research has been undertaken to elucidate the relationships between the biological activity and chemical structure of this group of compounds (Audus, 1953; Fawcett *et al.*, 1956; Wain, 1958; Fawcett *et al.*, 1959; 1960; Melnikov, 1971; Wain, 1975).

Veldstra (1944) had shown earlier that to induce growth response in a plant or plant tissue, the active molecule must meet three requirements: *(1)* it must penetrate the tissues, *(2)* after penetration it must be able to move freely within the cell, so as to reach the site of action, and to accumulate there, without becoming inactivated by chemical or biochemical reactions or by being bound to the passive parts of the cell, and *(3)* it must possess structural characteristics suitable to produce the desired growth response at the site of action. This activity has been called "primary activity".

Obviously, in order to plan a molecule to meet the above requirements all the laws according to which the different cell membranes can be penetrated ought to be known, as well as the physical and physicochemical laws regulating the movement and binding of the molecules within the cell, the functioning and interactions of the metabolising enzymes of the cells, and of course, at which part of the cell microstructure the molecule interferes with the physiological processes and in what direct of indirect way.

However, most of these processes and the "whys" of the actions depending on chemical structure are still unknown. Thus, structure–activity relationships can be established for phenoxy compounds only in synthesis laboratories by the comparison of activity measurements of compounds *in vitro* and *in vivo*, prepared in series, on the basis of structural analogies.

Several *in vitro* tests are suitable for the determination of the growth-regulating activity of hormone-type herbicides, among them the straight growth test of wheat or oat, and the pea curvature test. Both methods yield quantitative results of good reproducibility. The Avena test elaborated by Went cannot be used in this case, but the root growth inhibition test is suitable (Audus, 1949; 1951).

Activity values obtained by the tests mentioned or by other known methods cannot be compared with each other, because they yield results differing by orders of magnitude. It is recommended that several test methods be used simultaneously for comparative evaluation. With a view to future practical considerations, tests are carried out on several kinds of intact plants, to obtain at the same time information on selectivity.

The first detailed investigation of plant growth-regulating activity is linked with the names of Koepfli *et al.* (1938). On the basis of their experiments with indole and arylalkanoic acids, they established five structural requirements necessary for the biological activity of the molecule.

Accordingly, to have the growth hormone effect the molecule must contain a ring system in which at least one double bond is present, it must contain a side chain with

a carboxyl group substituent, and the carboxyl group of the molecule and the ring must be separated from each other by at least one carbon atom.

These requirements are valid for the groups of the compounds investigated, they are not valid, however, in the case of benzoic acid, naphthenic acids and aliphatic acid derivatives (e.g., S-carboxymethyl dithiocarbamate), compounds with plant growth-regulating action discovered later (Veldstra, 1952; Van der Kerk *et al.*, 1955). The carboxyl group in the former compounds is attached directly to the ring, while the latter compounds are acyclic.

The growth-regulating activity of these compounds of different structure indicates at the same time that the molecules of different structure but essentially the same effect interfere with the biochemical processes at different phases of the growth process.

On the basis of polarographic measurements of Veldstra (1944, 1947) a ring system of high surface tension and the specific steric position of the carboxyl group with respect to the ring should be added, to the structural conditions specified by Koepfli *et al.* (1938).

The structural requirements for activity established by Koepfli *et al.* include a carboxyl group in the molecule. As shown by numerous later investigations, this condition proved to be of general validity, with the modification that the parent compound need not necessarily contain a —COOH group; it is sufficient that the chain contain a group which is converted into a carboxyl group in the plant. Such compounds are the esters, amides, nitriles and alkanols, which are converted by hydrolysis or by biological oxidation into carboxylic acids. Phenoxycarboxylic acid esters are true herbicides, while the other derivatives should be considered as herbicide precursors, because in their original form they exhibit little or no herbicidal action, becoming herbicides only after their conversion.

The enzyme systems of single plant species differ specifically from one another; thus, the conversion of the precursor molecules will also be specific in them. For example, indolyl-3-acetonitrile shows strong activity on wheat and oat (Bentley and Housley, 1952), while it is inactive in the pea test (Seeley *et al.*, 1956).

Optical isomerism of phenoxycarboxylic acids also plays a decisive role in their activity. Of the amino acid derivatives of 2,4-dichlorophenoxyacetic acid and 2,4-dichlorophenoxypropionic acid only the derivatives of the DL- and L-amino acids are active, while the respective D-amino acid derivatives are completely inactive. This can be attributed to the fact that plants are unable to hydrolyse the peptide bond of the D-derivatives (Wood and Fontaine, 1952; Krewson *et al.*, 1956).

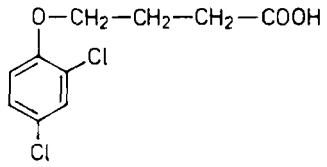
The statement of Koepfli *et al.* with respect to the unsaturated ring still holds true. All herbicides with auxin action that have been put on the market contain a phenyl ring.

Practice also proved the necessity for the side-chain in the case of the phenylacetic, phenoxyacetic and naphthoxyacetic acids. There must be an —O—, —NH— or —S— group between the ring and the side-chain, of which the O-moiety provides for highest activity (Fawcett *et al.*, 1955a).

In the case of indole and naphthalene derivatives, the position of the side-chain is also important from the point of view of activity. Indolyl-3-acetic acid is active, indolyl-2-acetic acid less so; 2-naphthoxyacetic acid is active, while 1-naphthoxyacetic acid is of modest activity (Kögl and Kostermans, 1935a, b; Zimmermann and Wilcoxon, 1935; Veldstra, 1944).

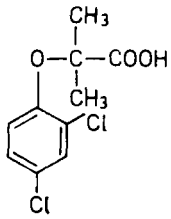
The "alpha-hydrogen" theory has been set up on the basis of a series of investigations of compounds with auxin action. According to this theory, phenoxy-, naphthoxy-, naphtho- and fluorenecarboxylic acid derivatives are active only if there is a hydrogen atom at the carbon atom adjacent to the carboxyl group (Osborne and Wain, 1949; Wain, 1953; Fawcett *et al.*, 1955b).

For example:



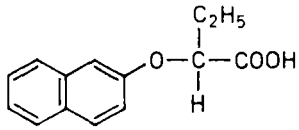
2,4-dichlorophenoxybutyric acid

active



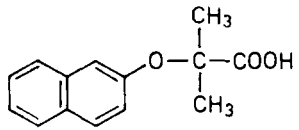
2,4-dichlorophenoxy-isobutyric acid

inactive



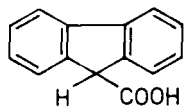
α-(2-naphthoxy)butyric acid

active



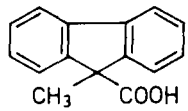
α-(2-naphthoxy)isobutyric acid

inactive



fluorene-9-carboxylic acid

active

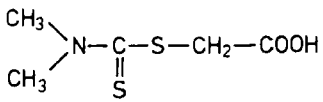


9-methylfluorene-9-carboxylic acid

inactive

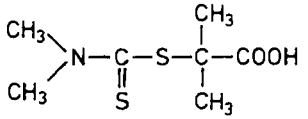
The importance of alpha-hydrogen is also illustrated by the dithiocarbamates with auxin action, discovered by Van der Kerk *et al.* (1955).

The recognition of the relationship between the carbon atom number of the side-chains of phenoxy acids and the activity of the compounds is due to the extensive work of Wain and his associates (Wain, 1955a).



S-carboxymethyldimethyl dithiocarbamate

active



S-(β-carboxyisopropyl)dimethyl dithiocarbamate

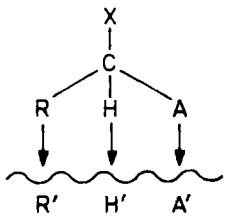
inactive

Indole-, naphthoxy- and phenoxyalkanoic acids contain an asymmetric carbon atom and are thus optically active compounds. Obviously, the question what is the relationship between the enantiomorphs and their biological activity may be raised. Investigations of Kögl and Verkaaik (1944), Thimann (1951), Fredga (1951), Smith and Wain (1951) and Aberg (1956) of various homologous series showed unequivocally that the D(+) form is considerably more active than the L(−) and the DL (racemic) forms.

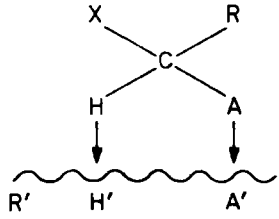
These observations suggest that molecules with auxin action interact with an asymmetric component of the cell responsible for growth.

Smith and Wain (1951), Smith *et al.* (1952), Schantz *et al.* (1955), and Wain and Wightman (1957) proposed a theory to explain the phenomenon, according to which the growth-regulating activity of aryloxy acids requires the presence of three essential groupings: an unsaturated ring system (R), an α-hydrogen atom (H) and a carboxyl group (A). These groups must make contact with the receptor groupings R′, H′ and A′ of the plant cell.

Considerable biological activity can be expected when a three-point contact is established between the molecule with auxin action and the groupings on the receptor surface; this is possible only in the case of the active stereoisomer. The inactive isomer can establish only a two-point contact, as shown by the following scheme:



3-point "active" attachment



2-point "inactive" attachment

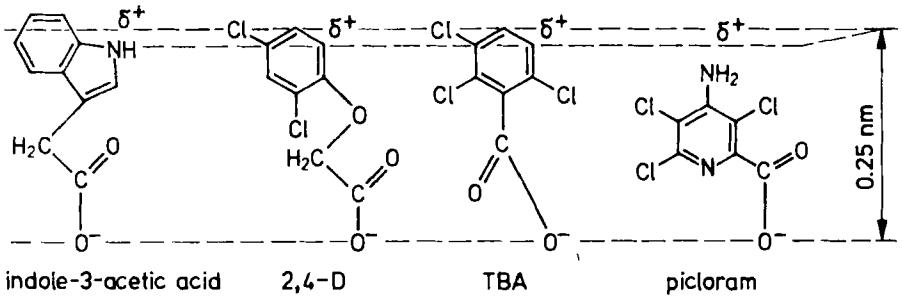
The investigations of Wain (1957) also showed that there exists a competitive antagonism between the stereoisomers. Thus, if the inactive isomer is present in a large quantity it will reduce the action of the active isomer, the molecules able to establish two-point contact exerting their antagonistic action by occupying the active receptor surfaces.

Other basic requirements for activity are, according to Jönsson (1955), that the molecule must have a near planar structure, that on at least one of its sides only hydrogen atoms can project, and that the carboxy group must be in a definite position with respect to the ring.

Schoot and Klassens (1956) extended the three-point theory to further aryl- and aryloxy-alkane carboxylic acids. In their opinion, the carboxyl group of the molecule attached to the active sites reacts to form high-energy phosphate, and subsequently S_N2 reaction proceeds at the α-carbon atom.

The receptor theory of auxin action has been further developed by Thimann (1969). Studying the auxin action by investigation of the electron structure of 4-indole-3-acetic acid, 2,4-D and 2,3,6-trichlorobenzoic acid (TBA), they found that the negative charge of the carboxyl group is at a distance of 0.55 mm from a fractional positive charge. They assumed that the receptor surface of the plant has a shape and charge distribution corresponding to these molecules. The theory is supported by the charge distance of 4-amino-3,5,6-trichloropicolinic acid (picloram) with auxin action later discovered to be 0.55 nm also. Moreover, 2,4,5-T has no auxin action, because position 6, needed for coupling, is occupied by chlorine.

The following diagram shows the steric configuration and the charge distribution of the compounds mentioned above:



The biological activity of unsubstituted phenoxyalkanoic acids is not substantial. The activity increases when a halogen substituent is present on the ring. Substitution of bromine and iodine increases the activity moderately; substitution of fluorine and chlorine increases it considerably, particularly in position 4. The activity of 4-chlorophenoxyacetic acid is ten times that of 2-chlorophenoxyacetic acid. However, monosubstituted phenoxy acids have not attained practical importance. The most biologically active compounds are to be found among derivatives disubstituted on the ring (Leaper and Bishop, 1951; Wain and Wightman, 1957).

The biological activity of isomeric dichlorophenoxyacetic acids is in the following order:

$$2,4- > 2,5- > 3,4- > 3,5- \geqq 3,6- \geqq 2,6$$

Of the isomers the 2,5- and 3,4- derivatives show considerable herbicidal activity, while the activity of the 3,5-, 3,6- and 2,6-derivatives is slight. It is interesting that 3,4-dichlorophenoxyacetic acid is well tolerated by some of the dicotyledonous crops, such as potato and cotton. Due probably to its more complicated and expensive synthesis, it has not been introduced in agriculture.

Of the disubstituted phenoxyalkanoic acids the 4-chloro-2-methylphenoxy derivatives (MCPA, MCPP, MCPB) are also of high activity.

Of the trisubstituted chlorine derivatives, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) is the most active. The order of activity of the isomers is:

$$2,4,5- > 2,3,4- > 3,4,5- > 2,3,5- > 2,4,6- > 2,3,6-$$

In this series only 2,4,5-trichlorophenoxyacetic acid has an activity of practical importance, the activities of the latter three derivatives are insubstantial. Tribromo derivatives show a similar order of activity. Exceptions of interest are 2,4-dichloro-6-fluorophenoxyacetic acid and 2,4-dibromo-6-fluorophenoxyacetic acid, which are very active. According to Toothill *et al.* (1956) this can be attributed to the steric properties of the molecules, as the free rotation of the side-chain is less hindered than in the 2,4,6-trichloro and 2,4,6-tribromo derivatives, because of the smaller diameter of the fluorine atom.

The activity of the compounds substituted in the 2,4,6 position at the same time disproves the earlier theory that a precondition of auxin action was a free *ortho* position.

Of the tetrachlorophenoxyacetic acids, only 2,3,4,5-tetrachlorophenoxyacetic acid is active, while the 2,3,4,6- and 2,3,5,6-isomers are inactive. Pentachlorophenoxyacetic acid has fungicidal activity, but no auxin action.

Alkyl substitution on the ring increases only the activity of chlorophenoxy acids. In practice, only 4-chloro-2-methylphenoxyacetic acid derivatives (MCPA, MCPP anc MCPB) are used in agriculture. Of the trisubstituted products, the structural analogue of 2,4,5-T — 2,4-dichloro-5-methylphenoxyacetic acid has considerable activity.

A longer alkyl chain, an alkoxy group, and nitro, amino, alkylamino, sulfo and other ring substitutions result in products of insubstantial activity. Aberg (1956) compared the growth-regulating actions of optically active methoxyphenoxypropionic acids and of their acetic acid analogues. He carried out similar investigations with optically active 4,5-dichloro-2-methoxy-, 2,4-dichloro-5-methoxy- and 2,5-dichloro-4-methoxyphenoxypropionic acids and the corresponding phenoxyacetic acids. 5-Chloro-2-methoxyphenoxyacetic acid, 4-chloro-2-methoxyphenoxyacetic acid and the corresponding racemic phenoxypropionic acid, 4-allyl-2-methoxyphenoxyacetic acid and 4-isoallyl-2-methoxyphenoxyacetic acid were also included in the investigations.

The main conclusions to be drawn from these investigations are that D(+) propionic acids have a stronger auxin activity than the corresponding acetic acids, while L(−) propionic acids have a marked antiauxin action.

An *ortho* substituted methoxy group reduces auxin activity, but does not cancel it in compounds of otherwise strong activity. The *meta* methoxy group strengthens the auxin action in phenoxyacetic acids, but causes decreased activity in otherwise strongly active compounds. The *para* methoxy group enhances activity in phenoxyacetic acids, but reduces it in phenoxypropionic acids.

The activity of methoxyphenoxyacetic acids with 4-allyl and 4-isoallyl substituents increases compared to the parent compounds, but they exhibit definite antiauxin action.

6.4.5 Mode of action and biodegradation of phenoxy herbicides

Several excellent survey studies have been published on research on the mode of action of phenoxyalkanoic acids (Woodford, 1958; Crafts, 1961; Wort, 1964; Penner and Ashton, 1966; Cast, 1975).

Phenoxy acid herbicides penetrate the plant through foliage, stem and roots alike and are translocated after absorption in the plant in both the phloem and xylem.

Phenoxy acid compounds, whether in the acid, salt or ester form, permeate the leaf culticule and, penetrating the plasmolemma through the apoplast, enter the living cell. Phenoxy herbicides affect almost all of the biological processes of plants. The first characteristic external symptom of the action is the abnormal growth of the axis, and the rapid decrease in growth of roots and foliage. This is followed by rapid senescene of the leaves, then by the wilting and collapse of the plant, and ends in complete destruction. Tolerant plants may endure the treatment without visible injury; they may suffer minor deformations which are later outgrown.

The characteristic growth-regulating auxin action of phenoxy herbicides brings about changes in water and mineral balance, in vitamin and oil content, in respiration and photosynthesis, nitrogen and phosphorus metabolism and in enzyme function (Wort, 1964b).

Obviously, many of these effects are indirect or secondary, as they become measurable only later, after the manifestation of the rapid auxin effect (Evans and Ray, 1969).

Most of the research on the mode of action of phenoxy herbicides concerns their effects on nucleic acid synthesis and enzymes.

Protein synthesis is regulated by enzymes, the necessary formation of which is regulated by repressors according to the biorhythm. The synthesis and functioning of enzymes begins when plant hormones stop the repressor effect. This increases the RNA level of the cells, and DNA fragments, latent until then, become activated. Natural auxins regulating the natural growth of plants exert their effect *via* DNA-dependent RNA and protein synthesis. On entering the plant, phenoxy herbicides with auxin effect exert a similar action. They cause abnormal growth by partly displacing and partly permanently substituting natural auxins, thus killing the plant (West *et al.*, 1960; Basler and Nakazawa, 1961; Chrispeels and Hanson, 1962; Key and Hanson, 1961; Shannon *et al.*, 1964; Moreland, 1969; Chen *et al.*, 1972).

There is experimental evidence that herbicides with auxin action also interfere at the gene level in the specific protein synthesis of plants. According to the investigations of Hanson and Slife (1969) and Key (1969), this probably occurs by the abnormal enhancement of messenger RNA production.

It can be considered that one bioactive function of herbicides with auxin action is the fundamental disturbance of vital protein synthesis; however, the primary rapid action, manifested a few minutes after treatment, cannot be explained by the disturbance of protein synthesis. Similarly, the contact effect produced at higher application rates of the herbicides cannot be explained by interference with gene function.

Earlier experiments of Evans and Ray (1969) with substances inhibiting protein synthesis also seem to disprove the theory that disturbance of protein synthesis is a fundamental determinant of biological action. Rubery and Northcote (1970) proved by *in vivo* experiments that herbicides with auxin action stimulate cell wall synthesis. The investigations carried out on cell-free plasma membranes isolated from onion stalk treated with 2,4-D, furnished further proof of the stimulation of polysaccharide synthesis.

The latter investigations also demonstrate another type of biochemical mode of action of herbicides with auxin effect.

Phenoxy acids are stable at normal temperatures, but they are decomposed by environmental factors — in sunlight, in the soil, in natural waters, and in plant and animal organisms.

Decomposition by different actions and in different media yields different metabolites and end-products.

None of the pathways of phenoxy decomposition result in the accumulation of toxic end-products. This group can be classed among the nonpersistent herbicides.

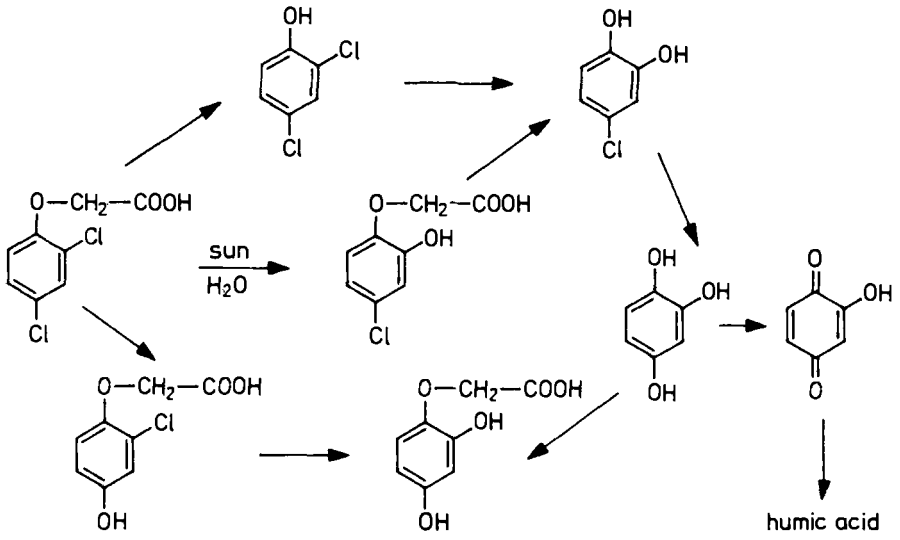
The most thoroughly studied of the phenoxy acids is 2,4-D. Its photochemical decomposition by hydrolysis and oxidation leads, through various intermediate products, to chlorine-free polyquinoidal humic acids. The cleavage of the phenyl—carbon bond, leading to the 2,4-dichlorophenol intermediate, is sensitised by riboflavin. 1,2,4-Trihydroxybenzene formed by hydroxy substitution is oxidised by air to 2-hydroxybenzoquinone, which is then polymerised (Crosby and Tutass, 1966) (see p. 523).

Crosby and Li (1969), on irradiating 2,4-DB and 2,4,5-T, observed the formation of similar humic acid polymers, which makes it very likely that decomposition proceeds by a similar route.

Degradation in the soil, however, proceeds mainly by the microbial route. The rate of microbial degradation depends on the biological activity, organic matter content, pH, temperature and water content of the soil (Loos *et al.*, 1967).

Soil microorganisms degrade chlorophenoxyacetic acids according to several schemes. The processes may proceed simultaneously (Audus, 1961) (see p. 524).

Soil organisms degrading chlorophenoxyacetic acids are mainly bacteria and a few *Actinomyceta* species. Among such bacterial species are *Achromobacter, Arthrobacter, Corynebacterium, Flavobacterium, Mycoplasma* and *Rhizobium* sp.



(Woodford and Sagar, 1960; Audus, 1964; Bounds and Colmer, 1965; Martin, 1963).

Certain soil microorganisms are remarkably selective; for example, they may decompose 2,4,-D, but not MCPA and 2,4,5-T (McRae and Alexander, 1965).

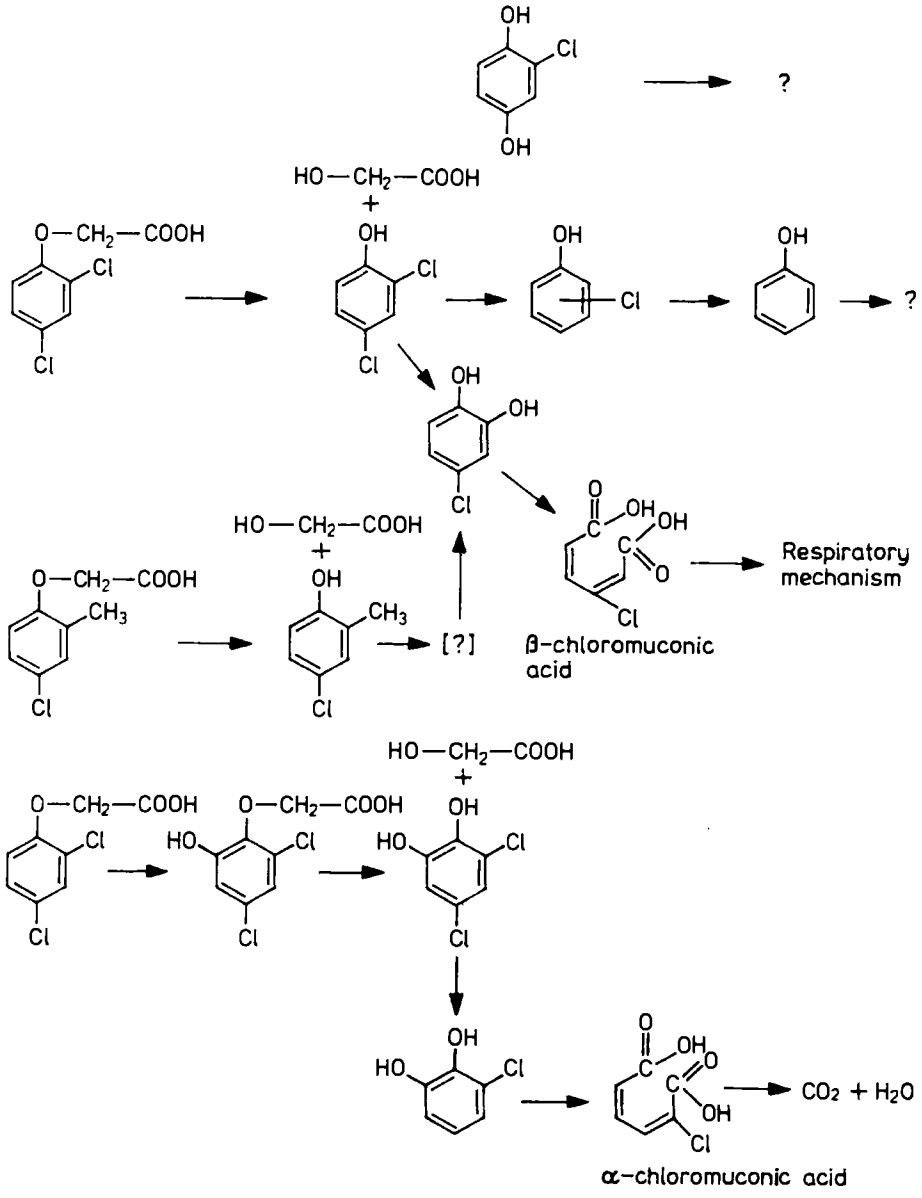
In microbiologically active soils degradation is rapid. Because of reasons mentioned above, the length of time of the herbicidal efficiency of 2,4-D at the usual application rate varies considerably. Generally, it is claimed to be 1–4 weeks (Audus, 1964; Sheets and Harris, 1965). In the maize fields of Mexico, Agundis (1964) measured a maximum of 60 days. Crafts and Robbins (1962) report on a 6–9-month persistence of 2,4-D in the dry southern and southwestern regions of the USA.

The metabolism of MCPA in plants of higher order and in the soil microorganisms is similar to that of 2,4-D (Luckwill and Lloyd-Jones, 1960; Leafe, 1962; Crafts, 1964). Similarly to 2,4-D, at normal rates it is not hazardous to the microflora, its action being even weaker than that of 2,4-D (Domsch, 1963).

Of the phenoxyacetic acids, 2,4,5-T is the slowest to degrade by the microbial route. In an identical soil and under identical climatic conditions its degradation time is three times that of 2,4-D (Sheets and Harris, 1965). Evidently, the fact that several microorganisms able to degrade 2,4-D do not decompose 2,4,5-T plays a part here (Newman *et al.*, 1951; Newman and Downing, 1958).

The persistence of the higher homologues of phenoxyalkanoic acids and the propionic acid and butyric acid derivatives is higher than that of the acetic acid derivatives (Van der Zweep, 1960).

Alexander and Aleem (1961), Burger *et al.* (1962), and Alexander and Lustigman (1966) found in their investigation of α-substituted and ω-substituted phenoxyal-



kanoic acids that those ω-substituted phenoxyalkanoic acids, containing a chlorine atom in the *meta* position in the ring with respect to the ether bond, are persistent, while ω-substituted compounds containing no *meta* halogen are rapidly detoxicated and their ring opens. α-Substituted phenoxyalkanoic acids are rather

persistent, however, independent of the position of chlorine atoms in the ring (see Table 6.2).

It can be seen from Table 6.2 that derivatives containing chlorine in the *meta* position, namely 3,4-dichloro- and 2,4,5-trichlorophenoxyalkanoic acids, are considerably more resistant to biological degradation than 4-chlorophenoxy- and 2,4-dichlorophenoxyalkanoic acids, which contain no chloro substituent in the *meta* position.

Table 6.2

Effect of chemical structure on the degradation of phenoxy compounds in soil suspensions in days required for ring cleavage (Alexander, 1972)

Fatty acid moiety	Ring portion of the molecule			
	4-chloro-phenoxy	2,4-dichloro-phenoxy	3,4-dichloro-phenoxy	2,4,5-trichloro-phenoxy
-acetic acid	11	26	205	205
-propionic acid	11	4	81	81
-butyric acid	53	11	205	205
-propionic acid	205	205	205	205
-valeric acid	81	81	81	81

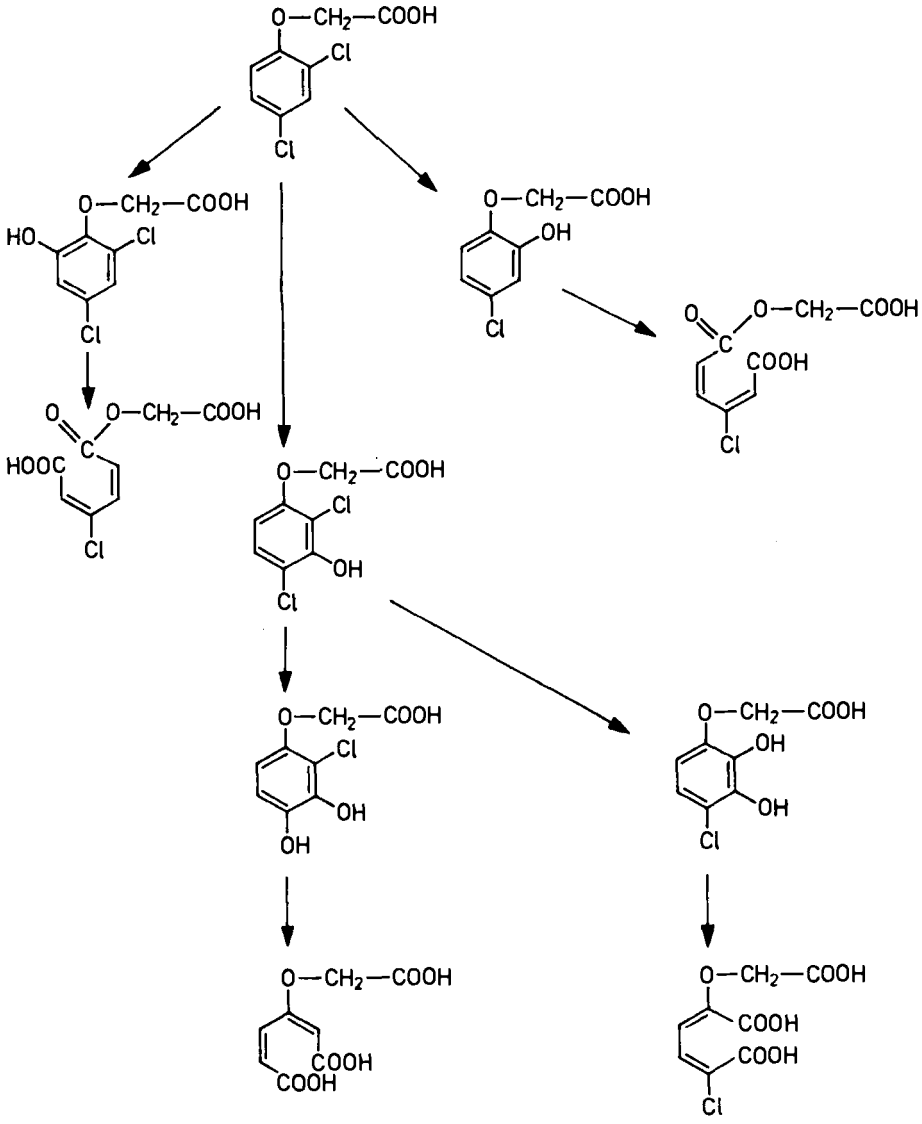
A similar relationship was also found in the microbial degradation of various halogenated phenols (Alexander and Lustigman, 1966). Further investigation of such structural correlations may create good possibilities for the preparation of biodegradable pesticides of shorter life.

The difference between the microbial degradability of α- and ω-substituted phenoxy compounds can be explained by the general metabolism of fatty acids. The degradation of fatty acids generally occurs by β-oxidation. For this two protons must be abstracted from the α- and β-carbons. If even one of these carbons carries a substituent other than hydrogen, the organism cannot carry out the β-oxidation, or if so, only with difficulty. The α carbon atom of α-substituted phenoxy compounds carries a phenoxy substituent. According to Alexander (1972) this is why they are not rapidly degraded.

Bach (1961), on the basis of metabolites isolated from bean stalks treated with ^{14}C 2,4-D, proposes a pathway for the metabolism proceeding in plant of higher order in which hydroxylation plays the main role in detoxication. The 2,4-D ether bond remains intact, throughout, even after the cleavage of the ring: (see pp. 526–527).

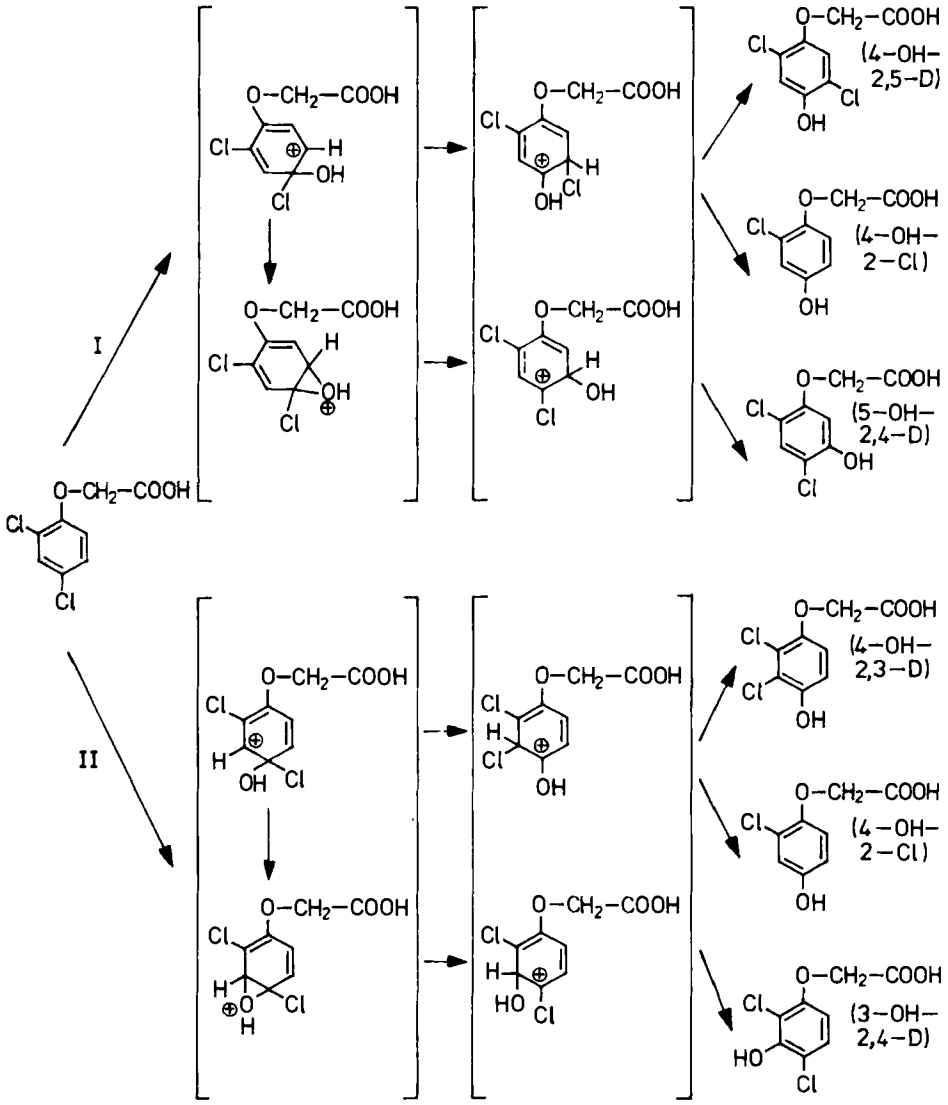
Between 1967 and 1975 several authors studied the metabolism of 2,4-dichlorophenoxyacetic acid in callus tissue cultures of soybean, beet, bean, sunflower, tobacco, maize and a few grasses. Hagin *et al.* (1970) found in their investigations that 2,4-D is metabolised by resistant grass species into 2,4-dichlorophenoxypropionic acid, the inactive homologue. The other plants investigated have a common metabolic pathway.

According to the investigations of Feung *et al.* (1971, 1973, 1974, 1975) callus tissue cultures metabolise 2,4-D by ring hydroxylation and conjugation with amino



acids. The relative ratio of metabolites, however, changes considerably according to the species. Tolerant maize contained 4-OH-2,3-D in unusually large quantities along with two metabolites, 3-OH-2,4-D and 4-OH-2-Cl, which could not be detected in the dicotyledons investigated.

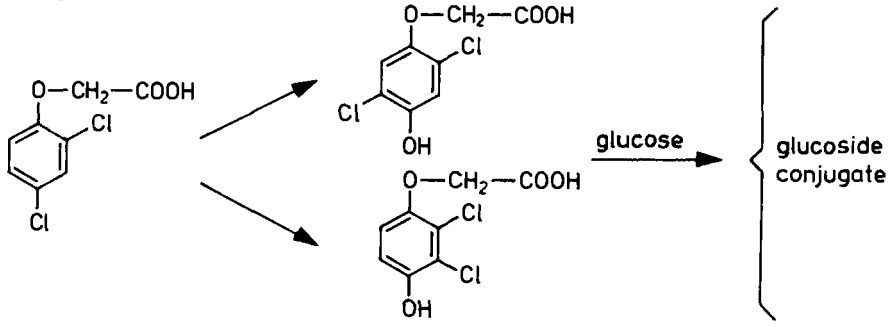
The probable pathway of the biological oxidation of 2,4-D is shown by the following scheme. Conversion pathway I is characteristic mainly of dicotyledons, while pathway II is characteristic of monocotyledonous maize:



The excretory activity of plants of higher order is considerably less than that of animals. For the elimination of harmful substances plants form conjugates in enzyme-catalysed reactions with compounds entering the cells. The pesticide metabolised by conjugation is deposited after or without polymerisation in the inactive parts of the cell, such as in the cell walls.

Of the cellular substances sugars, amino acids, peptides and macromolecular constituents are able to conjugate. Phenoxy acids form conjugates with the glucose, amino acids and proteins of the cellular substance of plants of higher order.

During metabolism, 2,4-D is hydroxylated at the ring, one of its chlorine atoms shifts into position 3 or 5, and the hydroxy group then conjugates with the glucose (Feung *et al.*, 1971):



In beans the β-D-glucoside of 4-hydroxy-2,5-dichlorophenoxyacetic acid has been detected. Several researchers had already found that non metabolised 2,4-D also forms ester conjugates in plants of higher order.

The amino acid conjugates of 2,4-D have been extensively investigated by Feung *et al.* (1971, 1973).

In the callus tissue cultures of soybean cotyledon 2,4-D is rapidly conjugated by one amide bond with several amino acids, thus glutamic acid, aspartic acid, alanine, valine, leucine, phenylalanine and tryptophan conjugates have a growth-stimulating action. Twenty L-form amino acid- 2,4-conjugates, prepared in later investigations, stimulated division and elongation in both the *Avena coleoptil* test and in callus tissue culture cells. As with 2,4-D, the conjugates inhibit elongation and growth at higher concentrations. These are typical auxin effects, so the formation of 2,4-D glutamic acid, aspartic acid, alanine, valine, leucine, phenylalanine and tryptophan conjugates cannot be considered a detoxication mechanism (Feung *et al.*, 1974).

Feung suggests two possibilities for the explanation of the activity of certain 2,4-D conjugates higher than that of 2,4-D. One is that 2,4-D is the active molecule, as it is later set free from the amino acid conjugate during metabolism, so that the higher activity of the conjugates is to be attributed to secondary factors, such as change in uptake or metabolism.

The other possibility is that these conjugates are necessary active intermediates for the plant in the detoxication process. Indeed, the glutamic acid conjugate of 2,4-D is more rapidly converted into the inactive 4-OH-2,3-D or 4-OH-2,5-D than 2,4-D itself.

2,4-D can be attached to macromolecules, such as proteins (Galston and Davies, 1969).

According to feeding experiments with phenoxy herbicides, these compounds do not accumulate in animal organism. They are rapidly absorbed through the intestines and distributed in the organs, some of them being bound to plasma proteins (Erne, 1966; Matlieb *et al.*, 1971). After a brief period, active absorbed

substances are excreted, mainly through the kidney. The average half-life of 2,4-D in rats is 3.1 hours (Khanna and Fang, 1966; Zielinski and Fishbein, 1967). Feeding experiments with sheep also showed rapid excretion. Of a 4.0 mg/kg dose fed to the sheep, 50% was excreted in the wire after 8.5 hours, more than 90% after 28 hours, and nearly 96% after 72 hours. The 2,4-D level in blood 1.5 hours after administration was 1.2 μg/ml; after 24 hours it could no longer be detected. 2.4-D could be detected only in traces (0.05 ppm) in the flesh of sheep (Clark *et al.*, 1964).

In 106-day feeding tests lactating cows were fed a diet containing 5.5 g of 2,4-D daily. At the end of the test no 2,4-D could be detected in the liver, kidney or fatty tissues, or in the milk. Blood serum contained 8.4 ppm of 2,4-D (Lisk *et al.*, 1963). 2,4-D ester derivatives undergo hydrolysis in the animal organism and are metabolised to 2,4-D acid, the total quantity of which is excreted unchanged. MCPA introduced with the food is similarly excreted in unchanged form in the urine (Bache *et al.*, 1964a).

On feeding 113.5 mg doses of 2,4-DB to sheep, Lisk *et al.* (1963) found that 3.4% of the dose is excreted in unchanged form and 8.2% as 2,4-D in the urine. This indicates that predominantly 2,4-DB metabolism does not proceed *via* β-oxidation.

Bache *et al.* (1964b) added the daily amount of 50 ppm of MCPB to the fodder of lactating cows for four days. The milk did not contain a detectable quantity (0.1 ppm) of MCPB.

Of the MCPB administered 7.2–9.2% was metabolised by β-oxidation to MCPA and was excreted on the first day in the urine. No data are given on the quantity of unchanged MCPB in the urine or on the metabolites.

2,4,5-T administered orally to rats, pigs, calves and chickens is rapidly absorbed by the intestines and concentrated in the liver, kidney, lung, spleen and other tissues. Its half-life is 5–30 hours (Erne, 1966).

Clark and Palmer (1971) administered a single oral dose of 2,4,5-T propylene glycol butyl ether to sheep and cattle; 86% of the dose was excreted in the urine in unchanged form and 1.4% in the form of 2,4,5-T in 72 hours. In blood the maximum concentration was measured 4 hours after administration. Even after 36 hours a low but measurable quantity of residue was found. Concentrations measured in the tissues and blood depended on the dose given and on the length of time of the treatment.

Piper *et al.* (1973) fed radiolabelled 2,4,5-T to rats and dogs in doses of 5–200 mg/kg body weight.

The most important finding of these investigations was that the half-life of 2,4,5-T is much shorter in the plasma of rats than in that of dogs, explaining why 2,4,5-T is more toxic to dogs than to rats.

After oral administration of a single 5 mg/kg dose of 2,4,5-T to humans, plasma concentration reached a maximum in about 6 hours, but even after 96 hours a detectable quantity of 2,4,5-T was present. 98% of the dose was excreted in unchanged form in the urine 98 hours after administration.

In 28-day subacute feeding tests Clark *et al.* (1975) fed sheep and cattle 300, 1000 and 2000 ppm 2,4-D, 2,4,5-T and 2,4,5-T propionic acid. Muscle and fat tissues

contained the smallest quantity of residue, renal tissue the highest. After a feeding pause of 1–2 weeks, the residue in the tissues decreased drastically. Adverse effects were observed only in the case of the highest dose. Smaller doses caused only a decrease in weight of the experimental animals because of anorexia.

Erbon administered perorally to sheep is metabolised to 2,4,5-trichlorophenol and 2-(2,4,5-trichlorophenoxy)ethanol and is excreted mainly in the urine. Rumen fluid is able also to metabolise erbon *in vitro* into 2-(2,4,5-trichlorophenoxy)ethanol.

On feeding Kuron 2-(2,4,5-trichlorophenoxy)propionic acid (fenoprop) for 4 days in doses of 5 ppm, it could not be detected in the milk or urine of cows. 64% of the Kuron administered was excreted in the form of silvex in the urine (St. John *et al.*, 1964).

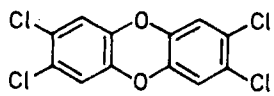
As phenoxy acids are used mainly in maize, pastures and aquatic weed killing, their residues or metabolites are possible hazardous in the food chain, and a thorough investigation of their environmental toxicology is justified.

On the basis of long experiences and an immense amount of investigative material, phenoxy herbicides have been judged to be medium acute toxic and nonpersistent, and it has been determined that they do not accumulate in the organism. They are relatively toxic to fish and to organisms that serve as food for fish, while their normal use does not involve hazards for wildlife (Rowe and Hymas, 1954; Erne, 1975). They are generally hazardous to bees, so that their use is not permitted on flowering weeds.

During the decomposition of phenoxy acids as discussed, no decomposition products or metabolites more toxic than the original compound are formed, so there is no acute or chronic hazard to humans or the environment.

For reasons of food hygiene, before plants treated with phenoxy acids are given to animals or humans, different waiting times, varying between 14 days and 1 month, are prescribed in various countries. The internationally tolerated amounts of residues vary between 0.01 and 0.1 ppm (Maier-Bode, 1971).

However, there was apparently grave concern over 2,4,5-T derivatives in 1969 in the USA. On the basis of the investigations of the Biogenetics Research Laboratory the Office of Science and Technology called attention to a possible teratogenic effect of 2,4,5-T, and in 1970 the use of 2,4,5-T on food plants was banned. Subsequent intensive investigations did not verify the teratogenic effect of pure 2,4,5-T in routine applications. In other investigations the teratogenic effect could be demonstrated in rats, rabbits and mice in the case of a technical product containing dioxin (3,4,6,8-tetrachlorodibenzo-1,4-dioxin, TCDD, **16**).



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Its acute toxicity for rats is 0.6 μg/kg. In doses of 0.001 mg/kg TCDD produces teratogenic effects in small mammals. This TCDD dose corresponds to 100 mg 2,4,5-T/kg/day.

It was found that in soils no TCDD is synthesised from the chlorophenol metabolites of 2,4,5-T, nor is it formed photolytically from 2,4,5-T. TCDD applied on the leaves is not taken up or translocated by the plants. Investigations showed that even after applying 2,4,5-T at high rates to the soil, no TCDD could be detected. Since 2,4,5-T manufactured by today's processes generally contains less than 0.5 ppm, usually 0.1 ppm, of TCDD, the authors are of the opinion that normal use of 2,4,5-T does not involve any hazard to humans.

The investigations of Wilson (1973) led to similar conclusions. After a 7-year application of 2,4,5-T at abnormal rates (1000 kg active ingredient/ha) no TCDD was found either in the soil or in the animals grazing in the treated area.

The slow decomposition by ultraviolet light of TCDD reaching the environment from other sources can be considerably accelerated by the process developed in the Dübendorf Laboratory of Givaudan SA. In this method the contaminated plants are sprayed with an oil-in-water emulsion of olive oil and water (Anonym, 1976).

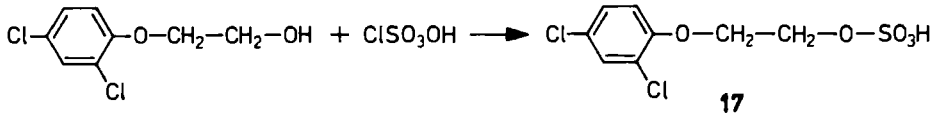
6.4.6 Phenoxyethanol herbicides

An interesting development of phenoxy herbicides is the preparation of the so-called precursor compounds. These herbicidal precursor compounds generally do not have much biological activity, but they are converted either by a purely chemical route or by chemical and biological oxidation into compounds with herbicidal activity.

During their investigation of phenoxy herbicides Synerholm and Zimmermann (1947) had already observed that in the homologous series of 2,4-dichlorophenoxy-alkanoic acids those compounds are biologically active in which the side-chain contains a methylene group with an uneven number of carbon atoms. The biochemical explanation of this phenomenon is linked with the names of Wain and Wightman (1955), who established that the homologues with herbicidal action are metabolised in the plant organism from the inactive precursor compound into 2,4-dichlorophenoxyacetic acid (see Section 6.4.3).

The manufacture of phenoxyethanols and their derivatives began in the 1950s on this basis. These derivatives generally act only through the soil, absorbed by the roots, while their foliar activity is moderate because of their anionic character.

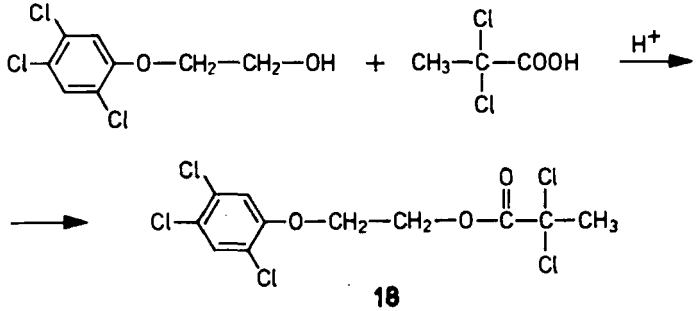
The first ethanol derivative made was sodium 2-(2,4-dichlorophenoxy) ethylsulfate (2,4-DES, sesone, **17**) (Lambrech, 1951). It is prepared by the reaction of 2,4-dichlorophenoxyethanol with chlorosulfonic acid.



17

2,4-DES was applied in the form of its sodium or ammonium salt for the preemergence control of broad-leaved and grassy weeds (Crag Herbicide-1®, Amchem).

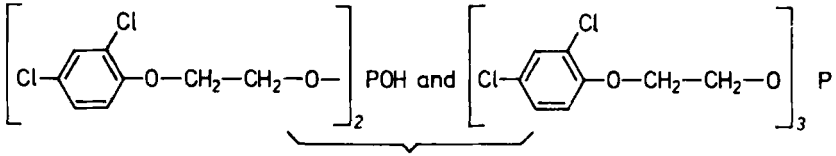
Erbon, 2-(2,4,5-trichlorophenoxy)ethyl 2,2-dichloropropionate (**18**) was prepared by esterification of 2,4,5-trichlorophenoxyethanol with an equimolar ratio of 2,2-dichloropropionic acid in ethylene dichloride, in the presence of sulfuric acid as catalyst:



18

Erbon is a translocatable herbicide absorbed through roots and foliage, applied pre- or postemergence as a total herbicide. Its action lasts over one season. It is converted in the soil and in the plant into 2,4,5-trichlorophenoxyacetic acid and dalapon with herbicidal action.

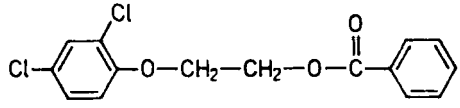
2,4-DEP (falone, **19**), a mixture of tris[2-(2,4-dichlorophenoxy)ethyl]phosphite and bis[2-(2,4-dichlorophenoxy)ethyl]phosphite is prepared by the reaction of 2,5-dichlorophenoxyethanol with phosphorus trichloride in the presence of pyridine:



19

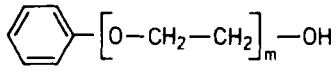
In maize, potato and peanut it is a selective herbicide effective for the control of mono- and dicotyledonous weeds in the seedling stages. It is hydrolysed by moisture in the soil to 2,4-dichlorophenoxyethanol.

[2-(2,4-Dichlorophenoxy)ethyl]benzoate (2,4-DEB, **20**) was developed by Lambrech (1951). It has attained a certain importance as a selective pre- and postemergence herbicide.

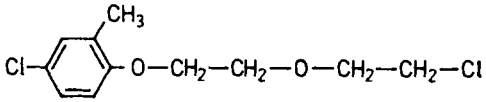


20

Other esters, acetates and other preherbicidal derivatives of phenoxyethanols are also known from the patent literature; however, they have not attained much importance so far. Glycol ethers with a longer carbon chain of the following formula exhibit herbicidal action:

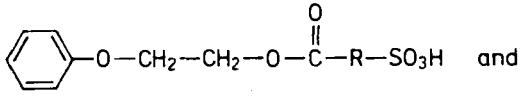


Japanese researchers recognised the herbicidal precursor activity of 4-chloro-2-methyl(phenoxyethyl)-1-chloromethyl ether **(21)**.



21

Derivatives of phenoxy- and alkylphenoxyalkanol esters are known, the acyl radical of which carries an SO_3H substitution **(22, 23)**:



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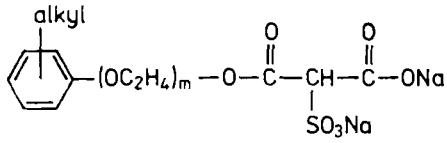


23

Südi *et al.* (1959, 1961) investigated the effect of various N-substituted amides of 2,4-D, 2,4-DP, 2,4,5-T and 2,4,5-TP, applying them alone and simultaneously with the parent acid. Of the 21 acid amides investigated 13 exhibited an antiauxin action, antagonising the auxin activity of the respective phenoxyalcanoic acid. At the same time, the compounds also had their own auxin action, showing on the one hand that amides too have an auxin action, and on the other hand that they are metabolised in plants by the enzymatic pathway to the respective acids and are thus the precursors of the acids.

Südi *et al.* extended their investigations to 2,4-dichlorophenoxyethanol (DCPE) and 2,4-dichlorophenoxyacetaldehyde (DCPA). These two compounds also differ with respect to selectivity, and there is a difference of about one order of magnitude between the activity of DCPA and that of 2,4-D. These results served as the basis for extensive research work started in the Budapesti Vegyiművek (Hungary), which eventually led to the development of 2,4,5-trichlorophenoxyethanol (TCPE,

Klorinol®) and a synergised herbicide (Buvinol®). The herbicide with the trade name Buvinol® contains 50% by weight TCPE as active ingredient and 50% atrazine (Vásárhelyi *et al.*, 1967, 1968; Bihari *et al.*, 1967; Bánki, 1973; Bánki and Bihari, 1976).

The first step in the synthesis of phenoxyethanols is the preparation of the respective chlorophenol. This is followed by its condensation to the phenoxyethanol compound.

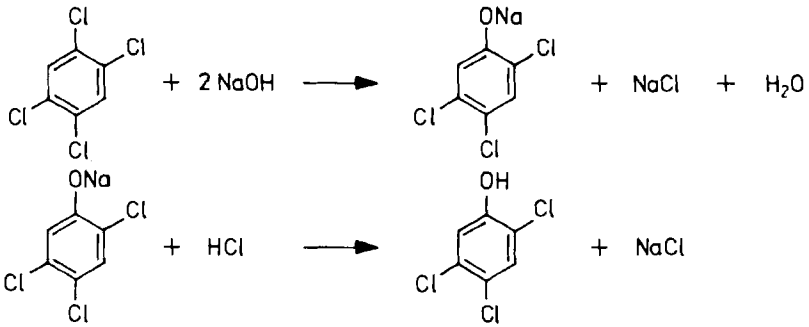
The main problem of 4-chlorophenol preparation is to prepare a chlorophenol mixture of the most favourable *para : ortho* ratio possible. On chlorinating phenol with a mixture of sulfur dioxide and chlorine in the presence of catalysts of Lewis acid type with chlorine a *para : ortho* ratio of 1.8 : 2.1 can be attained (Valovits, 1970). The *para : ortho* ratio can be further increased by using special solvents, such as acetonitrile and methyl nitrate (Zubarjav, 1966).

According to a patent of the Sumitomo Co. (1965), tris-phenol phosphate is prepared from phenol by esterification with phosphorus oxychloride, which is then chlorinated, yielding after hydrolysis a chlorophenol mixture with an *ortho : para* ratio of 8 : 1. Using sulfuryl chloride (SO_2Cl_2) as chlorinating agent, a chlorophenol mixture of *ortho : para* ratio 4.1 : 5.7 is formed in the presence of Lewis acid catalysts.

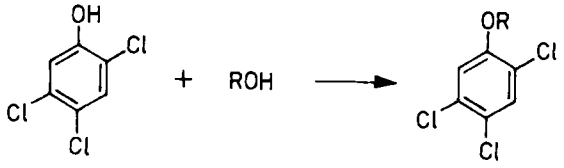
2-Methyl-4-chlorophenol (MCP) can be prepared by the chlorination of *o*-cresol, but to attain a better yield and an end-product of higher purity, in practice cresoxyethanol is preferably chlorinated to yield 2-(4-chloro-2-methylphenoxy)-ethanol (MCPE) (Ouchi, 1960), or 2-methylphenoxyacetic acid is chlorinated to yield 4-chloro-2-methylphenoxyacetic acid (Reisinger and Hinterbauer, 1966); 4-chloro-2-methylphenoxyethanol can be obtained from this by reduction with aluminium hydride (Kjelgaard, 1956).

2,4,5-Trichlorophenol is prepared indirectly, by the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene, because the direct chlorination of 2,5-dichlorophenol, difficult to achieve, proceeds with poor yield.

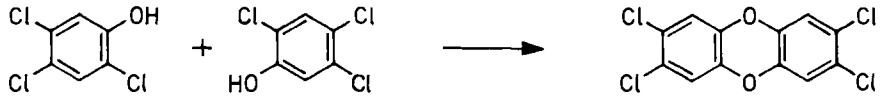
Alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene is carried out at a temperature of not less than 160°C in aqueous solution or in a solution of alcohol of low carbon atom number alcohol solution under pressure, or at normal pressure in glycol medium of high boiling point. In the latter case, 2,4,5-trichlorophenol glycolether is formed as a by-product:



and the side-reaction:



If the hydrolysis reaction "runs away with itself" and the temperature goes above 200°C and there are traces of Cu (II) ions present in the system, the very poisonous 3,4,7,8-tetrachlorodibenzo-1,4-dioxin (TCDD, **16**) is formed as a by-product:



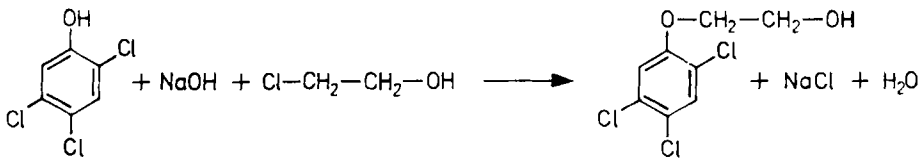
16

The above hydrolysis reaction is suitably carried out in methanol, because under these conditions the target product is formed at 160°C in 8 hours in a yield of about 90%. The alkaline methanolic reaction mixture is then directly condensed with ethylene chlorohydrin, and in this case 2,4,5-trichloroanisol, formed during the reaction, also yields 2,4,5-TCP (Vásárhelyi *et al.*, 1967). Solubility conditions of the organic components can be controlled by controlling the inorganic ion concentration of the condensation mixture, and thus secondary reactions can be suppressed (Vásárhelyi *et al.*, 1968).

The second reaction step in the preparation of chlorophenoxyethanols is condensation with ethylene oxide, ethylene chlorohydrin or diethyl carbonate. Reduction of the respective acetic acid derivative is also feasible but uneconomical.

Condensation with alkene oxide can be carried out in solution or melt at a yield of about 90% (Begin, 1955; Distler and Schneider, 1966; Yasuhiro, 1966).

Condensation with diethyl carbonate gives a pure product with a good yield (Lacombe and Stewart, 1963), but is more expensive than condensation with ethylene chlorohydrin, which is used almost exclusively today. Several methods for this process have been patented (Bingler and Model, 1955; Bliznyuk, 1966; Vásárhelyi *et al.*, 1967, 1968), differing from one another with respect to technical details, molar ratios used, reaction medium and temperature. The process is described by the following reaction scheme:



24

The 1 : 1 mixture of 2-(2,4,5-trichlorophenoxy)ethanol (TCPE, **24**) and atrazine (Buvinol®) is a selective pre- and postemergence herbicide with a broad range of herbicidal action. Many species of mono- and dicotyledonous weeds are sensitive to it in their various stages of development. Postemergence treatment is recommended in soils with extremely low humus content (below 1%) because of the hazard of phytotoxicity, and in soils with extremely high humus content because of strong adsorption.

Digitaria spp. and *Panicum* spp. are tolerant in all stages of development; *Echinocloa crus galli* is tolerant in the seedling stage and in stages beyond the 3–4-leaf stage.

Used pre- and postemergence in maize at rates of 4.5–7.0 kg/ha, in vineyards and apple and pear orchards at rates of 10–18 kg/ha, and in seed alfalfa (2-years old or older) at rates of 5–8 kg/ha, its action lasts for a year.

At a rate of 25–45 kg/ha, it can be used as a total herbicide in industrial areas and on roadsides. At this rate the action lasts several years (Bihari and Radvány, 1976).

The diffusive movement of TCPE in various soils saturated up to water capacity has been investigated by Stefanovits and Tomkó (1976). Applied at rates of 1.2 and 2.5 kg/ha, the diffusive movement of TCPE in the soil is slight. Even the higher dose applied at the soil surface did not reveal any bioactivity characteristic of TCPE at a soil depth of 1 cm. With increasing humus content adsorption increases, that is, the movement of the herbicide decreases. The number and properties of the adsorption sites formed at the surface of the humus molecules depend on the circumstances of humus formation, or, on the genetic properties of the soil. Forest soils of acid character contain more free humic acids; thus there are more phenolic hydroxy groups and carboxy groups at the surface of the molecules. During chernozem formation in weakly alkaline medium, humus molecules containing fewer OH and COOH groups are formed, and most of these are bound to calcium or clay minerals. The number of adsorbing sites is therefore less. This explains the different measures of adsorption observed in soils of identical humus content. However, the various adsorption properties of different kinds of humus do not essentially affect the quantity of adsorbed TCPE. The movement of the herbicide in the soil is also influenced by the pH of the soil. The herbicide is washed in to a greater depth with increasing pH. This is obvious, because the solubility of 2,4,5-T of acid character, formed during the biological oxidation of TCPE, changes as a function of pH.

Results of the acute toxicological tests of TCPE and Buvinol® (25% TCPE + 25% atrazine) are contained in Table 6.3 (Bordás *et al.*, 1976).

On the basis of the results of acute toxicity tests, TCPE and Buvinol® can be classed as "weak poisons". They irritate the eye mildly or not at all and are mildly inflammatory to the skin. Oral doses of 80 mg/kg are still toxic from the standpoint of pathological histology, injuring the heart, liver and kidney. Transitory lesions of the tissues are manifested by parenchymal and hyaloid degeneration.

The initial toxic symptom of absorbed Buvinol® is a narcotic state, which may be followed by transitory of permanent paralysis of the central nervous system (Bordás, 1976).

Table 6.3
Results of the acute toxicological tests of TCPE and Buvinol®

Toxicological parameters (animal species)	TCPE active substance	Buvinol® WP
Acute oral LD_{50} (rat)	1490 ± 89 mg/kg	5000 ± 358 mg/kg
Acute intraperitoneal LD_{50} (rat)	450 ± 22 mg/kg	—
Acute percutaneous LD_{50} (dermal) (rat)	7100 mg/kg	> 2100 mg/kg
Acute inhalation LC_{50} (rat)	—	> 1070 mg/m³
Cumulative toxicity (rat)	—	daily 0.5 g/kg nonlethal over 50 days
Acute irritative effect on the eye (rabbit)	transitory mild irritation	transitory mild irritation
Acute dermal irritative effect (rabbit)	transitory mild irritation	moderate irritation
Sensitising effect (guinea pig)	—	does not sensitise

Dési *et al.* (1976) investigated the acute and subacute toxicity and irritating effect of CPE, DCPE, TCPE, MCPA, atrazine and Buvinol®, and the effect of these compounds on the learning process, learning index, and EEG of rats. Acute toxicity values of the compounds investigated showed the following increasing order: Buvinol® < atrazine = TCPE < CPE = MCPE < DCPE; numerically: (LD_{50}: mg/kg) 2810, 1870, 1870, 1270, 1270 and 840.

In 90-day feeding tests the increase in weight of animals receiving ethanols was the same as that of the control animals, while the weight of animals fed an atrazine diet was considerably less than that of the controls.

An evaluation of changes in erythrocyte and leucocyte count showed that DCPE and MCPE considerably increased the erythrocyte-count, while DCPE considerably reduced the granulocyte count.

Histological examination of lung, heart, spleen and kidney showed no effects. The liver of animals fed an MCPE diet showed grave acinocentral adiposis.

The learning index of the TCPE group approximated that of the control group. The learning index was worst in the group treated with CPE. EEG curves indicated no cases of neurotoxic disturbances; results of the group fed an MCPE diet were the most favourable.

To establish the subacute toxic threshold value (ADI = allowable daily intake) of Buvinol®, Barta-Bedő and Geffert (1976) carried out 90-day feeding tests in male and female albino rats. Mixed with the food, the herbicide was fed at levels of 1,3,4,5 and 8 mg per kg body weight per day. The gain in body weight, carbohydrate metabolism—starving sugar level, glucose tolerance—the glycogen content of liver, glucose-6-phosphatase activity and pyruvic acid concentration of the serum were investigated. None of these functions revealed pathological changes. In the serum

of females fed on an 8 mg/kg level and in that of males fed on 4 and 8 mg/kg levels, the amount of total lipids significantly decreased and the lipase activity of the serum decreased in a similar measure. In protein metabolism and in the alkaline phosphatase and β-glucuronidase tests no pathological changes could be observed. The feeding of Buvinol® did not cause significant changes in the detoxicating function of the liver or in the aminopyrine-demethylase and aniline-dehydroxylase activities; the aminopyrine-demethylase enzyme function was significantly reduced only in females fed a diet containing Buvinol®, at the level of 8 mg/kg.

On the basis of these results, researchers suggest 4 mg Buvinol®/kg/day as the subacute toxic threshold level (ADI). This value is larger by several orders of magnitude than the normal application and consumption level.

Czeizel and Király (1976) carried out chromosome tests in male labourers 20–61 years of age engaged in the manufacture of TCPE and Buvinol®. Using the method of Moorhead *et al.* (1960) they investigated the lymphocytes of peripheral blood after 48 hours culture. The Edinburgh method (Buckton *et al.*, 1962; Court-Brown *et al.*, 1967; Buckton and Evans, 1973) was used for evaluation, that is, the numerical distribution of chromosomes and the chromatid and chromosome-type injuries were recorded. The modal and nonmodal chromosome numbers of zero-control and factory control did not differ considerably.

A difference of considerable significance ($p < 0.001$) was found between the *o*-control and the factory control groups in aberrations of unstable chromosome type; however, the values of workers manufacturing TCPE and Buvinol® and those of workers not in contact with these substances did not differ significantly, so the difference in aberrations may be attributed to a general chemical mutagenic effect. The phenomenon has been observed in the less pathognomonic gaps and in the isogaps. On the other hand, it is remarkable that the greatest number of chromosome aberrations has been observed after exposure to tetrachlorobenzene, used as positive control, and exchange forms occurred in this group alone.

Kellner *et al.* (1976) investigated the carcinogenic effect of TCPE. In the first phase of the experiments 100 male and 100 female mice were fed once a week for a year the maximum tolerated dose (MTD), 70 mg unpurified TCPE per kg (1.6 ppm TCDD content), and purified TCPE (> 0.1 ppm TCDD content). In the first phase of the experiments no difference was observed in longevity or in the number of death among offspring born of untreated and treated mice. The number of hepatomas doubled in male mice, the macroscopic and microscopic characteristics of the tumors being the same as those of the controls.

In the second phase of the experiments, varying doses of TCPE and TCDD were fed for 52 weeks. Preliminary evaluation on the 79th day showed that by reducing the TCPE dose to 1/10 and 1/100 of the MTD, the frequency of hepatomas was the same as in the control, even if the level of TCDD was increased to 10 ppm.

It is probable that the increase in the number of hepatomas found in the first experimental series is not to be attributed to TCDD, but to the extremely high doses of TCPE, which exhausted the detoxication capacity of the liver and produced hepatic lesions, furthering the formation of hepatomas.

Fábián (1976) reports on the investigation of the acute and subacute effect of Buvinol® on Japanese quail *(Coturmix coturmix japanica)*. The approximate oral LD_{50} was found to be 520 mg/kg. In the 75-day subacute toxicological test a diet containing 1/12 of the acute LD_{50} dose was fed to the quails. The TCPE component of Buvinol® contained 1.6 ppm of TCDD. The treatment had no toxic effect on the parents, and egg laying and hatching were also normal, but in the embryos of the F_1 generation toxic and teratogenic action far exceeding that in the control group was observed. The feeding of chemicals was stopped, and after a waiting time of 45 days, 3 successive trial hatchings were made with the experimental animals at 1-month periods from eggs of parents exposed to chemical treatment. This experiment showed that the teratogenic effect is eliminated when the feeding of the chemical is stopped, because the deformities of the animals that died did not exceed those in the control group in number or in severity.

Experiments with Buvinol® were repeated, but the TCPE component now contained 0.1 ppm of TCDD, and only 1/40 of the acute LD_{50} dose was administered. No toxic symptoms could by observed in quails exposed to the chemical for 268 days.

Abafy *et al.* (1976) investigated the toxicity of TCPE and Buvinol® containing a TCPE + atrazine mixture to insects such as housefly *(Musca domestica)*, bean beetle *(Acanthoscelides obtectus)*, giant cockroach *(Blaberus giganteus)*, honeybee *(Apis melifica)*, to aquatic organisms (*Tubifex* sp.), crustaceans of lower order (*Daphnia magna, Cyclops* sp.), fish such as guppy *(Lebistes reticulatus)*, fry of carp and one-summer carp *(Cyprinus carpio)*, amur *(Ctenopharingodon idella)*, and to floating unicellular algae (*Ankistrodesmus* sp.).

The dose experiments covered the range from the no-effect level up to 100% effect.

It can be seen that the toxicity of the compounds investigated to insects is of the following order: blank test $\ll$ atrazine < TCPE < Buvinol®. A toxicological synergism, similar to the herbicidal synergism of the two active ingredients, can be observed in the case of Buvinol®. The oral LD_{50} for *Blaberus giganteus* is 6500 mg/kg, considerably higher than the LD_{50} values measured for mammals. There is no measurable difference in toxicity between Buvinol® containing 1.6 ppm and 0.1 ppm of TCDD.

The hazard of normal doses to honeybees is low.

Of the small aquatic organisms crustaceans are less sensitive, *Tubifex* more sensitive. The tolerance of fish is remarkably high. When fish were placed in fresh water after exposure to a 10 ppm dose, they rapidly recovered and showed no ill effects later.

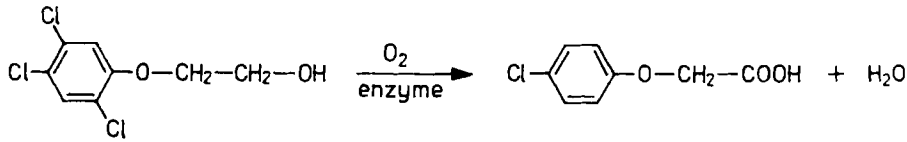
According to Bathe's water conservancy classification, Buvinol® and its components belong to the "moderately toxic" pesticides.

The modes of action and metabolism of TCPE have been investigated *in vitro* and *in vivo*, in plants and soils by several Hungarian research groups (Bihari and Radvány, 1970; Bihari and Vásárhelyi, 1972; Bánki, 1973; Bánki and Bihari, 1976; Pecznik and Kampfl, 1976; Josepovits *et al.*, 1976).

The herbicidal precursor action of compounds being degraded into chlorophenoxyacetic acids was recognised as early as in the 1950s. Though their mode of action has not been extensively investigated, it has been experimentally shown that phenoxyethanol derivatives are oxidised by the soil bacterium *Bacillus cereus var. mycoides* to the respective acetic acids; thus in the process 2,4-DES→DCPE→2,4-D, the compounds 2,4-DEP, 2,4-DEB, MCPE and 2,4,5-TES are activated by the same oxidative pathway (Carrol, 1952; Vlitos, 1952, 1953; Vlitos and King, 1953; Hill and Alban, 1956; Newman and Downing, 1958).

2,4,5-Trichlorophenoxyethanol, having a chemical structure closely related to that of the phenoxy compound just mentioned, can undergo similar chemical and biochemical reactions.

The most important of these with respect to herbicidal activity is its enzyme-catalysed oxidation into 2,4,5-T according to the following overall reaction scheme:



In the soil and plants abiotic and biotic degradation and metabolism take place alongside activation.

The germination- and growth-inhibiting actions of TCPE, DCPA and 2,4,5-T have been investigated in mustard *(Sinapis alba)* and barley *(Hordeum sativum)*, and have been followed also by the measurement of polyphenol-oxidase, peroxidase and dehydrogenase enzyme activity.

The pH-dependent activity of the two precursors shows two maxima and is in good correlation with the enzyme activities measured.

Owing to the changing NAD level of their mitochondria, germinating seeds and certain developed plants respond differently to treatment with TCPE. The maximum effect is to be expected when the NAD level of the plants is high, as on germination, strong mitotic activity, and, in the case of perennial plants, during blossoming, and during the basipetal translocation of nutrients.

Bánki and Bihari (1976) suggest several alternative pathways for the metabolism of TCPE and the detoxication mechanism involved:

$$\text{TCPE} \xrightarrow{(A)} \text{4-oxy-2,5-dichlorophenoxyethanol} \quad (\text{4-OH-2,5-DE}) \nearrow \text{4-OH-2,5-D} \searrow \text{2,5-dichlorohydroquinone}$$

$$\text{TCPE} \xrightarrow{(B)} \text{6-oxy-3,4-dichlorophenoxyethanol} \quad (\text{6-OH-3,4-DE}) \nearrow \text{6-OH-3,4-D} \searrow \text{4,5-dichloropyrocathecol}$$

$$\text{TCPE} \xrightarrow{(C)} \text{5-oxy-2,4-dichlorophenoxyethanol} \quad (\text{5-OH-2,4-D}) \nearrow \text{5-OH-2,4-D} \searrow \text{4,6-dichlororesorcinol}$$

TCPE and 2,4,5-T $\xrightarrow{(D)}$ 2,4,5-trichlorophenol (TCP)

↙ ↓ ↘

4,5-dichloro- pyrocatechol | 2,5-dichloro- hydroquinone | 4,6-dichloro- resorcinol

Carbon atom 5 is the less stable, thus it is thought that pathway C is the most probable, though TCP and as 4,6-dichlororesorcinol formed by pathway D have also been detected among the metabolites.

A study of metabolism in beans and maize with TCPE radiolabelled in the ring (Josepovits *et al.*, 1976) supported in certain points the metabolic scheme given above. Moreover, it has been established that the sensitive bean takes up through the roots about five times as much TCPE as maize. Translocation in both the acropetal and the basipetal direction is slight, and in both directions from the site of treatment the compound is to be found in a quantity decreased by an order of magnitude even 2–3 weeks after the treatment. As for metabolism, it has been established that in general 2 weeks after treatment about half the quantity of TCPE administered is metabolised in the plant. In addition to the metabolic pathway, TCPE applied on the foliage is photochemically decomposed to TCP. This process is analogous to the photochemical pathway described by Crosby and Wong (1973) for 2,4,5-T.

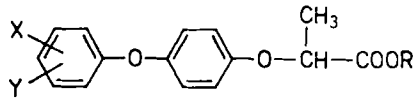
TCDD could not be detected among the metabolites, nor could it be detected even after the application of TCP, the precursor of TCDD.

The main difference between the metabolic processes proceeding in the two kinds of plants is that in maize the main metabolite is 2,4,5-T, while in bean it is TCP.

6.4.7 Phenoxy-phenoxy acids

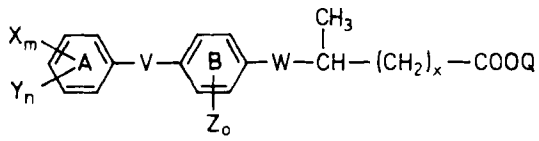
This group of herbicides was discovered in the research laboratories of the Hoechst AG (Langelüddecke *et al.*, 1975).

The series first investigated can be described by the following structural formula:

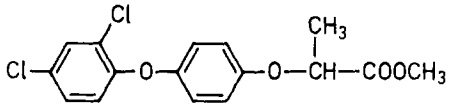


Though this molecular structure is rather similar to that of dichlorprop **(8)** and mecoprop **(9)**, this group of compounds proved to be efficient for the control of grass weeds in monocotyledonous (e.g. cereals) and dicotyledonous crops.

Further extensive investigations were undertaken on the following variants of the parent molecule:

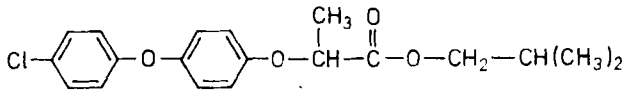


The substituents of the molecule, X, Yand Z and their number from 1 to 4 were changed; ring A was replaced by heterocyclic ring systems; the bridge atoms V and W were substituted with O, N, S and CH_2, and the groups $(CH_2)_x$ and Q were varied. Of the compounds investigated diclofop-methyl, methyl {2-[4-(2,4-dichlorophenoxy)phenoxy]}propionate **(25)**, introduced under the code number Hoe 23 408, proved to be the most active (Nestler *et al.*, 1979).



25

A compound closely related to diclofop-methyl is clofop-isobutyl, isobutyl {2-[4-(4-chlorophenoxy)phenoxy]}propionate **(26)**, introduced under the code number Hoe 22 870 (Alopex®) (Schwerdtle *et al.*, 1975).



26

Both herbicides are translocating compounds used for the control of annual grassy weeds, and both can be combined with dicotyledon weedkillers with the exception of hormone-type herbicides. Diclofop-methyl is recommended for preemergence but mainly for postemergence use, clofop-isobutyl for preemergence use, both at rates of 0.3–1.2 kg active ingredient/ha.

Toxicologically they are weak poisons. The acute oral LD_{50} of the technical active substances for rats is 580 and 723 mg/kg, respectively. The acute dermal LD_{50} for rats is greater than 5000 mg/kg; the eight-day dietary LD_{50} for quail and duck greater than 20000 mg/kg; LC_{50} for fish (96 h) 1 ppm (!); LD_{50} for honeybees is greater than 40 kg active ingredient/ha.

In the period 1974 to 1978, the selective applicability of diclofop-methyl was investigated in several places in spring barley and wheat (Schumacher and Schwerdtle, 1975; Hewson, 1976; Todd and Stobbe, 1977; Lutmann and Thornton, 1978; Smith *et al.*, 1978). It was found that diclofop-methyl controls the grassy weeds *Avena fatua, Poa trivialis, Lolium* spp. and *Alopecurus myosuroides* up to the early tillering stage.

Foliar application is the most efficient, in wheat at a rate of 0.8–2.2 kg/ha, in barley at a rate of 0.8–1.1 kg/ha. Doses can be substantially reduced by additives.

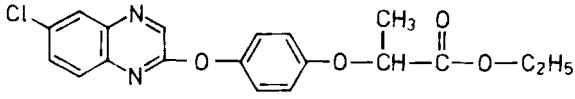
Several workers investigated the selective applicability of diclofop-methyl in broad-leaved vegetable crops in various European countries. At a rate of 0.6–1.2 kg active ingredient/ha, sugar beet, oilseed rape, cabbage, field bean, onion and potato showed an excellent tolerance (Manning and Hewson, 1978).

These herbicides are auxin antagonists. They inhibit growth in the roots and stems of sensitive grassy weeds. Chlorophyll contents and photosynthetic activity are reduced in sensitive plants. The translocation of the photosynthesis in the roots is also reduced, and the accumulation of sugars increases in the stem (Chow and La Barge, 1978).

Diclofop-methyl is rapidly metabolised in plants and soils to dichlofop, which is then further degraded (Smith *et al.*, 1978).

On investigating the causes of the selectivity of dichlofop-methyl and clofop-isobutyl and the metabolism of the herbicides, it has been established that selectivity is due to the different rates of metabolism in sensitive and tolerant plants, to the different nature of the metabolites formed and to the fact that both the unchanged active substances and their derivatives demethylated in the plants by the metabolic pathway (clofop and diclofop) act at different sites in *Avena* spp. and cereals (Shimabukuro *et al.*, 1978; Gorecka *et al.*, 1978).

Quinofop-methyl (NCI-96 683, **27**) in a new phenoxy herbicide which was discovered in 1979 and currently being developed by the Nissan Chemical Industries Ltd. Its chemical name is ethyl {2-[4-(6-chloro-2-quinoxalinyloxy)-phenoxy]}propionate.



27

Its chemical and biological properties were first reported in 1983 (Sakata *et al.*). This new selective, postemergence herbicide is highly active against annual and perennial grasses in all climatic conditions.

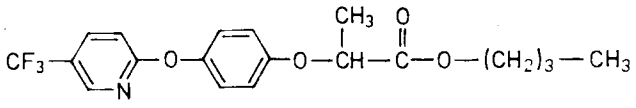
A wide range of broad-leaved crops show tolerance to quinofop-methyl. The recommended rates of application are 0.05–0.25 kg active ingredient/ha against annual grasses and 0.125–0.5 kg active ingredient/ha against perennial grass weeds as *Sorghum halepense, Cynodon dactylon, Elymus repens.* Moderately resistent are *Poa annua* and *Imperate cylindrica.* After foliar application the first symptoms are yellowing and growth-retardation. In 5–7 days these symptoms are followed by necrosis of the leaves and nodes. The death of the plant follows within 14 days.

Quinofop-methyl is of low mammalian toxicity. Acute oral LD_{50} for rats: male 1670, female 1480 mg/kg. Acute dermal LD_{50} for rats, mice: 10000 mg/kg. The compound is not skin-irritant or sensitiser. It is moderately toxic to fish. LC_{50} (96 h) on rainbow trout: 10.7 mg/l.

Fluazifop-butyl **(28),** formerly PP 009, is a patented herbicide of the Ishihara Sangyo Kaisha Ltd. (Plowman *et al.*, 1980.), it's chemical name is butyl {2-[4-(trifluoromethyl-2-pyridyloxy)phenoxy]}propionate.

Fluazifop-butyl is a systemic herbicide, very active against annual and perennial grass weeds and selective to broad-leaved crops. It has been widely tested in about

seventy countries and has given consistent performance as a postemergence herbicide in selectively controlling annual grasses at rates of 0.125–0.5 kg active ingredient/ha and perennial weeds at rates of 0.5–2.0 kg. (Sarpe and Dinu, 1980).



28

Studies on the mode of action of fluazifop-butyl have shown that it moves in the xylem and the phloem, which may account for the fact that its effect does not depend on the growth stage of grasses.

After treatment, within 48 hours, there is a cessation of growth. Nodes and buds become necrotic. Young leaves show chlorosis, then necrosis, followed by older leaves which show pigment colour changes (anthocyanin formation). Death of the weeds usually occurs after three weeks.

Fluazifop-butyl has a preemergence activity too, lasting about 3–6 weeks according to soil type. This activity is only 25–50% of the herbicidal effect of post-emergence application. Its selectivity is believed to be due to rapid degradation followed by conjugate formation in broad-leaved plants (Plowman *et al.*, 1980).

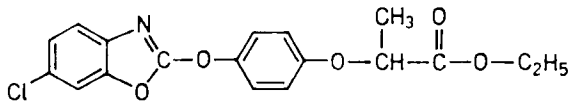
Results from acute and sub-acute toxicological studies indicate that fluazifop-butyl and its first metabolite (fluazifop-acid) are of low order of toxicity.

The acute oral LD_{50} of fluazifop-butyl for rats is 2925 and for mice 1490 (male), and 1770 (female) mg/kg respectively. The 24-hour dermal LD_{50} for rats and rabbits are 5000 and 8000 mg/kg, respectively.

Fluazifop-butyl is slightly irritant to rat and rabbit skin and is a weak sensitiser of guinea pig skin.

Fluazifop-butyl is also of low toxicity to birds and invertebrates, the acute oral LD_{50} for mallard ducks is 17 000 mg/kg, the highest dose that could be administered. No effect was seen on bees when administered both orally and by contact at 240 μg active ingredient/bee and 120 μg/bee, respectively. Earthworms were unaffected 1 and 6 months after application to field plants at 5 kg active ingredient/ha. The EC_{50} for *Daphnia magna* was > 10 mg active ingredient/l after 24 and 48 hours. Fluazifop-butyl is moderately toxic to fish. The LC_{50} at 96 hours, for rainbow trout *(Salmo gairdneri)* is 1.6 ppm.

Fenoxaprop-ethyl **(29),** formerly on its code number Hoe 33 171, ethyl {2-[4-(6-chloro-2-benzoxaloxy)phenoxy]}propionate, was discovered in the laboratories of the Hoechst AG (Bieringer *et al.*, 1982).



29

This is a new postemergence herbicide being developed for the selective control of annual and perennial grass weeds in broad-leaved crops. Field trials conducted in 5 main climatic regions showed an excellent activity against many warm climate grass weeds. Fenoxaprop-ethyl controls selectively several problem grass weeds as *Alopecurus myosuroides, Avena fatua, Echinocloa crus-galli, Setaria viridis, Digitaria sanguinalis, Sorghum halepense* and *Cynodon dactylon* at rates of 0.1–0.5 kg.

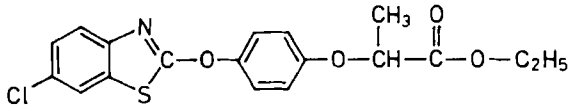
Graminaceous crops are sensitive to fenoxaprop-ethyl with the exception of wheat and rye. Tolerant broad-leaved crops are clover, cotton, field beans, peas, potatoes, soybean, (Schumacher *et al.*, 1982a, b), sugar beet, sunflower, tobacco, alfalfa and oilseed rape.

Fenoxaprop-ethyl is absorbed through the leaves and moves in both the xylem and the phloem. The actual site of action is the meristematic tissue of the shoot where it accumulates (Köcher *et al.*, 1982). In plants the compound rapidly degrades to polar products. In soils it is saponified and in 32 days a complete degradation takes place.

The first symptom after application is the cessation of growth (2–3 days). Then chlorosis begins and the plants die in 2 to 4 weeks depending on climatic conditions.

Fenoxaprop-ethyl is weakly toxic to mammals (Bieringer *et al.*, 1982). Acute oral LD_{50} is for rats: male 2357, female 2500mg/kg. Subchronic toxicity (90-day feeding study), the no-effect level for rats is 80 ppm and for dogs 16 ppm. The compound is slightly irritant to rabbit skin and slightly irritant to rabbit eye. It is nonmutagenic in the Ames Test.

Fenthiaprop-ethyl, ethyl {2-[4-(6-chloro-2-benzothiazolyloxy)phenoxy]} propionate (Hoe 35 609, **30**) is a new herbicide being first synthesised in 1976 and currently developed by the Hoechst AG (Randte *et al.*, 1982).



30

Fenthiaprop-ethyl is a selective postemergence herbicide with certain preemergence activity. It controls annual and perennial grass weeds in broad-leaved crops. The residual activity is of short persistence. Field trials were carried out in France and FRG at rates up to 1.5 active ingredient/ha. Most grass species were controlled at rates of 0.24–1.0 kg active ingredient/ha. Resistant grass weeds are the *Cyperus* spp., *Festuca* spp. and *Poa* spp. Fenthiaprop-ethyl is very active against *Agropyron repens* at a rate of 0.5 kg active ingredient/ha. As it is very active against cereals it shows promise in controlling volunteer cereals in broad-leaved crops.

Tolerant broad-leaved crops are: carrot, clover, cotton, field beans, flax, linseed, alfalfa, oilseed rape, peas, potatoes, soybean, strawberries, sugar beet, sunflower, tobacco and vines. Its mode of action is similar to that of fenoxaprop-ethyl.

The toxicological properties are also similar to those of fenoxaprop-ethyl. Fenthiaprop-ethyl is about twice as toxic to mammals as fenoxaprop-ethyl (Randte *et al.*, 1982).

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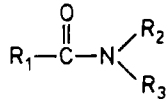
6.5 Amides

Several compounds of this herbicide group of varied structure are used for selective weed control in large quantities all over the world.

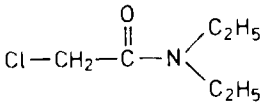
Their general formula is:



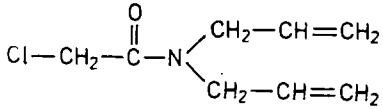
The most important compounds are the N-substituted α-chloroacetamides, particularly the substituted anilides, which are used partly for preemergence treatment and partly for postemergence treatment of many kinds of crops.

6.5.1 N-Substituted α-chloroacetamides

The herbicidal effect of N-substituted α-chloroacetamides has been described by Hamm and Speziale (1956a,b). Of the great number of compounds prepared, N,N-diethylchloroacetamide (CDEA, **1**) and N,N-diallylchloroacetamide (CDAA, allidochlor, **2**) exhibit marked biological activity.



1



2

Of the two aliphatic chloroacetamides allidochlor is the more active herbicide and has been introduced into agricultural use.

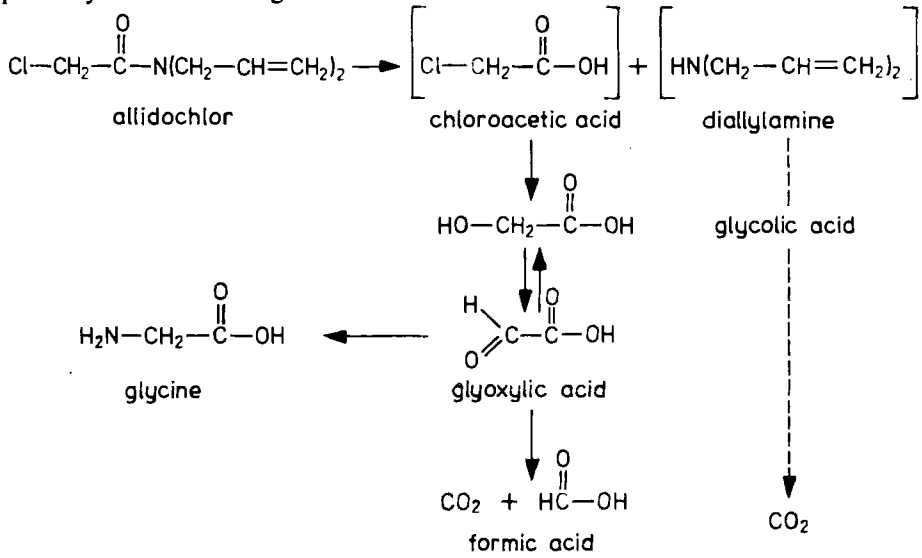
Allidochlor is a liquid of pungent odour, slightly soluble in water. It is prepared by the reaction of diallylamine and chloroacetyl chloride in an inert solvent at 0°C. For the binding of hydrochloric acid NaOH is used (Hamm and Speziale, 1956a).

Allidochlor is a selective preemergence herbicide used at rates of 4–5 kg active ingredient/ha for the control of annual grass weeds and some broad-leaved weeds. It is selective in maize, millet, soybeans, vegetables and sugar cane.

An interesting side-effect is its increasing selectivity of thiol carbamate herbicides in maize.

Allidochlor inhibits the germination of grass weeds and the growth of roots and shoots. Biochemically it inhibits the functioning of certain enzymes, protein synthesis and respiration (Jaworski, 1956).

The compound is absorbed through the roots of the plants and is rapidly translocated and degraded (Jaworski, 1964, 1969). The proposed degradation pathway is the following:



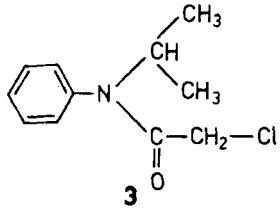
In the soil allidochlor is degraded mainly by microorganisms. At normal rates of application it persists in the soil for 3–6 weeks.

The active substance is slightly toxic, its acute oral LD_{50} for rats being 700 mg/kg, its acute dermal LD_{50} for rats 360 mg/kg. It is an irritant to the eyes and the skin.

The herbicide Randox T® is a combined granulate, containing 11.6% allidochlor and 23.3% trichlorobenzoyl chloride.

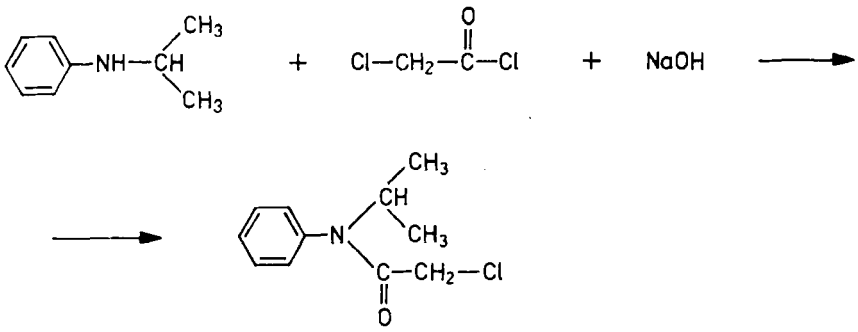
Acylanilides are of greater variety, and are still being intensively developed.

The most important of the α-chloroacetamides with a phenol group substituent is 2-chloro-N-isopropylacetanilide (propachlor, **3**), introduced in 1965 by the Monsanto Co. under the code number CP 31 393 (Baird, 1964):



3

Propachlor is prepared by the reaction of N-isopropylaniline with chloroacetyl chloride at -10 to $+5$°C in ethylene dichloride solvent, using sodium hydroxide solution as acid binder (Hamm and Speziale, 1956b):



Propachlor is a light tan solid, slightly soluble in water and readily soluble in organic solvents, with the exception of aliphatic hydrocarbons. It is a stable compound not sensitive to light.

Propachlor is a preemergence selective herbicide effective against annual grass weeds and several broad-leaved weeds in maize, cotton, soybean, sugar cane and several vegetable crops. Applied on the moist soil surface it is generally used at rates of 3.5–5 kg active ingredient/ha. Moist soil is needed for the exertion of its action, hence, subsequent irrigation may be required (Beinhauer and Will, 1967; Orth, 1966; Würzer, 1967).

To extend its range of action, propachlor is usually combined with atrazine, 2,4-D, monolinuron, prometryne or metobromuron.

Propachlor is not persistent in the soil. At normal application rates it is efficient for 3–6 weeks.

Propachlor is absorbed by germinating plants mainly through the stem, but also through the roots (Nishimoto *et al.*, 1967; Knake and Wax, 1968). The absorbed compound is rapidly translocated in both sensitive and tolerant plants. There is no correlation between selectivity and the quantity of propachlor absorbed (Jaworski and Porter, 1965; Smith *et al.*, 1966).

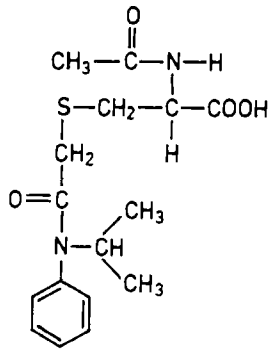
Propachlor inhibits root and stem growth, cell division and protein synthesis, the last presumably by inhibiting the transfer of an enoacyl-*s*RNA into the polypeptide chain (Duke, 1968). Penner (1970) found inhibition of the phytase enzyme in squash treated with propachlor.

The chlorine atom of α-chloroacetamide herbicides is activated by the adjacent carbonyl group, so chlorine easily reacts with nucleophiles, and hence with thiol groups. The covalent bonds formed result in inhibition of protein synthesis and wilting of the plant (Jaworski, 1969).

Propachlor is almost completely metabolised in plants in 5 days. It is only weakly adsorbed by the soil and is rapidly degraded, about 94% microbially and 6% chemically. Jaworski and Porter (1965) and Jaworski (1969) studied the metabolism of propachlor in maize and soybean. The sole metabolite found was a water-soluble acid compound, giving N-isopropylaniline after alkaline hydrolysis. The metabolite produced 2-hydroxy-N-isopropylanilide on acid hydrolysis. Presumably, the active chlorine atom of propachlor is transferred during metabolism to some endogenous nucleophyle, with which it forms a glucoside conjugate. This conjugate is fairly stable and presumably not phytotoxic.

According to the investigations of Lamoureux *et al.* (1971), 75% of the propachlor absorbed by higher plants is metabolised within 18 hours to water-soluble glutathione conjugates.

Lamoureux and Davison (1975), investigating the metabolism of propachlor in rats, found that here too the mercapturic acid pathway plays an important role. Rats treated with ^{14}C-propachlor excerted 20% of the dose in the form of mercapturic acid conjugate 24 hours after treatment:

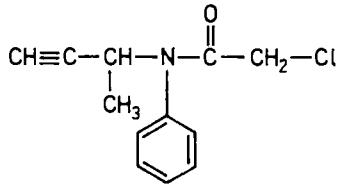


Moreover, they detected two major metabolites in the urine, presumably formed by the oxidation and conjugation of the parent compound. It thus seems that animals perform aryl and alkyl oxidations more rapidly than plants, but the pathway of metabolism is similar.

Propachlor is moderately toxic to mammals and is not toxic to birds. The acute oral LD_{50} of the active substance for rats is 710 mg/kg and for rabbits more than 5010 mg/kg. The 90-day no-effect level for rats and dogs is more than 133 mg/kg. Propachlor is moderately toxic to fish, the LC_{50} (96 h) being 0.4–1.3 mg/l.

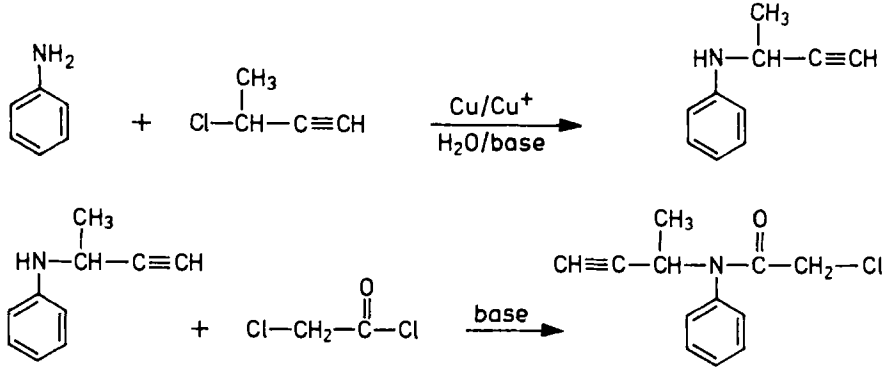
Propachlor is irritating to the skin, mucous membranes and the eyes, and occasionally causes allergic skin reactions.

A compound closely related to propachlor is 2-chloro-N-(1-methyl-2-propynyl)acetanilide (prynachlor, **4**) (Fischer *et al.*, 1965):



4

In the first step of prynachlor synthesis N-(1-methy-2-propynyl)aniline is prepared by the reaction of butynyl chloride with aniline, which is then reacted with chloroacetyl chloride to give prynachlor:



The intermediate N-(1-methyl-2-propynyl)aniline can be prepared by the reaction of aniline with acetylene on copper acetylide catalyst (Reppe, 1955).

Prynarchlor is a preemergence selective herbicide effective in maize, soybean, rape, kohlrabi and onion against annual grass weeds and several broad-leaved

weeds at a rate of 3–4 kg active ingredient/ha. Owing to its low solubility in water, ample soil moisture is needed for satisfactory activity. Prynachlor decomposes in one vegetation period. Rohr and Fischer (1972) prepared a series of structural analogues of prynachlor and investigated their herbicidal action. Experiments revealed some interesting relationships between the structure of the haloacetanilides and their action. It seems that the most important precondition of activity in this group of compounds is the unsubstituted chloroacetyl group. Substitution of chlorine for another halogen atom or pseudohalogen considerably reduces the herbicidal action. Alkyl substitution in the methylene group results in completely inactive compounds.

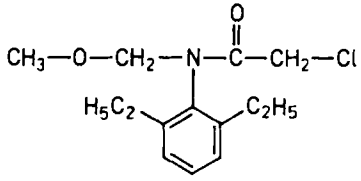
Substitution of two or three chlorine atoms at the α-carbon atom similarly stops herbicidal action.

It has been established on the basis of investigation of the effect of the second substituent of amide nitrogen that this substituent cannot contain more than 5–6 carbon atoms. In the compounds of highest activity the substituent contains 3 or 4 carbon atoms. Another critical characteristic of active compounds is the branched substituent on carbon atom 1. Increased polarity of the hydrocarbon chain strongly reduces activity, and this phenomenon becomes particularly marked if the nonpolar carbon — carbon triple bond is substituted by a polar carbon — nitrogen bond. Results of other polar substituents are similar.

A CH_3 or Cl substitution on the benzene ring similarly reduces preemergence activity. This, however, does not hold true for 2,6-substituted compounds.

Cyclised chloroacetanilides, such as 2,3-dihydroindole and 1,2-dihydroquinoline derivatives, are completely inactive.

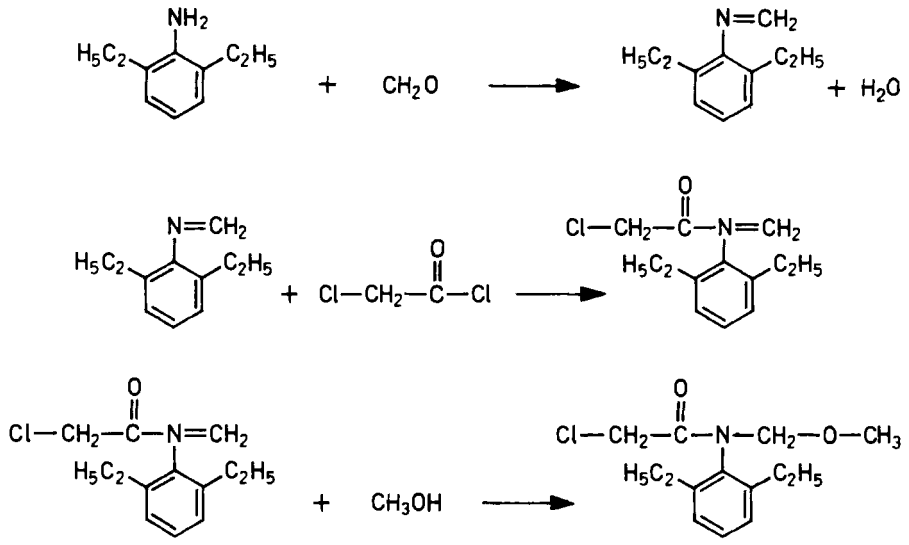
Phenylsubstituted α-chloro-N-alkoxyalkylanilides have been developed by the researchers of the Monsanto Chemical Co. The first active product has been described by Husted *et al.* (1966), Allott (1966) and Roberts and Wilson (1966). This compound is alachlor, 2-chloro-2′,6′-diethyl-N-methoxymethylacetanilide (CP 50 144, **5**).



5

Alachlor and its related compounds are prepared from azomethines substituted at the phenyl group with alkyl groups by reaction first with chloroacetyl chloride, then with the respective alcohol (Olin, 1965). Intermediate azomethine is prepared from alkylaniline with formaldehyde.

The reaction scheme for the preparation of alachlor is:



The homologues are prepared according to the same reaction scheme.

Alachlor is a nonvolatile crystalline substance, the technical product is a viscous oil. It is less soluble in water than propachlor. It is hydrolysed under strongly alkaline or acid conditions. With the exception of aliphatic hydrocarbons, it is readily soluble in organic solvents. It is not sensitive to ultraviolet light or to heat.

Alachlor is a selective preemergence soil herbicide with action similar to that of propachlor. With its poorer solubility in water it needs more soil moisture than propachlor to exert its action, and irrigation must be used in a dry spring to obtain a satisfactory herbicidal action. On a molar basis, alachlor is twice as efficient as propachlor, and its activity lasts 2–4 weeks longer (Evans *et al.*, 1968).

The recommended rate of application of alachlor is 2 kg active ingredient/ha. It is effective for the control of annual grass weeds and several broad-leaved weeds. It is particularly efficient against the annual grass weeds *Setaria* spp., *Brachiara* spp., *Digitaria sanguinalis*, *Echinocloa crus galli*, *Sorghum halepense* and *Poa annua*. Of the broad-leaved weeds *Polygonum* spp. and *Raphanus raphanistrum* are resistant.

Maize, soybean, peanut, cotton, fruit trees and some ornamental plants are tolerant to alachlor. For the broadening of its herbicidal range alachlor can be combined with atrazine (Monsanto, 1971b).

Alachlor is absorbed mainly by the shoots of the plant and, to a lesser degree, by the roots. From the site of uptake it is rapidly translocated into the vegetative parts of the plant. In the plant alachlor is metabolised almost completely in 10 days.

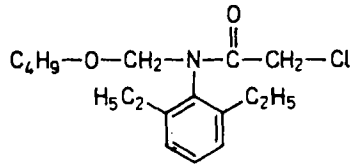
Absorbed alachlor inhibits the growth of the shoots and roots and lateral root development of sensitive plants (Keeley *et al.*, 1972).

It is interesting that although alachlor is closely related to acylanilides, it does not inhibit the Hill reaction (Chandler *et al.*, 1972).

On the bais of information presently available, the biological mode of action of alachlor is probably the inhibition of protein synthesis.

Alachlor is virtually nontoxic to mammals, its acute oral LD_{50} for rats being 1800 mg/kg, and LD_{50} for pheasants 10 000 mg/kg. It is toxic to fish, the LC_{50} (96 hour exposure) for rainbow trout being 2.3 ppm, for bluegill 13.4 ppm.

The emulsifiable concentrate (6 lb active ingredient/US gallon) is a strong irritant to the skin and eyes of rabbit. This and alachlor granules occasionally cause allergic skin reactions.



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Butachlor, 2-chloro-2',6'-diethyl-N-butoxymethylacetanilide (**6**), previously known under the code number CP 53 619, is the butyl homologue of alachlor.

Butachlor is less soluble in water than alachlor by one order of magnitude and thus needs a higher soil moisture to exert a suitable herbicidal action.

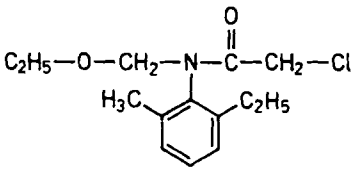
Butachlor is a pre- and early postemergence selective herbicide for the control of grass weeds and a few broad-leaved weeds. Depending on the organic components of the soil, it is used at a rate of 1.5–3 kg active ingredient/ha on seeded and transplanted rice in Asia, and in Central and South America.

It seems promising in maize, cotton, sugar beet and vegetable crops, mainly in irrigated areas. For the extension of its herbicidal range, butachlor can be combined with dicots herbicides.

Butachlor is not persistent; it is degraded in 10 weeks in the soil.

Butachlor is moderately toxic to mammals and is a mild eye and skin irritant. Its acute oral LD_{50} for rats is 1740 mg/kg (Anonym, 1972).

Of the homologues of this group of compounds several herbicides have been described in the stage of experimental development. One of these is acetochlor, 2-chloro-N-(ethoxymethyl)-6'-ethyl-*o*-acetotoluidide (Mon-097, **7**).



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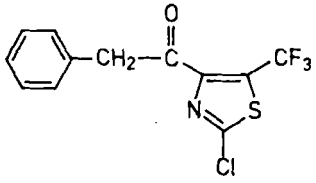
At the same application rate as alachlor, acetochlor has stronger and longer lasting action. It is also effective for the control of *Agropyron repens* and *Cyperus* spp. (Anonym, 1971). Its selectivity is the same as that of alachlor.

The inherent phytotoxicity of alachlor and acetochlor against grain sorghum has precluded their use in this crop. Recently Monsanto discovered a new safener. The new compound, Mon-4606, is benzyl 2-chloro-4-trifluoromethyl-5-thiazole carboxylate (**8**), proposed common name flurazole (Brinker *et al.*, 1982).



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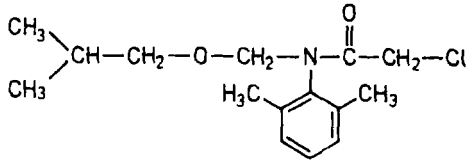
Exprerimental formulations include emulsifiable concentrate (6 lb/US gallon), an 80% WP and a 1% granular formulation. Its acute oral LD_{50} for rats is 7700 mg/kg.

Field trials showed that grain sorghum seed treated with Mon-4606 at a rate of 1.25–2.5 g active ingredient/kg tolerated more than 4 kg active ingredient/ha alachlor and 3 kg active ingredient/ha acetochlor, which is more than twice that needed for effective weed control. Furrow treatment of sorghum seeds with Mon-4606 granules (0.12–0.25 kg active ingredient/ha) was also effective.

Delachlor, 2-chloro-N-isobutoxymethyl-2,6-acetoxylidide, code number CP 52 223 (**9**) was found to be a promising herbicide in beet on soil rich in humus at a rate of 1–2 kg active ingredient/ha. Delachlor is also selective in many other crops including wheat. Its half-life in the soil is 21 days (Anonym, CP 52 223).



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Further experimental products are:

2-Chloro-N-ethylacetanilide (CP 6936, **10**)

2-Chloro-6-*t*-butyl-*o*-acetotoluidide (CP 31 675, **11**)

2-Bromo-6'-*t*-butyl-*o*-acetotoluidide (CP 39 179, **12**)

2-Bromo-6'-*t*-butyl-N-methoxymethyl-*o*-acetotoluidide (CP 45 592, **13**)

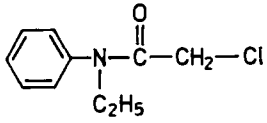
2-Chloro-2',6'-dimethyl-N-(isopropoxymethyl)acetanilide (CP 52 665, **14**)

2-Chloro-2',6'-dimethyl-N-(methoxyethyl)acetanilide (CGA 17 020, **15**)

2-Chloro-N-(ethoxyethyl)-N-(2-methyl-6-propyl-1-cyclohexen-1-yl)acetamide (CP 56 250, **16**)

2-Chloro-N-(butoxymethyl)-N-(2,6-dimethyl-1-cyclohexen-1-yl) acetamide (CP 57 117, 17)

A new active substance of the chloroacetanilide herbicide group, previously known by the code number CGA 24 705, is metolachlor, 2-chloro-6'-ethyl-N-(2-methoxy-1-methylethyl)-*o*-acetotoluidide (metolachlor, **18**), the herbicidal properties of which have been described by Gerber *et al.* (1974).



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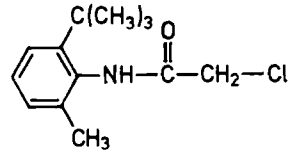

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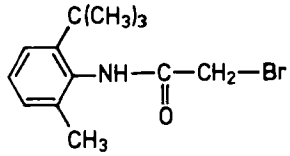

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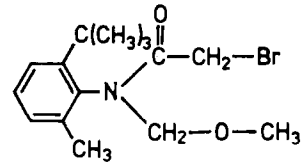

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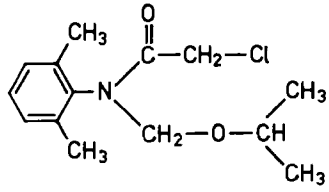

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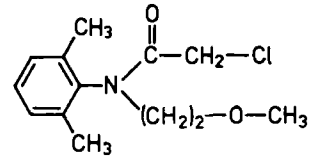

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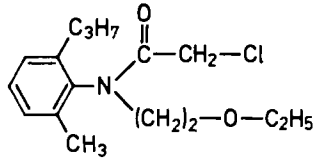

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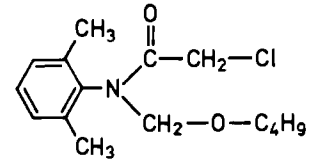

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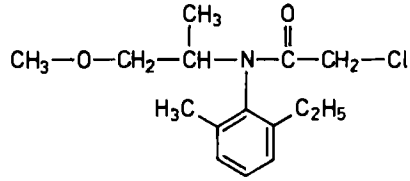

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Metolachlor is a colourless liquid. Its solubility in water is 530 ppm at 20°C, higher than those of the chloroacetanilides discussed so far. It is nonvolatile (0.2 mg/m^3) and its vapour pressure is insubstantial. It is miscible with organic solvents.

Its mobility in the soil determined according to the method of Gerber *et al.* (1970), the so-called "leaching index" is 6, it is the same as that of alachlor.

The dissipation of metolachlor in the soil is three times slower than that of alachlor. Gerber *et al.* (1974) found, at 22°C and a 50% soil moisture content in sandy loam of 3.8% organic content, a 50% dissipation time of 26 days. Under identical laboratory conditions this value was 60 days for atrazine, 100 days for trifluralin and 80 days for diuron. Under field conditions, metolachlor is completely degraded in a growing season, and thus does not interfere with crop rotation.

Metolachlor is a selective preemergence soil herbicide, effective at a rate of 1.5–3.0 kg active ingredient/ha against germinating annual grass weeds and, to a lesser degree, against broad-leaved weeds. It is a selective herbicide in maize, soybean, peanut, potatoes, sugar beet, vegetables and fibre crops. To increase its effect against dicotyledonous weeds, it can be combined with dicot herbicides, such as atrazine, urea herbicides and terbutrin (Anonym, 1975).

Metolachlor is absorbed by grass weeds mainly through the shoots, uptake through the roots being much slower. On the other hand, cotton and soybean absorb it more rapidly through the roots (Gerber *et al.*, 1974). This general behaviour of grass herbicides explains to a certain extent their selectivity in broad-leaved crops. The cotyledon protects the emerging plant from contact with the herbicide.

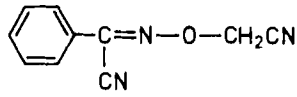
Selectivity in maize can be partly attributed to the size of the seed, and partly to the fact that the enzyme system of maize has the ability to detoxicate metolachlor rapidly.

So far only certain details of the biochemical mode of action of metolachlor are known. Pillai and Davis (1975) found that in 2 hours metolachlor at a concentration of $1 \cdot 10^{-4}$ mole/dm^3 reduced the photosynthesis of *Chlorella pyrenoidosa* by 33%. It is remarkable that the other structural analogue investigated CGA 17020, 2-chloro-N-(2-methoxyethyl)-2,6-dimethylacetanilide, does not inhibit photosynthesis at this concentration.

According to the same investigations, metolachlor reduced the respiration of *Chlorella pyrenoidosa* and mitochondria isolated from beans. Pillai *et al.* (1975) established that treatment with metolachlor (10^{-4} to 10^{-5} mole/dm^3) changes the permeability of the roots. They investigated the leakage of ^{32}P, previously absorbed by the plants, in onion sensitive to metolachlor, in moderately sensitive cucumber and in tolerant maize. Leakage from onion and cucumber was fifty and twenty times that of maize, respectively. This high leakage is indicative of cell membrane injury and probably accounts for a large part of the phytotoxic activity of metolachlor.

Metolachlor is practically nontoxic to mammals, its acute oral LD_{50} for rats being 2780 mg/kg, its acute dermal LD_{50} for rats 3170 mg/kg. It irritates the skin of rabbits slightly, but not the eyes. It is toxic to fish.

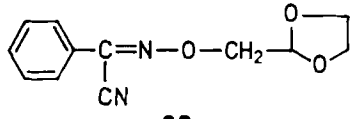
Metolachlor at the recommended doses is more or less phytotoxic to grain sorghum. To counteract this effect a safener has been developed by the Ciba Geigy AG in 1977. The compound is cyometrinil, cyanomethoxyimino(phenyl)-acetonitrile (CGA 43089, **19**) (Ellis *et al.*, 1982).



19

Cyometrinil is applied as a seed dressing on sorghum at a rate of 1.25 g active ingredient/kg seed. Though it performs well as a safening agent, its commercialisation was hindered by adverse effects on crop seed vigor and viability. Furthermore a restriction excluded its application on certain yellowsperm hybrids (Rufener *et al.*, 1982). The same authors reported on the recently developed new safener — CGA 92 194 of the Ciba Geigy AG, which does not show the afore-mentioned drawbacks of cyometrinil (Dill *et al.*, 1982).

CGA 92 194, N-(1,3-dioxolan-2-yl)methoxyimino(phenyl)acetonitrile (oxabetrinil, **20**) is a white crystalline powder insoluble in water, soluble in methylene dichloride. It is practically not toxic to mammals. Acute oral LD_{50} for rats is 5000 mg.



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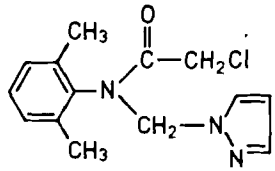
Rufener *et al.* showed that sorghum seeds pretreated with 1–2 g CGA 92 194 were well protected against metolachlor injury over a broad range of temperature and soil moisture conditions. Sorghum tolerance did not decrease when metolachlor was applied with *s*-triazines.

Metazachlor (**21**) is a halogenated acetanilide developed by the BASF, with the chemical name 2-chloro-2,6-dimethyl-N-(1H-pyrazol-1-yl-methyl)acetanilide (Stormonth and Woodroffe, 1982).



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Metazachlor is a selective preemergence herbicide active on a wide range of both broad-leaved and grass weeds. It can be used selectively in *Brassica* spp. crops including winter oilseed rape at a rate of 1–1.8 kg active ingredient/ha.

For the control of volunteer cereals (Eicken *et al.*, 1982), it can be mixed with TCA, fluazifop-butyl, alloxydim sodium or dalapon.

The newest member of the acetanilide herbicide group is pretilachlor, 2-chloro-2,6-diethyl-N-(2-propoxyethyl)acetanilide **(22).**

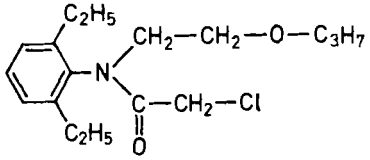
Pretilachlor is a selective herbicide, developed by the Ciba Geigy AG. Its properties and uses were reported by Rufener and Quadranti (1983).

This herbicide has a broad activity spectrum in hand- or mechanically transplanted rice. It controls the most important weeds such as *Echinocloa crus-galli*, sedges and many broad-leaved weeds at rates of 500–1000 g active ingredient/ha.

Applied alone, pretilachlor is not sufficiently selective in direct-seeded (wet-sown) rice.

Pretilachlor has a low level of acute mammalian toxicity. Acute oral LD_{50} for rats is 6099 mg/kg.

Direct-seeded rice does not tolerate pretilachlor in doses required for adequate weed control. The Ciba Geigy AG has discovered and developed a new safening agent, 4,6-dichloro-2-phenyl-pyrimidine (CGA 123 407, **23**), which protects the rice seedling from damage and does not interfere with the herbicidal activity of pretilachlor.



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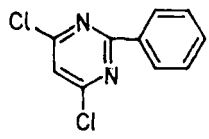


23

CGA 123 407 is a crystalline compound slightly soluble in organic solvents and weakly toxic to mammals (acute oral LD_{50} for rats > 5000 mg/kg).

The commercial product Sofit® are emulsifiable concentrate (30EC) and granules.

The emulsifiable concentrate is recommended for mud-sown rice in subtropical and tropical climates, the granular formulation for water-sown rice in temperate climates.

The recommended application timing is between one day before sowing and four days after sowing.

6.5.2 N-Substituted amides of other acids

A structural characteristic of some of these derivatives is that the nitrogen of the aniline substituted on the ring is substituted by aliphatic, cycloaliphatic, aromatic or aliphatic and aromatic acyl radicals.

The herbicidal properties of this acylanilides were discovered almost simultaneonsly by the research workers of the Bayer Leverkusen, the Monsanto and the

Rohm and Hass (Shäfer *et al.*, 1957; Huffman, 1957; Wilson and McRae, 1958). Propanil, N-(3',4'-dichloropropion)anilide **(24)** is the most active herbicide in this group.

Propanil is prepared by the reaction of 3,4-dichloroaniline with propionyl chloride in the presence of triethylamine (Huffman, 1957), or 3,4-dichloroaniline with propionic acid in the presence of thionyl chloride.

Propanil is a contact herbicide recommended for postemergence use in rice, effective mainly for the control of grass weeds (*Echinocloa* spp.) at rates of 1–4 kg active ingredient/ha (Smith, 1961). In the USA it is used also on potatoes. The combined postemergence herbicide of the Hadogaya Chemical Co. (Japan), known by the trade name Wydac®, contains 25% propanil and 5% carbaryl, and is used postemergence on citrus.

Propanil is more rapidly absorbed by sensitive grass weeds than by tolerant rice, and is degraded about ten times as rapidly in rice as in barnyard grass (Adachi *et al.*, 1966; Matsunaka, 1969).

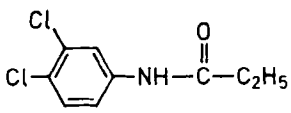
The degradation of propanil in plants of higher order has been investigated by numerous research workers. Experimental results are rather contradictory, but the process suggested by Yih *et al.* (1970) seems to be the most probable. Accordingly, 3,4-dichloroaniline and lactic acid are formed by β-oxidation and enzymatic hydrolysis. From 3,4-dichloroaniline glucose and lignin complexes are then formed.

Propanil produces chlorosis and local or general necrosis in sensitive plants, as a consequence of the inhibition of photosynthesis and disruption of the cell membranes (Moreland and Hill, 1963; Hofstra and Schwitzer, 1968). Moreland *et al.* (1969) found in their experiments on barley that propanil strongly inhibits RNA and protein synthesis, as well as α-amylase synthesis induced by gibberellic acid.

In moist, warm soil propanil is degraded by microorganisms in a few days. Propanil is mildly toxic to mammals and fish, its acute oral LD_{50} for rats being 1384 mg/kg. Up to 10 ppm it is nontoxic to fish.

Blackburn and Weldon (1964) described chloranocryl, the herbicidal properties of a compound closely related to propanil, N-(3,4-dichlorophenyl)methacrylamide (Dicryl®). This postemergence contact herbicide is selective in cotton against mono- and dicotyledonous weeds. It has now lost its commercial importance.

Monalide, 4'-chloro-2,2-dimethylvaleranilide **(25)** was first described by Arndt (1965).



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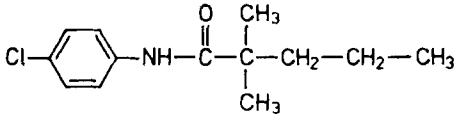

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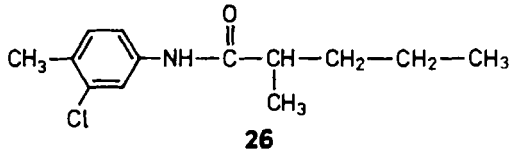
Monalide is a pre- and postemergence contact herbicide absorbed through leaves and roots. At rates of 1–4 kg active ingredient/ha it can be used postemergence in umbelliferous crops, and preemergence in beans and onions. It is rapidly (in 4–6

weeks) degraded in the soil. It is nontoxic to mammals, its acute oral LD_{50} for rats being 4000 mg/kg.

Two compounds of structures closely related to monalide are pentanochlor, 3'-chloro-2-methylvaler-*p*-toluidide (**26**) and NCA, 3',4'-dichloro-2-methylvaleranilide (**27**).

Both compounds are postemergence selective herbicides with short residual activity used in vegetables, strawberries and tomatoes. They are nontoxic to mammals (Moore, 1960; Freund *et al.*, 1962). Pentanochlor is still used, while NCA has been replaced by more efficient herbicides.

Hopkins *et al.* reported the development of cypromid, 3',4'-dichlorocyclopropane carboxanilide (**28**) (in 1965).



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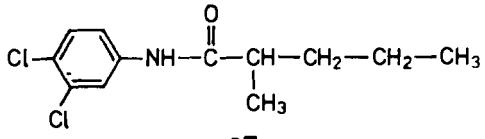

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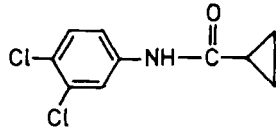


28

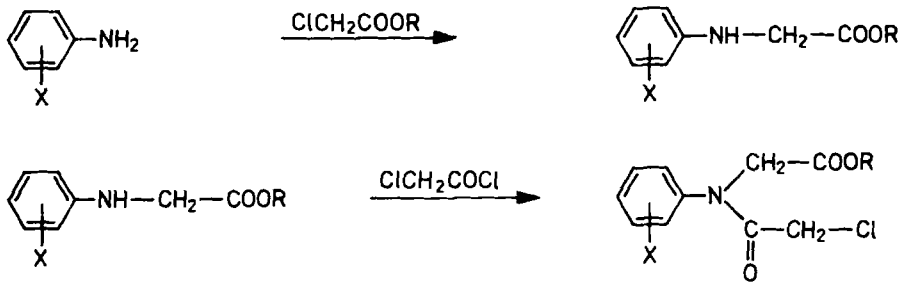
Cypromid is a selective contact herbicide for postemergence use in cereals, maize, umbelliferous crops, onion and cotton. Its rather high toxicity to mammals, its LD_{50} for rats being 218 mg/kg, probably explains its disappearance from the market.

6.5.3 N-Chloroacetyl-N-phenylglycine esters

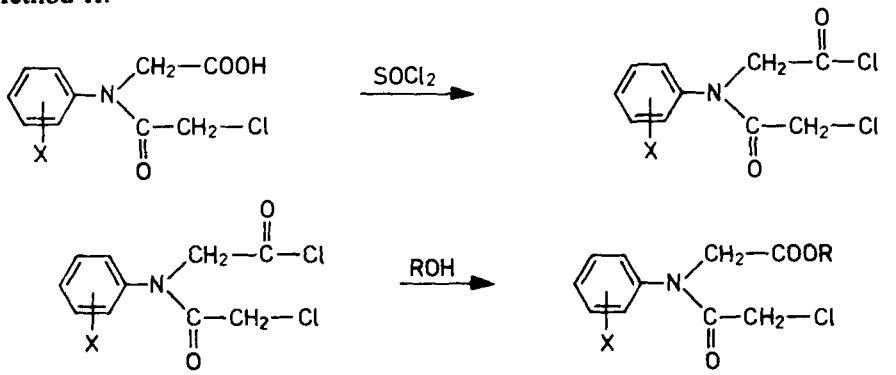
The investigations of Clarke and Wain (1963) established that N-phenylglycines substituted on the ring have a considerable auxin action. It was to be expected that anilides obtained by substitution of the imide nitrogen of N-phenylglycines would exhibit a herbicidal action, primarily against grass weeds.

N-chloroacetyl-N-phenylglycine esters can be prepared by two synthesis routes:

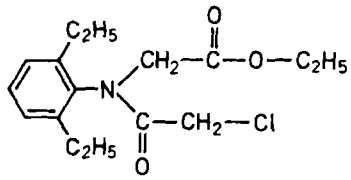
Method I:



Method II:



At present, only one herbicide of glycine ester type is sold: diethatyl-ethyl, N-chloroacetyl-N-(2,6-diethylphenyl)glycine ethyl ester, code number Hercules 22 234 **(29)** (Thompson, 1976; Lehman, 1972).



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Used preemergence at rates of 1.7–6.7 kg active ingredient/ha, diethatyl-ethyl is effective for the control of many annual grass weeds and some broad-leaved weeds in sugar beet, cotton, soybean, maize, wheat and vegetables. Owing to its poor solubility in water (105 ppm at room temperature), under dry climatic conditions incorporation of shallow improves its herbicidal action. The tolerance of sugar beet to the herbicide is excellent; transitory distortion by overdosage is rapidly outgrown.

Diethatyl-ethyl is absorbed through the shoots and coleoptyl of the plants; absorption through the roots is minor. The range of action can be extended by the combination of pyrazone or lenacil, and by postemergence after-treatment with phenmedipham. Diethatyl-ethyl is slightly toxic to mammals, its acute oral LD_{50} for rats being 2328 mg/kg. Its toxicity to fish is similar to that of the other anilides.

Diethatyl ethyl is a selective preemergence herbicide, effective mainly for the control of grass weeds on moist soil at an application rate of 1.7–6.7 kg/ha. It is selective in sugar beet, cotton, maize, wheat, soybean and vegetable crops. Its acute oral LD_{50} for rats is 2318 mg/kg.

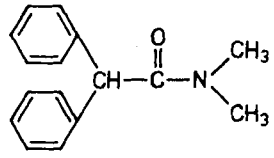
Fujinami *et al.* (1976) synthesised fifty-eight N-chloroacetyl-N-phenylglycine esters to study the structure–action relationships in this group of herbicides.

Prepared by the above synthesis routes, the activity of N-chloroacetyl-N-phenylglycine esters containing various aromatic substituents and ester groups has been determined on rice *(Oryza sativa)* and on barnyard grass *(Echinocloa crus galli)*. From the activity values measured by the method of Fujinami *et al.* (1974) and from the analysis of the physicochemical parameters of the molecules, valuable correlations can be obtained for the designing of an effective herbicide.

6.5.4 Other amides

The dimethylamide of diphenylacetic acid has been known as a compound since 1949. Its herbicidal properties were first described by Alder *et al.* (1960).

N-N-Dimethyl-2,2-diphenylacetamide (**30**) is known by the common name diphenamid.



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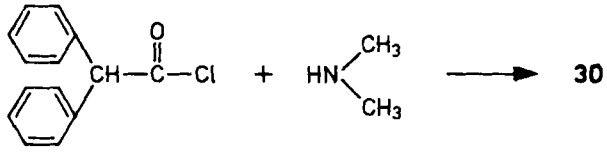
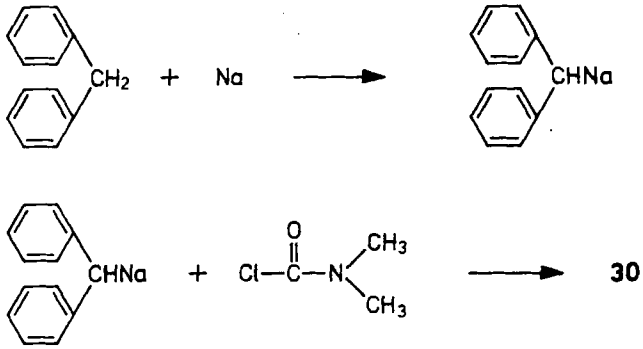
There are several synthesis routes for the preparation of diphenamid. Pohland (1960) made diphenamid by the reaction of diphenylacetyl chloride with dimethylamine in benzene solution:



The intermediate diphenylacetyl chloride can be prepared with a good yield by the acylation of diphenylacetic acid with thionyl chloride.

Taylor (1962) prepared diphenylmethane sodium from diphenylmethan with sodium metal and/or sodium amide in an apolar solvent, and then reacted this with dimethylcarbamoyl chloride to give diphenamid:



Tilley and Sayign (1963) recommend for the synthesis of diphenamid the reaction of 1,1-diphenyl-2,2,2-trichloroethane or of 1,1-diphenyl-2,2-dichloroethylene with dimethylamine in the presence of a quantity of base sufficient to bind the chlorine content of the reactants.

Diphenamid is a crystalline substance moderately sensitive to ultraviolet light and heat.

Diphenamid is a selective preemergence soil herbicide. It is absorbed through the roots, rapidly translocated to all above-ground parts of the plant and metabolised (Lemin, 1966; Golab *et al.*, 1966; Bingham and Shaver, 1971).

Diphenamide is used for the selective control of germinating annual grass weeds and broad-leaved weeds at a rate of 4–6 kg active ingredient/ha in peanuts, peppers, tomatoes, strawberries and potatoes. The cause of selectivity is rapid metabolic degradation in tolerant plants.

As a summary of the experimental results of several authors, metabolic degradation in higher plants begins with step-wise desmethylation, leading through diphenylacetamide to diphenylacetic acid and finally to its *p*-hydroxy derivative.

Generally, the major metabolites are N-methyl-2,2-diphenylacetamide and their acid-hydrolysable, water-soluble conjugates in the form of *β*-glucoside and *β*-gentiobioside (Kesner and Ries, 1967; Schultz and Tweedy, 1971, 1972). According to the investigations of Hodgson *et al.* (1973), when tomato plants were fumigated with a small amount of ozone, the proportions of the specific conjugates are considerably altered.

In mammals the metabolic pathway is presumably similar. McMahon and Sullivan (1965) reported that diphenamid is rapidly metabolised in rats and excreted mainly in the form of N-methyl-2,2-diphenylacetamide N-glucuronide in the urine.

The biochemical mode of action of diphenamid is not known in detail. It does not inhibit germination, but it kills sensitive germinating plants before emergence. In sublethal doses it severely inhibits root growth.

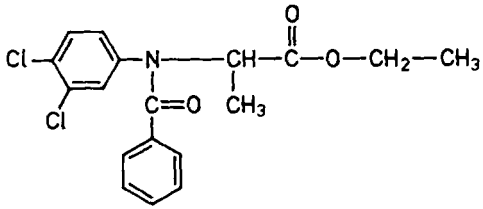
On the basis of the otherwise contested results of Briquet and Viaux (1967), diphenamid inhibits the RNA synthesis of the roots, and it was shown that it inhibits the uptake of inorganic ions in sensitive plants and also affects calcium distribution in the plants (Nashed and Ilnicki, 1968).

Diphenamid is of moderate persistence in soil. Its action under hot, moist conditions lasts for 3–6 months. Diphenamid can become persistent in the soil if there is a lack of precipitation.

The acute oral LD_{50} of diphenamid for rats is 1717 mg/kg. It is nontoxic to the skin. In a two-year feeding test the no-effect level in rats was 100 ppm, in dogs 250 ppm.

Benzoylprop-ethyl **(31)** and flamprop-isopropyl **(32)**, two anilide herbicides selective in cereals with specific efficiency for the control of wild oat (*Avena* spp.), have been developed in the research laboratories of the Shell Research Ltd.

Ethyl N-benzoyl-N-(3,4-dichlorophenyl)-DL-alaninate, its common name is benzoylprop-ethyl (WL 17731, **31**).



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The herbicidal properties of benzoylprop-ethyl were elucidated by the field tests of Chapman *et al.* (1969). Applied at rates of 0.5–8 kg active ingredient/ha for the postemergence treatment of wheat, it killed with specific selectivity *Avena fatua* and *A. ludoviciana*. Bowden *et al.* (1970) established in subsequent experiments that the optimal time of application is the period between the beginning of the tillering of wheat and the appearance of nodes. In this period, benzoylprop-ethyl controls *Avena* spp. at a rate of application of 1.5 kg active ingredient/ha with 100% efficiency, and with 95% efficiency at an application rate of 1 kg/ha. They found that the herbicide does not cause a decreased yield even at a fourfold overdosage. Benzoylprop-ethyl cannot be safely used in barley, because, though it is effective against wild oats (*Avena fatua, A. ludoviciana, A. sterilis*), it reduces the yield by 17%.

Treatment with benzoylprop-ethyl hinders the longitudinal growth of *Avena* sp.; stunted plants develop which are unable to compete with the crop.

Benzoylprop-ethyl itself is moderately phytotoxic. However, the absorbed compound hydrolyses in the plant; the ester bond is ruptured and the acid formed ("benzoylprop") is translocated in the phloem to the growing cells of the stem. During detoxication the acid is conjugated with the components of the plants, including sugars. Deesterification process most rapidly in oat and most slowly in

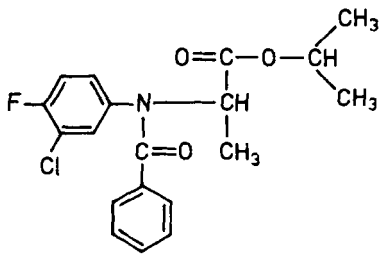
wheat. Subsequent detoxication is so rapid in wheat that the acid does not accumulate to a phytotoxic level. Though detoxication is more rapid in oat, deesterification is even more rapid, so that benzoylprop of a phytotoxic level does accumulate in the plant. Detoxication in barley is slow, causing accumulation of the acid and, thereby, phytotoxicity (Jeffcoat and Harris, 1973).

The fate of benzoylprop-ethyl in winter and spring wheat and in the soil has been investigated by Beynon *et al.* (1974a,b). In 71–98 days, benzoylprop-ethyl was detoxicated both in the plants and in the soil. The residue found in the plants consisted mainly of conjugates formed with sugars, and of a small quantity of N-benzoyl-3,4-dichloroaniline and benzoic acid. In the soil benzoylprop-ethyl is degraded into 3,4-dichloroaniline and its humic acid complex.

Benzoylprop-ethyl cannot be combined either with oil or with 2,4-D amine salt, because it antagonises both substances (Colbert and Appelby, 1972). For the same reason, benzoyl chloride does not accumulate in animal organisms (Crayford *et al.*, 1976).

Benzoylprop-ethyl is a weakly toxic compound, its acute oral LD_{50} for rats being 1555 mg/kg, for mice 716 mg/kg, and for poultry 1000 mg/kg. It is toxic to fish, the LC_{50} (100-hour exposure) for harlequins being 5 mg/l.

Benzoylprop-ethyl is a postemergence wild oat herbicide selective in wheat, while the chemically closely related flamprop-isopropyl, isopropyl N-benzoyl-N-(3-chloro-4-fluorophenyl)-DL-alaninate (WL 29 762, **32**) is a wild oat herbicide selective in barley.



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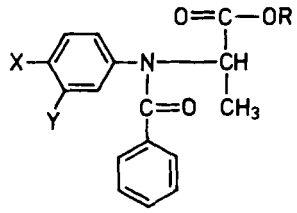
The technical substance is a crystalline powder stable both photochemically and with respect to hydrolysis.

The herbicidal properties of flamprop-isopropyl were first described in 1974 (Mouillac *et al.*, 1974; Warley *et al.*, 1974; Haddock *et al.*, 1974). The excellent wild oat killing properties of benzoylprop-ethyl could not be utilised in barley, because it occasionally causes considerable phytotoxic injuries, and hence a decrease in yield. Since the investigation of the mode of action and of the metabolism of benzoylprop-ethyl showed that the free acid is the carrier of the herbicidal action, it stood to reason that there might be a compound among those of closely related structure, which was selective also in other cereal species.

Haddock *et al.* synthesised in 1971 fifty-five compounds of the following structural formula (Haddock *et al.*, 1974):



where X and Y are Cl, F or H, and R is a substituted alkoxy or alkylthio group.

Screening tests showed that of this series of compounds isopropyl (±) 2-[N-(3-chloro-4-fluorophenyl)benzamido]propionate, flamprop-isopropyl, possesses the desired biological properties. The optimal application rate and time of application were subsequently determined by field experiments in several countries.

Flamprop-isopropyl is used postemergence at a rate of 1 kg active ingredient/ha in barley in the period between tillering and the appearance of the first node. Control of over 90% of all of the *Avena* spp. can thus be attained. Barley tolerates twice this dose without phytotoxic injury. For the efficient control of wild oat the vigorous competition of the crop is needed (Jeffcoat and Harris, 1973).

Activity and selectivity of flamprop-isopropyl are similar to those of benzoylprop-ethyl. Flamprop-isopropyl too becomes active as the free acid ("flamprop") after deesterification. The acid is rapidly translocated in the phloem to the growth sites of the plant cell. The rate of translocation is five times that for benzoylprop-ethyl. The growth of wild oat is stunted by the inhibition of cell elongation.

The selectivity of flamprop depends on the rate of hydrolysis relative to the rate of subsequent detoxication. In the course of detoxication flamprop is metabolised to inactive conjugates in the plant. The activity of flamprop is about twice that of benzoylprop-ethyl (Jeffcoat and Harris, 1975).

Flamprop-isopropyl is not toxic to mammals, its acute oral LD_{50} for rats being 3000 mg/kg, for mice 2554 mg/kg. It is of moderate to low toxicity to fish.

Haddock *et al.* (1974) described, along with flamprop-isopropyl, another compound, flamprop-methyl ester, code number WL 29 761, which is selective in wheat (Mataven®). WL 29 761 gives a higher yield in wheat than benzoylprop-ethyl, and is also effective against *Alopecurus pratensis* (Chow, 1974; Gompf, 1974). Scott *et al.* (1976) reported on the preparation and biological activity of the levorotatory optical isomer of flamprop-isopropyl, known by its code number WL 43 425.

WL 43 425, (−)isopropyl N-benzoyl-N-(3-chloro-4-fluorophenyl)-2-amino-propionate, is a crystalline substance optically active; rotation: $\alpha_D^{25} = -38.6°$ (C_2, ethanol). It is readily soluble in *ortho*xylene.

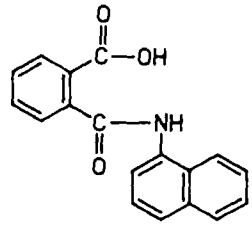
The provisional trade name of the herbicide with WL 43 425 active substance is Super Barnon®. It is a 20% emulsifiable concentrate. WL 43 425 is prepared from flamprop-isopropyl by resolution. Flamprop-isopropyl is hydrolysed to the acid

and then resolved with an optically active amine. This is followed by the liberation and esterification of the dextrorotatory acid. The dextrorotatory isomer is racemised, and the amine is recovered. By recycling the total quantity of the racemic compound can be converted into the levorotatory herbicide, the process gives WL 43425 in a good yield.

Levorotatory flamprop-isopropyl is twice as efficient for the control of wild oat (*Avena* spp.) as the racemate, and under poor culture conditions this difference is considerably larger. WL 43425 is also selective in wheat, though somewhat less active than racemic flamprop-methyl.

Several compounds with growth-regulating action are known among the cyclic N-phenylimides. These are used for the stimulation of pollenation, and in the growing of partenocarpic fruits, such as tomatoes.

Hoffman and Smith (1949a) reported in the plant growth activity of N-aryl-phthalamic acids. The only one used as a herbicide is N-1-naphthylphthalamic acid (naptalam, 33).



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In the patented process of Hoffman and Smith (1949b), naptalam is prepared by the reaction of phthalic acid with 1-naphthylamine in an apolar solvent at room temperature. The sodium salt, of naptalam readily soluble in water (300 g/l at room temperature), is used as the herbicide.

Naptalam is a preemergence soil herbicide with systemic action and some hormone action. It can be used selectively at rates of 4.5 kg active ingredient/ha in cucurbits, soybean, potatoes and peanuts. It is not persistent, being degraded within 3–8 weeks in the soil.

Naptalam inhibits the germination of seeds, and has the unique property of disturbing the geotropism of the plant roots, though it is not known whether this latter action is connected with the herbicidal action (Mentzer and Netien, 1950; Tsou *et al.*, 1956).

Keith and Baker (1966) found that naptalam strongly inhibits the transport and function of the basipetal polar auxin, 4-(indol-3-yl)acetic acid (IAA).

Naptalam is degraded in the plants by enzymatic hydrolysis, in the soil mainly by the microbial pathway into 1-naphthylamine and phthalic acid.

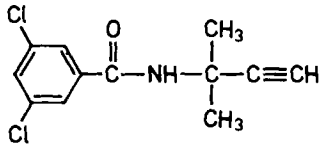
Alanap is also combined with dinoseb or chlorpropham to enhance its action against partly emerged weeds.

Naptalam itself in special formulation is suitable for peach thinning during blossoming.

Naptalam is weakly toxic, the acute oral LD_{50} of the acid for rats being 8 200 mg/kg, and of the sodium salt 1770 mg/kg.

The herbicidal properties of benzamides have been recognised since the early 1960s (Baker and Chupp, 1963, 1967; Moffett, 1964). Lemin (1966) and Gialdi *et al.* (1969) described the herbicidal properties of the alkyl derivatives of 3,5-dichlorobenzamide.

The herbicidal properties of alkynyl benzamides were described by Perrot (1969), Viste *et al.* (1970), and Sumpter *et al.* (1970). The most active member of this group is 3,5-dichloro-N-(1,1-dimethylpropynyl)benzamide **(34)**, known by the common name propyzamide (in the USA pronamide).



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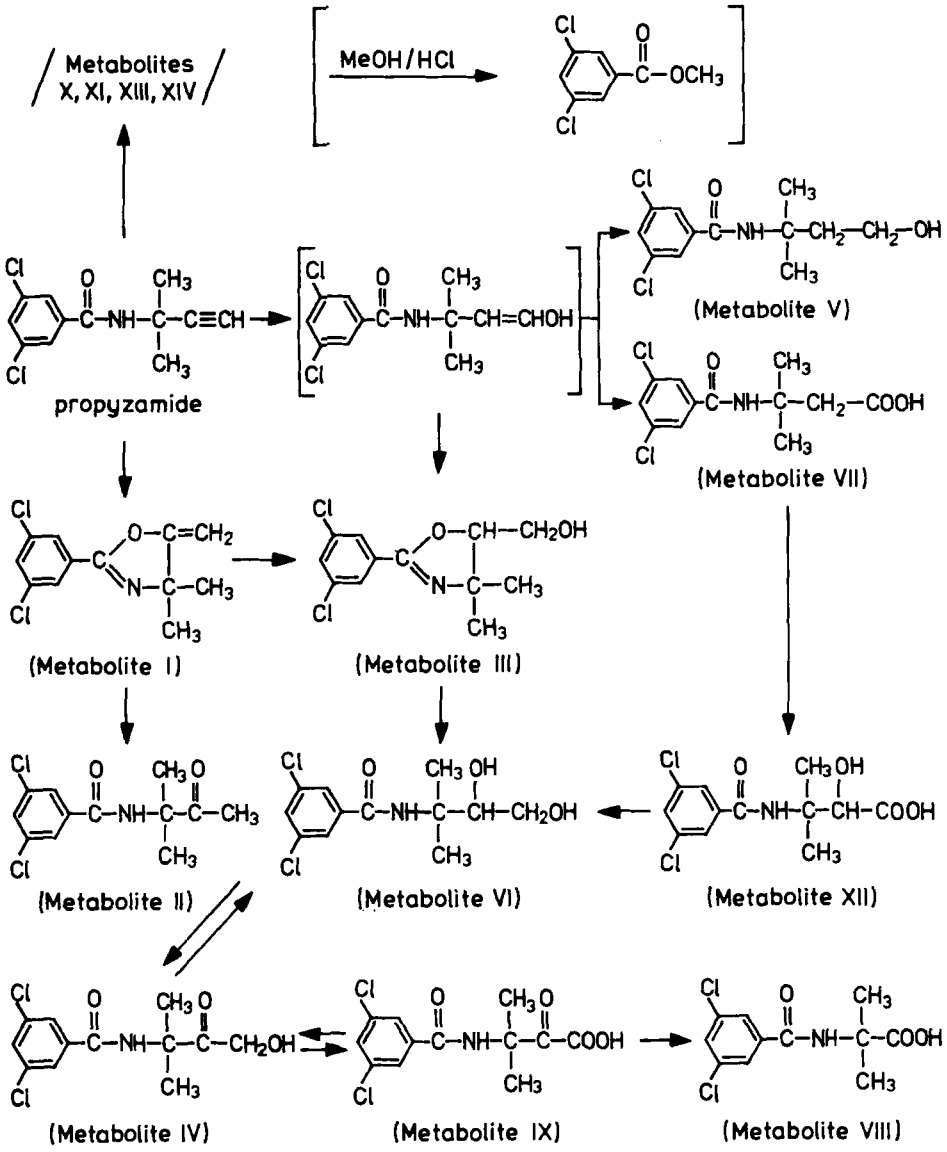
Benzamides, including propyzamide, can be prepared by Schotten–Baumann's method. Propyzamide is made by the reaction of 3,5-dichlorobenzoyl chloride with 1,1-dimethyl-2-propynylamine in aqueous alkaline medium.

Propyzamide is a residual pre- and postemergence selective herbicide effective against mono- and dicotyledonous weeds. Investigations revealed a particular selectivity in *Compositae* and *Leguminosae* for the control of *Gramineae*, *Carizophyllaceae* and *Polygonaceae* families. Sumpter *et al.* (1970) reported excellent herbicidal efficiency in the control of *Avena* spp. and *Alopecurus myosuroides* in field beans *(Vicia faba)* in fallow and cereal stubbles. The suppressive action is also good against *Agropyron repens*. For the control of dicotyledons the action of propyzamide is about the same as that of simazine. Propyzamide is also effective for the control of *Poa annua* in turf. It can be used selectively in alfalfa and other small-seed legumes, in lettuce, nurseries and orchards at application rates of 0.75–2 kg active ingredient/ha.

Adequate soil moisture is needed for the activation of propyzamide. In cold soils (+5°C) it is persistent for several months, at 25°C it is degraded within weeks.

Propyzamide is effective mainly for the control of germinating weeds. It is absorbed through the roots, in *Agropyron repens* also through the rhizomes when applied in their vicinity. The absorbed herbicide inhibits the root and stem growth of sensitive plants. After treatment, normal cell division stops within a short time. Thus, primary action is manifested by the inhibition of mitosis (Carlson *et al.*, 1975). Accordingly, the increase in DNA, RNA, protein and cellulose activity, observed earlier by Smith *et al.* (1971) in *Agropyron* on treatment with propyzamide, can be considered as effects of secondary importance.

The first visible symptoms of propyzamide treatment are chlorosis and inhibition of root growth. Later abnormal stem growth can be observed, and the plants wither in a few weeks.



Swithenbank *et al.* (1971) synthesised forty related benzamide derivatives to study the relationship between chemical structure and action. The herbicidal activity of N-alkyl-3,5-dichlorobenzamides was enhanced by β,γ-unsaturation, and activity was further improved by α,α-dimethyl groups. In the case of dimethylpropynylbenzamides, derivatives with halogen substituents on the aromatic ring are the most active, substitution in positions 3 and 5 being optimal.

In summary, the structural elements of optimal herbicidal activity in propyzamide are the 3,5-dichloro-phenyl group, the dimethlypropynyl group and the carbamoyl function.

The metabolism of propyzamide in soil, plants and mammals has been investigated by several research workers (Yih and Swithenbank, 1970, 1971a,b; Swisher, 1972; Fisher, 1974).

Metabolism is slow both in sensitive and tolerant plants and begins with cyclisation. The oxazoline derivative formed is then degraded by hydrolysis and oxidation into a product with polar side-chain. In the soil, degradation proceeds mainly by the microbial pathway and leads to similar decomposition products.

For the metabolic decomposition mechanism of propyzamide in soil, alfalfa, in the urine of rat and cow and in the feces of rat Yih and Swithenbank (1971b) proposed the following pathway (see p. 573).

It is interesting that neither derivatives hydroxylated on the ring, nor 3,5-dichlorobenzoic acid, were found as end-products of metabolism.

Propyzamide is very slightly toxic to mammals, its acute oral LD_{50} for male rats being 8350 mg/kg, for female rats 5600 mg/kg, and for mongrel dogs 10 000 mg/kg. In two-year feeding tests the no-effect level for rats and beagles was 300 ppm.

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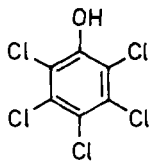
6.6 Phenols

The first known pesticide of these compounds is the potassium salt of 4,6-dinitro-*o*-cresol (DNOC) which had been patented already in 1982 as a miticide and aphicide.

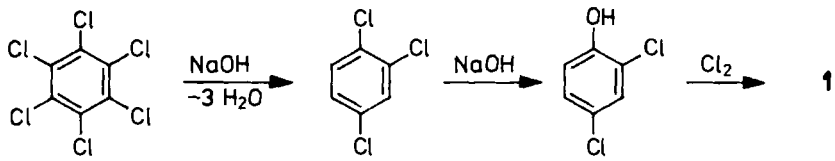
The herbicidal activity of the dinitro-*o*-cresol was discovered in 1932 (Truffaut and Pastac). Thus the sodium salt of 4,6-dinitro-*o*-cresol was the first organic compound used for selective weed control.

In 1940 pentachlorophenol (PCP, **1**) was introduced for weed control in cereals (Chabrolin®). PCP was later followed by several dinitroalkylphenols.



1

The herbicides of this group are mostly superseded and replaced by less toxic chemicals. Pentachlorophenol (PCP, **1**) was introduced in 1936 as a timber preservative in the United States. It is produced by catalytic chlorination of phenol (Stoesser, 1937). Other procedure for the synthesis of pentachlorophenol uses the inactive hexachlorocyclohexane isomers as starting material. The isomer mixture is partially hydrolised, then from the polychlorophenol mixture formed pentachlorophenol is obtained by chlorination:

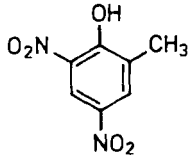


The technical product is a dark grey powder or flakes soluble in most organic solvents. The sodium salt forms a monohydrate.

Pentachlorophenol is a general herbicide and is also used as a preharvest defoliant. It was developed in 1959 in Japan as a selective herbicide for grasses, especially barnyardgrass *(Echinocloa crus galli)* in transplanted rice (Matsunaka, 1976). Because of its very high toxicity to fish, it has been superseded by diphenyl ethers which have low toxicity to fish. Pentachlorophenol is an uncoupling agent and can prevent ATP formation in mitochondrial respiration. (Weinbach and Garbus, 1966).

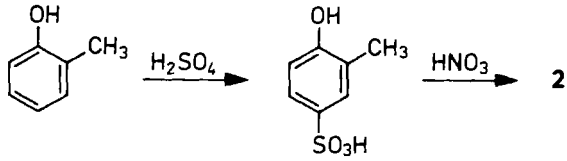
Pentachlorophenol is toxic to mammals. Its acute oral LD_{50} for rats is 210 mg/kg. It irritates mucous membranes and causes skin irritation. It is extremely toxic to fish, the LC_{50} (48 h) for rainbow and brown trout is 0.17 mg sodium pentachlorophenoxide (Alabaster, 1958).

4,6-Dinitro-*o*-cresol (DNOC 2) is in the form of its sodium salt a selective postemergence contact herbicide.



2

The yellowish crystalline compound DNOC is manufactured by the sulfonation of *o*-cresol with concentrated sulfuric acid, followed by nitration with diluted (30–35%) nitric acid (Mills and Fayerweather, 1983):



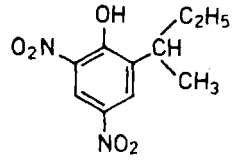
DNOC is used as its ammonium- or sodium salt, which are water-soluble. The salts are contact herbicides for the control of broad-leaved weeds in cereals, onion and garlic at rates of 3–5 kg active ingredient/ha. In emulsifiable concentrate formulation DNOC can be used for the preharvest desiccation of potatoes and leguminous seed crops (Worthing, 1979).

The weed control activity of DNOC can be enhanced by adding acidic ammonium salts to the spray solution (Crafts and Reiber, 1945; Robbins *et al.*, 1958).

DNOC is strongly toxic to mammals. The acute oral LD_{50} is for rats 25–40 mg/kg. Dinoseb, 2-*sec*-butyl-4,6-dinitrophenol (**3**) was first described as a herbicide by Crafts (1945).

Technical dinoseb is an orange-brown liquid, pure dinoseb is crystalline. It is mostly used as the ammonium or amine salt, which are soluble in water.

Dinoseb is manufactured by the direct nitration of a watery emulsion of 2-*sec*-butyl phenol with diluted nitric acid (Boileau and Aubertein, 1961).



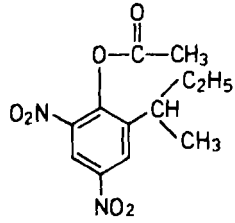
3

Dinoseb is a contact foliar herbicide with some activity through the soil. The salts are used postemergence in cereals (including undersown), peas, beans, clover, alfalfa soybeans and potatoes against broad-leaved weeds at about 2 kg active ingredient/ha. As a preemergence treatment in the same crops it is recommended at 2.5 kg active ingredient/ha. Dinoseb in oil is used for desiccation and defoliation of clover, alfalfa and hop and for potato haulm destruction.

Dinoseb is strongly toxic to mammals. The acute oral LD_{50} for rats is 58 mg/kg; the acute dermal LD_{50} for rabbits is 80–200 mg/kg. In 180-day feeding trials rats receiving 100 mg/kg diet suffered no ill effect.

Dinitrophenol derivatives affect many biological processes in both plant and animal living systems. Although many investigators examined them, the exact mechanisms of their complex effects are not known (Kaufmann, 1976).

According to Simon (1953) five different mechanisms can be distinguished by which dinitrophenols affect the living cells. These include oxidative phosphorylation and photosynthetic phosphorylation which are considered as their main effects. Dinitrophenols in addition affect glycolytic phosphorylation, respiration and fermentation reaction. General other observed effects are protein denaturation and their inhibiting action on lipid synthesis, RNA and protein synthesis.



4

The acetylation of dinoseb yields dinoseb acetate (**4**). It is somewhat less toxic than the parent compound. Dinoseb acetate was introduced by the Hoechst AG in 1958 and its herbicidal properties were first reported by Haertel (1960).

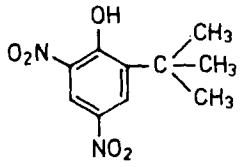
The ester is slowly hydrolysed in the presence of water. It is formulated as emulsifiable concentrate (492 g/l) or as WP (372 g active ingredient/kg).

Dinoseb acetate is mostly used as a mixture with various amounts of monolinuron.

Dinoseb acetate is a selective postemergence herbicide against broad-leaved weeds in peas, beans, potatoes, clover, alfalfa, barley, maize at rates of 1.5–2.5 kg active ingredient/ha. It controls also sucker growth on hop.

The acute oral LD_{50} for rats is 60–65 mg/kg. The no effect level for rats in 90-day feeding trial is 10 mg/kg diet.

Dinoterb, 2-*t*-butyl-4,6-dinitrophenol (**5**) was developed and introduced by the Pepro Co. (now subsidiary of Rhône-Poulenc) in 1963 (Poignant and Cristnel, 1967).



5

Dinoterb acetate forms pale yellow crystals, it is formulated as its ammonium salt in the form of an aqueous paste with 500 g active ingredient/l. Other commercial products include mixtures with MCPP (DM 68), with isoproturon (Tolkan S) and with nitrofen (Phenoterb).

The herbicidal activity of dinoterb is similar to that of dinoseb acetate and so is its application. It is also recommended as a preemergence treatment in peas and beans.

Dinoterb is strongly toxic to mammals. The acute oral LD_{50} for mice is 25 mg/kg, the acute dermal LD_{50} for guinea pigs 150 mg/kg.

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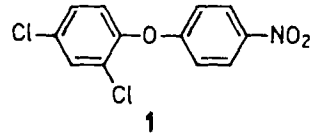
6.7 Nitrodiphenyl ethers

The development of this selective herbicide group begun in the 1960s in the United States. Nitrofen (**1**) was the first member of this group, introduced by Rohm and Haas (Wilson and McRae, (1960).



1

Nitrofen, 2,4-dichlorophenyl-4-nitrophenyl ether is a white crystalline solid, practically insoluble in water, soluble in most organic solvents.

It is produced by the condensation of 1-chloro-4-nitrobenzene with an alkali, 2,4-dichlorophenoxide.

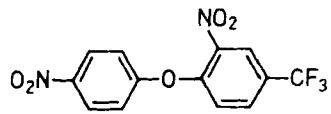
Nitrofen selectively controls a number of broad-leaved and grassy weeds as preemergence or postemergence treatment in rice, cereals, *Brassica* crops and many other vegetable crops. It is applied mainly as surface preemergence spray, but sometimes as directed postemergence spray.

Absorption occurs through the roots and leaves but translocation is limited only (Hawton and Stobbe, 1971; Arai *et al.*, 1966).

The mode of action studies suggest that nitro-diphenyl ethers act on the photosynthetic systems of plants. Two pathways are involved, one requiring light, the other not. Thus they can inhibit noncyclic electron transport and coupled photophosphorylation in chloroplasts, and in mitochondria they inhibit electron transport. (Matsunaka, 1969a, 1969b and Moreland *et al.*, 1970).

Nitrofen is weakly toxic to mammals. The acute oral LD_{50} for rats is 2630 mg/kg. Neither the active ingredient nor the formulation emulsifiable concentrate caused irritation to rabbit skin. Rats on dietary levels of 100 and 500 ppm for 13 weeks and on 10 100 and 1000 ppm for 97 weeks showed no definite differences in growth, feed consumption or mortality, when compared to controls (Ambrose *et al.*, 1971).

4-Nitrophenyl α,α,α-trifluoro-2-nitro-*p*-tolyl ether (fluorodifen, **2**) was developed by the Ciba Geigy AG in 1962 (Martin *et al.*, 1962).



2

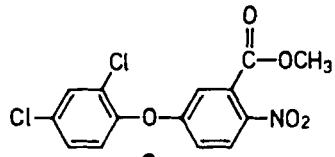
It was introduced in 1968 as an experimental herbicide (Ebner *et al.*, 1968) produced by the reaction of sodium 4-nitrophenoxide with 4-chloro-α,α,α-trifluoro-2,3-nitrotoluene.

Fluorodifen is a contact herbicide used as a preemergence and postemergence spray on rice, soybeans and beans at a rate of 3–4 kg active ingredient/ha. It is not

recommended for surface seeded rice. The half-life of fluorodifen ranges from 20 to 55 days, depending on environmental factors.

Fluorodifen has low mammalian toxicity and its wildlife toxicity is also low. The acute oral toxicity for rats is 9000 mg/kg; the acute dermal LD_{50} for rats is 3000 mg/kg. The 10-day LC_{50} for pheasants, ducks and quail varies from 10 250 to 15 380 mg/kg in diet. The LC_{50} (96h) is for trout 0.18 mg/l; for catfish 0.92 mg/l; for bluegill 0.60 mg/l.

Methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate (bifenox, **3**) was introduced in 1970 by the Mobil Chemical Co. as an experimental herbicide.



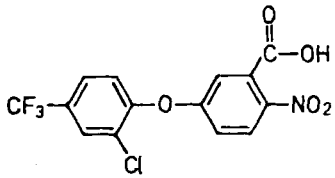
3

Bifenox is synthesised by the condensation of potassium 2,4-dichlorophenoxide and methyl 5-chloro-2-nitrobenzoate. Its herbicidal properties were first reported by Dest *et al.* in 1973.

Bifenox is applied as surface preemergence and directed postemergence spray for controlling broad-leaved weeds and several germinating grass weeds in soybeans, corn, sorghum, rice and small grains. The recommended rates as pre-emergence treatment are 1.68–2.24 kg active ingredient/ha depending on soil types and climatic conditions and as directed spray at rates of 1.12–1.68 kg active ingredient/ha.

Residual control persists for 35–70 days depending upon plant species, soil type and rainfall. The acute oral LD_{50} for rats is > 6400 mg active ingredient/kg. The acute dermal LD_{50} for rabbits is > 20 000 mg/kg. It does not cause eye irritation.

Rohm and Haas introduced recently two new members of the diphenyl ether group, namely 5-(2-chloro-4-trifluoromethyl)phenoxy-2-nitrobenzoic acid (acifluorfen, **4**) and 2-chloro-4-(trifluoromethyl)phenyl 3-ethoxy-4-nitrophenyl ether (oxyfluorfen, **5**) (Biroli *et al.*, 1980; Theissen, 1982; Swithenbank, 1982). Acifluorfen is used as its sodium salt soluble in water.



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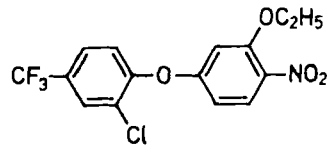


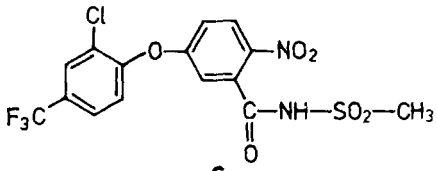
5

The commercial formulation contains 240 g active ingredient/l. It is recommended as a postemergence application at a rate of 0.3–0.6 kg active

ingredient/ha in soybeans and peas. Acifluorfen controls a number of broad-leaved weeds when they are small and actively growing. Its activity can be enhanced by adding wetters to the spray solution (Bundick and Regehr, 1981).

Oxyfluorfen is applied as a preemergence herbicide in soybeans, cotton, tomatoes, tobacco and green pepper at a rate of 0.2–0.4 kg active ingredient/ha. Grassy weeds are not well controlled by oxyfluorfen, but in the case of heavy grass weed infestation it can be tank—mixed with thiocarbamates, dinitroanilines, chloroacetamides, dalapon and paraquat. Oxyfluorfen is also recommended in tree fruits, vineyards and in conifer nurseries as an early postemergence treatment.

Oxyfluorfen is weakly toxic to mammals. Acute oral LD_{50} for rats is 5000 mg/kg. Acute dermal LD_{50} for albino rats is 10 000 mg/kg (Biroli *et al.*, 1980). Fomesafen (code number PP 021) is a new diphenylether herbicide which was invented at the ICI's Jealott's Hill Research Station. Its chemical name is 5-(2-chloro-4-trifluoromethyl)phenoxy-N-(methylsulfonyl)-2-nitrobenzamide (fomesafen, Flex®) **(6)**.



6

Analytical grade fomesafen is a white crystalline compound stable for over 14 months at 37°C. It is formulated as an aqueous concentrate (Flex®) containing 250 g active ingredient/l of the sodium salt. In the USA the formulation contains 238 g/l.

Fomesafen is a selective herbicide for postemergence broad-leaved weed control in soybean (Anonym, 1982).

Several hundred field trials, conducted throughout the major growing areas of the world showed that fomesafen at 0.14–0.5 kg active ingredient/ha gave good to excellent seasonlong control of broad-leaved weeds. Its weed control activity can be enhanced by adding nonionic surfactant to the spray solution.

Fomesafen was found to be less phytotoxic to soybeans than acifluorfen, but it is more phytotoxic than bentazon.

Fomesafen is weakly adsorbed by soils. Its adsorption coefficients (k_d) are in the range of 0.5 to 3.0 depending on the organic matter content of the soils. Under aerobic conditions fomesafen degrades slowly in soil, its half-life is generally greater than 6 months.

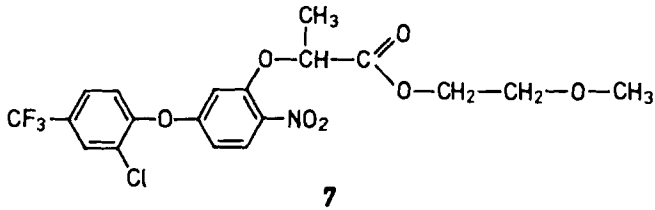
The full toxicological evaluation of fomesafen is at progress. The acute oral LD_{50} for rats is 120–1600 mg/kg. It is a mild irritant to rabbit skin, and a mild to moderate irritant to rabbit eyes.

No-effect level (90 days) for rats is 5.0 mg/kg, equivalent to 0.25 mg/kg body weight/day. No-effect level (26 weeks) for dogs is 30–40 mg/kg in the diet (1.0 mg/kg body weight/day).

Fomesafen is of low acute and subacute toxicity to birds too. Acute oral LD_{50} for mallard ducks is greater than 5000 mg/kg.

Technical and formulated fomesafen are of low toxicity to *Daphnia magna*. LC_{50} (48 hours) 330 and 960 mg/l, respectively for the technical and formulated materials. Formulated fomesafen is of low toxicity to fish. The LC_{50} (96 hours) is for *Salmo gairdneri* 680 mg/l and for *Lepomis macrochirus* 6030 mg/l.

Fomesafen has no adverse effect on earthworm populations when applied at normal field use rates. 2-Methoxyethyl 2-[5-(2-chloro-4-trifluoromethyl)-phenoxy-2-nitrophenoxy]propionate (CGA 84446, **7**) is a new selective herbicide from the diphenylether group, being developed by the Ciba-Geigy AG (Gerber and Maurer, 1982).



7

CGA 84446 shows a very high foliar activity and selectively controls many broad-leaved weeds, including the problem weeds like *Veronica*, *Viola* and *Galium*, in wheat and barley. Applied preemergence at rates of 0.25–0.5 kg active ingredient/ha; combined with 1.5–2.0 kg chlortoluron controls both grasses and broad-leaved weeds. Postemergence at rates of 0.125—0.25 kg active ingredient/ha CGA can also be used with isoproturon (or chlortoluron). CGA 84446 herbicidal activity is attributed to the loss of plant membrane integrity (Ashton and Crafts, 1982). After preemergence application the visible symptoms are necrosis of shoot and meristems on sensitive weeds.

After postemergence treatment tilting begins within 24 hours. In two days necrosis occurs, then sensitive plants die rapidly.

CGA 84446 is of low toxicity to mammals. Acute oral LD_{50} for rats is 5000 mg/kg. Acute dermal LD_{50} to rats is 2000 mg/kg. Skin and eye irritation to rabbits is minimal.

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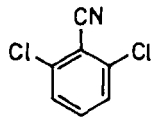
6.8 Nitriles

The plant physiological actions of aromatic nitriles were first studied at the end of the 1930s by Wegler and Binder (1938) in the research laboratories of the former I.G. Farbenindustrie. The plant growth modifying action of several aromatic nitriles and the importance of 2,6-dichloro-substitution from the aspect of biological activity were recognised in the same laboratories.

Nitrile herbicides for agricultural use were developed in 1960 and 1963 in the laboratories of the Dutch Philips and Shell, and almost at the same time, as a result of the work of Wain, a further important group of nitrile compounds, the bis-halogen-4-hydroxybenzonitriles were described.

The latter group of compounds might also be chemically classed among the benzoic acid derivatives, but due to the nitrile group of the compounds, their action differs basically from that of the benzoic acid derivatives, and thus will be suitably described in this group.

The herbicidal properties of 2,6-dichlorobenzonitrile, dichlobenil (**1**) were first described by Koopman and Daams (1960).



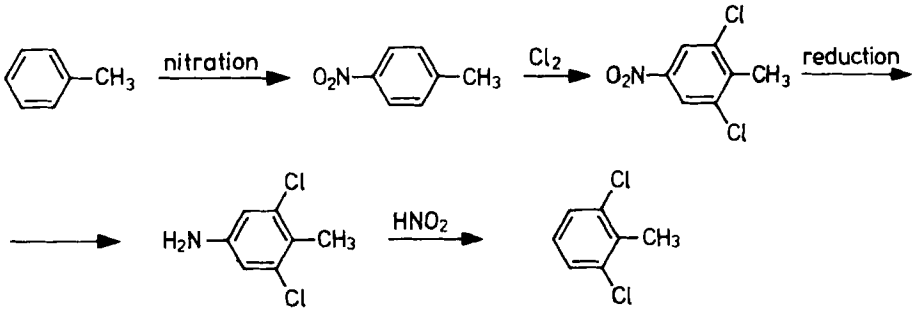
1

Dichlobenil is a crystalline compound hydrolysable by alkalies to 2,6-dichlorobenzaldehyde. The technical product is of 94% purity.

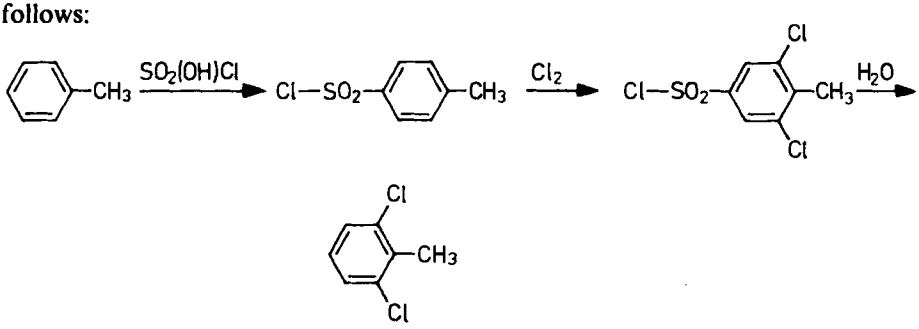
An important property from the aspect of application is the considerable volatility of dichlobenil. Its vapour pressure at 25°C is $5 \cdot 10^{-4}$ mm Hg, and it is quickly lost from a warm soil surface (Parochetti *et al.*, 1971).

Several routes are feasible for the synthesis of dichlobenil, the key intermediate generally being 2,6-dichlorotoluene, rather difficult to prepare. 2,6-Dichlorotoluene cannot by obtained by the direct chlorination of toluene.

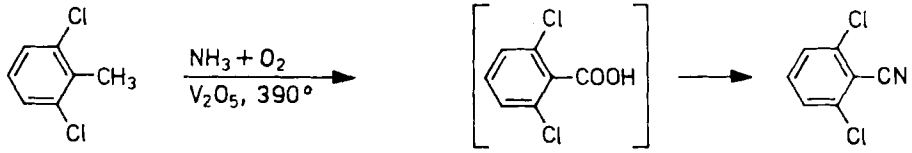
One of the possible indirect syntheses is the following reaction route:



The patented process of the Shell research team (DAS 1 169 914; 1961) is as follows:



Dichlobenil too can be prepared by several routes from 2,6-dichlorotoluene. The most feasible way for industrial synthesis seems to be the process patented by Shell (DAS 1 206 422; 1964). In this process, 2,6-dichlorotoluene is catalytically converted with an $NH_3 + O_2$ mixture into dichlobenil:



Dichlobenil is a selective pre- and postemergence herbicide effective against several annual and perennial weeds. It is suitably applied after the emergence of the crops and preemergence to the weeds. It is recommended at rates of 2.5–10 kg active ingredient/ha in orchards, vineyards and cranberry bogs. To counterbalance its volatility, dichlobenil is conveniently incorporated in the soil. It is efficient in vineyards for the inhibition of *Convolvulus* spp. and nutsedge sprouting, when applied to the bare soil as a subsurface layer with a spray blade. Dichlobenil can be used for the control of aquatic weeds at a rate of 4–14 kg active ingredient/ha. (Comes and Morrow, 1971).

Dichlobenil is a potent inhibitor of germination, inhibiting the actively dividing cells of meristems. It stops the growth of sprouts of perennial weeds, but their root systems survive the treatment, so the weeds may resprout. Dichlobenil is ineffective against dormant tubers (Hardcastle and Wilkinson, 1968).

The symptoms of plants treated with dichlobenil are very similar to symptoms of boron deficiency. After the inhibition of growth the apical meristems blacken and the plant dies. Sublethal doses of dichlobenil increase the chlorophyll content in the leaves of the treated plant, so that their colour becomes darker (Milborrow, 1964).

The biochemical mode of action of dichlobenil is not yet fully known.

The activity of dichlobenil incorporated in the soil persists for a few months and is then slowly broken down by microorganisms. Owing to its strong adsorption in soil, it is not leached from deeper soil layers.

Dichlobenil is apoplastically translocated in the plants, and most of it volatilises through the leaves. The residual part is metabolised to 3- and 4-hydroxy derivatives, and these form conjugates (Verloop and Nimmo, 1969, 1970).

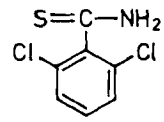
Dichlobenil is rather persistent in water. Doses of 0.6–10 ppm disappear in 50–160 days from water (Van Valin, 1966; Walsh *et al.*, 1971; Rice *et al.*, 1974).

The fate of dichlobenil in animals has been reviewed by Beynon and Wright (1972).

Dichlobenil is slightly toxic to mammals. Its acute oral LD_{50} for rats is 3160 mg/kg. The LC_{50} (48 hours) for guppies is more than 18 mg/l, for water fleas 9.8 mg/l.

Koopman and Daams (1965) investigating the structure–activity relationship of substituted benzonitrile, were the first to report that compounds easily converted into nitriles may also be efficient herbicides.

Such a compound is 2,6-dichloro(thiobenzamide), developed and introduced in 1963 by the Shell Research Ltd. under code number "WL 5792" and trade mark Prefix®. Its approved common name is chlorthiamid **(2)**.



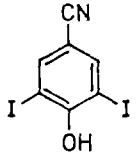
2

It is converted in alkaline solution by heat and by U.V. light into dichlobenil. This conversion proceeds also in soil.

Chlorthiamid is a preemergence herbicide inhibiting germination, used at a rate of 20–30 kg active ingredient/ha for total weed control, at 4–14 kg active ingredient/ha for selective weed control. It is recommended as spot treatment to control docks (*Rumex* spp.) and thistles (*Cirsium* spp.) in the renovation of old pastures. Its other areas of application are the same as those of dichlobenil (Sandford, 1964; Jenner, 1977).

Chlorthiamid is slightly more toxic to mammals than dichlobenil. Its acute oral LD_{50} for rats is 757 mg/kg. The no-effect level (90-day with rats) is 100 mg/kg diet. The LC_{50} (24 h) is 41 mg/l for harlequin fish.

The herbicidal activity of 3,5-dihalogen-4-hydroxybenzonitriles was reported independently by several research laboratories. Wain, Carpenter and Heywood and the Amchem Co. described in 1963 the herbicidal properties of 4-hydroxy-3,5-diiodobenzonitrile (ioxynil, **3**) and of 4-hydroxy-3,5-dibromobenzonitrile (bromoxynil, **4**).



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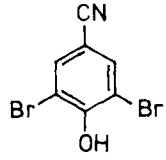
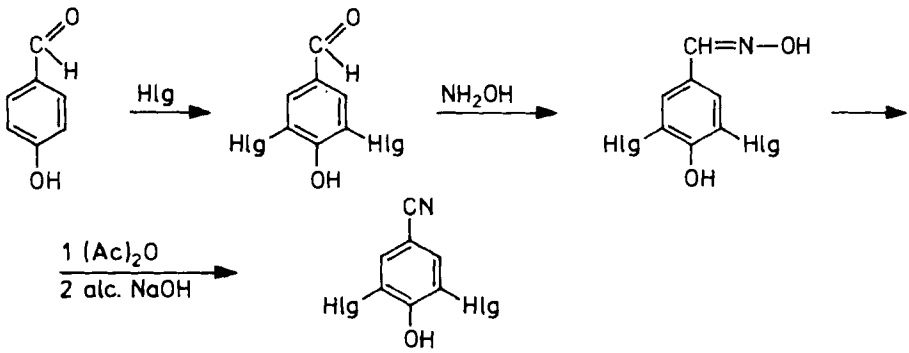


4

Pure ioxynil is a colourless crystalline compound insoluble in water and poorly soluble in organic solvents. Owing to its acid character (pK_a 3.96) it forms salts with alkali metals, which are readily soluble in water. Its amine salts are also readily soluble in water.

The physical properties of bromoxynil are very similar to those of ioxynil. Its alkali and amine salts are soluble in water too, but less so than the ioxynil salts.

Both compounds are made by the halogenation of 4-hydroxybenzaldehyde, conversion to the oxime and dehydration to the nitrile according to the following reaction scheme (Auwers and Reis, 1896):



Ioxynil and bromoxynil can be easily esterified with acid chlorides with longer carbon atom chains. Thus, esterified with octanoyl chloride, ioxynil octanoate and bromoxynil octanoate are formed. These derivatives are readily soluble in xylene (500 and 400 g/l resp.), and are thus, suitable for the preparation of emulsifiable concentration formulations (Totril®, 250 g ioxynil/l) and Brominal®, 240 g active ingredient/l. In the plants the esters are degraded to the parent herbicide and exert their action in this form.

Ioxynil and bromoxynil are postemergence contact herbicides identical in range of action and nearly identical in activity. Though ioxynil is more efficient than bromoxynil per mole, by weight their activity is almost identical.

The two herbicides are used for the selective control of broad-leaved weeds in cereals and grass crops. Their main importance lies in their efficiency against hormone-resistant weeds, thus, they are almost always used in combination with phenoxy herbicides. Recommended rates are 250–800 g active ingredient/ha.

Among 2,4-D-resistant weeds controlled by ioxynil are: douglas fiddle neck *(Amsinckia douglasiana)*, tartary buckwheat *(Fagopyrum tataricum)*, hempnettle *(Galeopsis tetrahit)*, bedstraw *(Galium aparine)*, kochia *(Kochia scoparia)*, pineapple weed *(Matricaria matricaroides)* and prostrate knotweed *(Polygonum aviculare)*.

Bromoxynil efficiently controls blue mustard *(Chorispora tenella)*, corn gromwell *(Lithospermum arvense)*, cow cockle *(Sapenaria vaccaria)*, coast fiddleneck *(Amsinckia intermedia)*, field pennycress *(Thlaspi arvense)*, green smartweed *(Polygonum scabrum)*, common lambsquarters *(Chenopodium album)*, London rocket *(Sisymbrium irio)*, shepherd's purse *(Capsella bursa-pastoris)*, silverleaf nightshade *(Solanum elaeagnifolicum)*, Tartary buckwheat *(Fagopyrum tataricum)*, tarweed (*Hemizonia* spp.), tumble mustard *(Sisymbrium altissimum)*, wild buckwheat *(Polygonum convolvulus)* and wild mustard *(Brassica kaber)* (Ashton and Crafts, 1973).

In cereals ioxynil and bromoxynil must be used before the reaching of the root stage; the 3–4 leaf stage of the weeds is the most advantageous for weed killing. At later stages the dosage must be increased, and the action also becomes less certain. To ensure good spray coverage, the herbicides must be applied with an adequate quantity of water.

In the broad-leaved weeds sprayed the action is manifested in a few hours in the form of burns, and this is followed by the collapse of the leaf cells. After 24 hours necrosis becomes more severe, and all the leaf tissues and the whole plant are killed. Cereals may also be slightly burnt, particularly as a result of overdosage or wetting agents, but they quickly recover (Carpenter *et al.*, 1964).

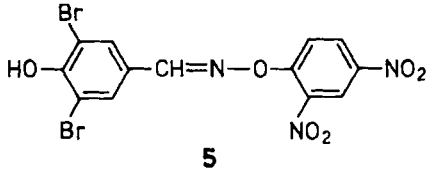
Ioxynil and bromoxynil are photosynthesis inhibiting herbicides. They inhibit the electron flow near the quinone component of electron transport (Wain, 1964; Smith *et al.*, 1966; Paton and Smith, 1965, 1967). In addition to the strong inhibition of oxidative phosphorylation, both herbicides prevent CO_2 fixation (Friend and Olson, 1967).

Ioxynil and bromoxynil are rapidly metabolised in plants and animals. During hydrolysis first amide, then carboxylic acid derivative is formed, the latter being accompanied by a small degree of dehalogenation (Wain, 1964; Buckland, 1973).

These herbicides are also rapidly broken down in the soil by microorganisms (in 2–3 weeks). The pathway of degradation is similar to that in plants (Swanson, 1969; Collins, 1973; Ingram and Pullin, 1974).

Ioxynil and bromoxynil are moderately toxic to mammals, but are strongly toxic to fish.

Bromofenoxim, 3,5-dibromo-4-hydroxybenzaldehyde 2,4-dinitrophenyl oxime (5), was introduced in 1969 by the Ciba-Geigy AG under the code number C 9122. Though chemically not a nitrile, bromofenoxim is presumably hydrolysed to nitrile. This seems to be supported by its action, which is very similar to that of the two nitrile herbicides discussed above.



5

Prepared by the reaction of 3,5-dibromo-4-hydroxy-benzaldehyde oxime with 1-chloro-2,4-dinitrobenzene (BP 1 096 037), bromofenoxim is a postemergence selective herbicide with strong contact activity. It is used for the control of annual broad-leaved weeds in winter- and spring-sown cereals at a rate of 1–2.5 kg active ingredient/ha. To enhance the effect against grassy weeds, it is also available in combination with terbutylazine in active substance ratios of 3 : 1 and 1.65 : 1.

Bromofenoxim is a moderately toxic compound. Its acute oral LD_{50} for rats is 1217 mg/kg. Its avian toxicity is low. Its toxicity to fish depends on the species (Green, 1969).

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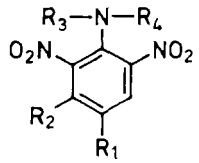
6.9 Dinitroanilines

The development of this group of selective herbicides began in the research laboratories of the Eli Lilly and Co., Alder and Bevington 1962 and Alder *et al.* (1960) described the first biologically active 2,6-dinitroaniline group, and since then one member of the group, trifluralin, has been used in large quantities all over the world for selective weed control on ploughed land.

The unsubstituted 2,6-dinitroaniline molecule has virtually no biological activity, but derivatives substituted in the nucleus and at the N atom exhibit herbicidal activity Wilder, 1969).

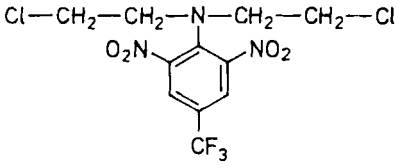
The general formula of dinitroaniline derivatives with herbicidal properties is the following:



The more important dinitroaniline derivatives known today are: N,N-bis(2-chloroethyl)-4-trifluoromethyl-2,6-dinitroaniline (BAS 3870 H, **1**); N-butyl-N-ethyl-α,α,α-trifluoro-2,6-dinitro-*p*-toluidide (benfluralin, **2**); N-*sec*-butyl-4-*t*-butyl-2,6-dinitroaniline (butralin, **3**); N-ethyl-N-tetrahydrofurfuryl-4-trifluoromethyl-2,6-dinitroaniline (CGA 11 607; GS 39 985, **4**); N,N-bis(2-chloroethyl)-4-methyl-2,6-dinitroaniline (chlornidine, **5**); N^1,N^1-diethyl-2,6-dinitro-4-trifluoromethyl-*m*-phenylenediamine(dinitramine, **6**); N,N-dipropyl-2,6-dinitro-4-methylaniline (dipropalin, **7**); N-ethyl-N-(2-methylallyl)-2,6-dinitro-4-trifluoromethylaniline (ethalfluralin, **8**); N-(2-chloroethyl)-N-propyl-2,6-dinitro-4-trifluoromethylaniline (fluchloralin, **9**); 4-isopropyl-2,6-dinitro-N,N-dipropylaniline (isopropalin, **10**);

4-methylsulfonyl-2,6-dinitro-N,N-dipropylaniline (nitralin, **11**); 3,5-dinitro-N^4, N^4-dipropylsulphanylamide (oryzalin, **12**); N-(1-ethylpropyl)-2,6-dinitro-3,4-xylidine (penoxalin, **13**); N-(cyclopropylmethyl)-α,α,α-trifluoro-2,6-dinitro-N-propyl-*p*-toluidide (profluralin, **14**); 3,5-dinitro-N^4,N^4-dipropyl-dimethylsulphanylamide (prosulfalin, **15**); and α,α,α-trifluoro-2,6-dinitro-N,N-dipropyl-*p*-toluidide (trifluralin, **16**).

The nitroaniline herbicides are generally stable compounds, fairly volatile at room temperature, and slightly soluble in water. Owing to their poor water solubility and strong adsorbability, they are located in the top layers of the soil and



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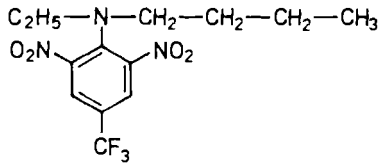

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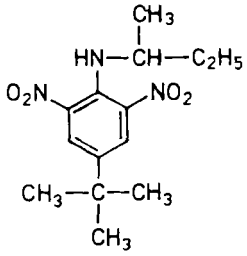

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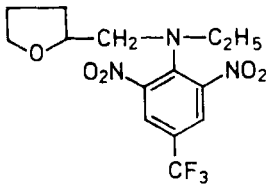

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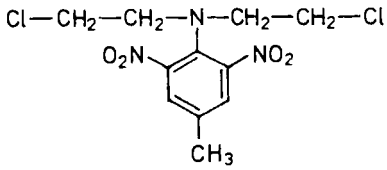

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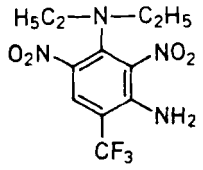

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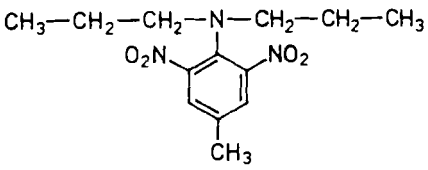

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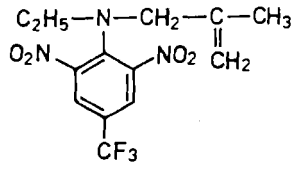

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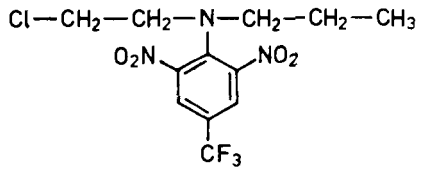

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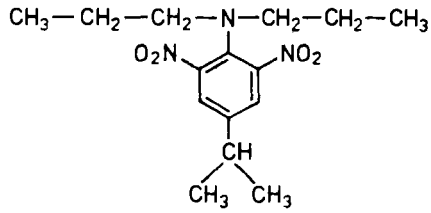

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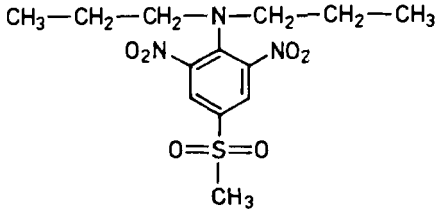

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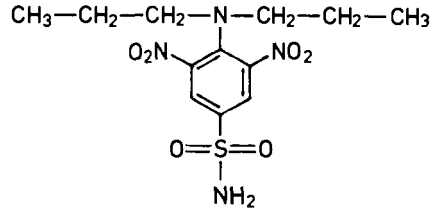

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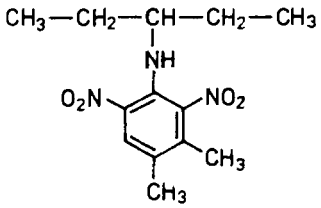

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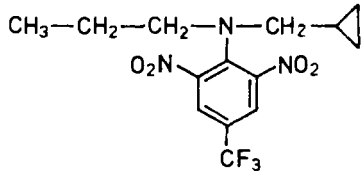

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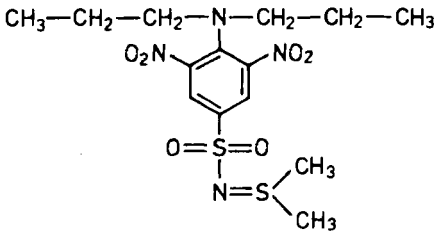

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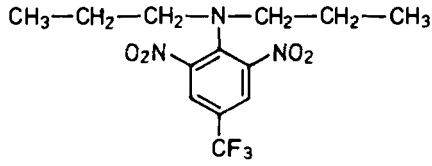

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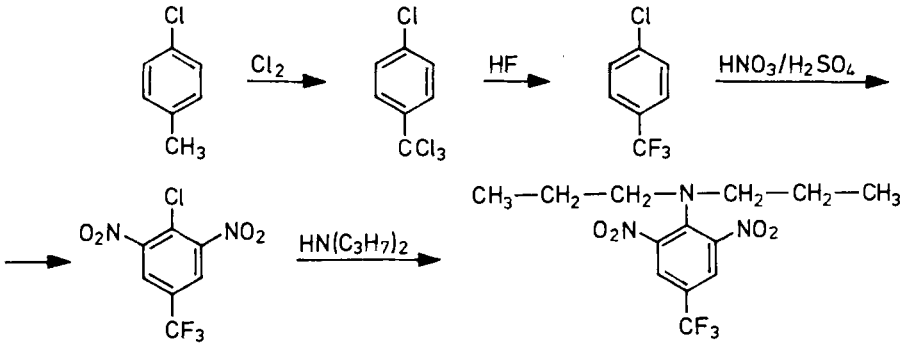
have little tendency towards leaching. Another characteristic property of nitroaniline herbicides is their relatively rapid degradation by the action of ultraviolet light.

Some characteristic methods for their synthesis are given in the following.

Starting with *p*-chlorotoluene, several synthesis routes can be used for the preparation of trifluralin (Soper, 1960a, 1960b; Urenovitch and Dixon, 1971a):

Method I:



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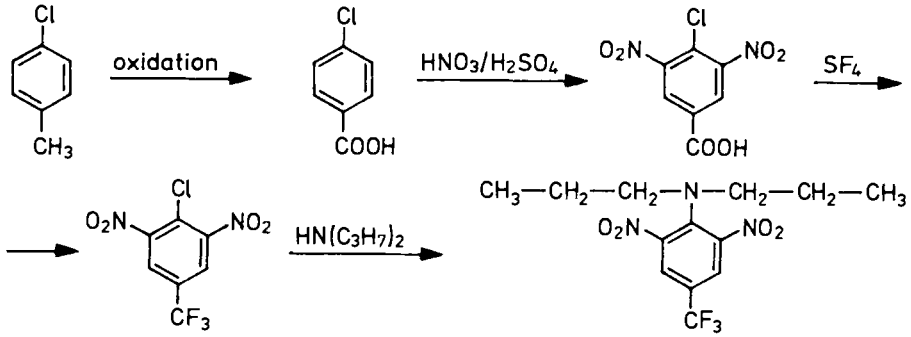
Method II:



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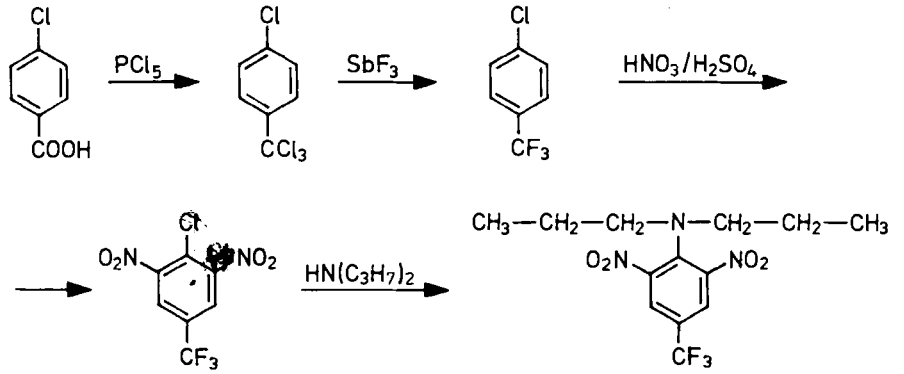
Method III (Marshall and Jones, 1966):



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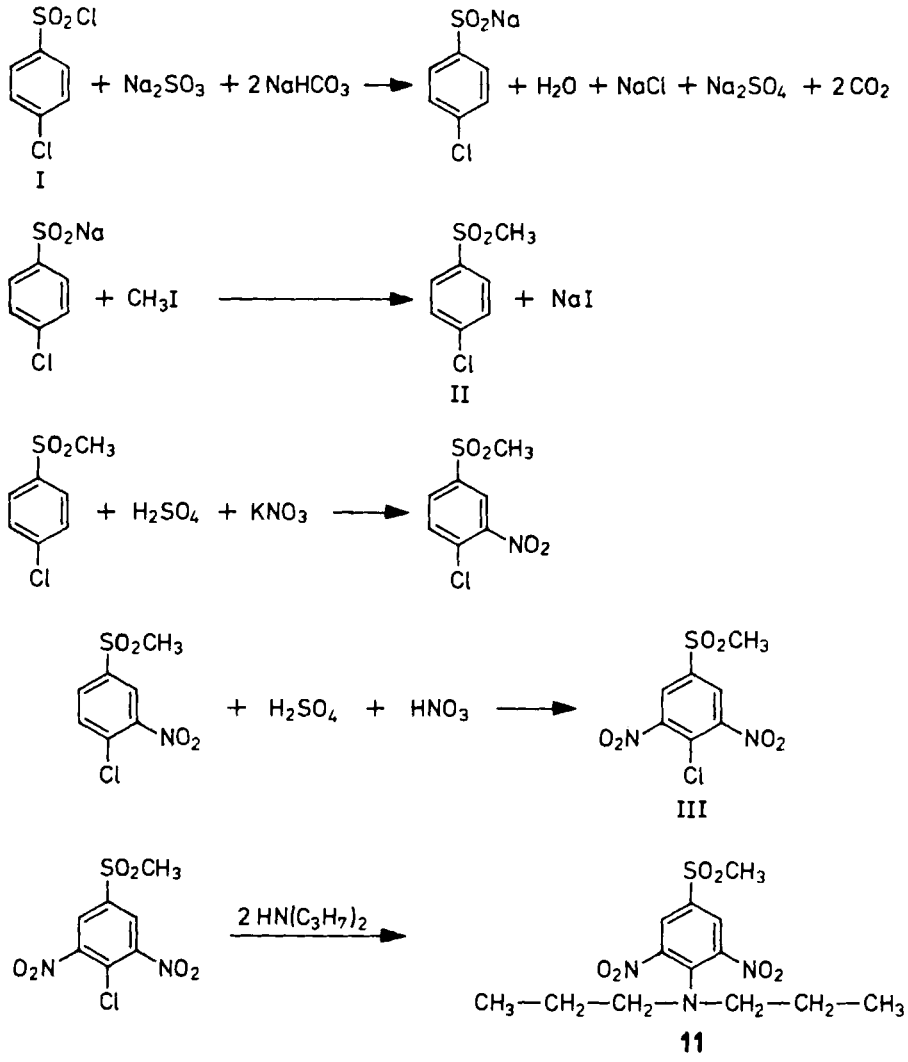
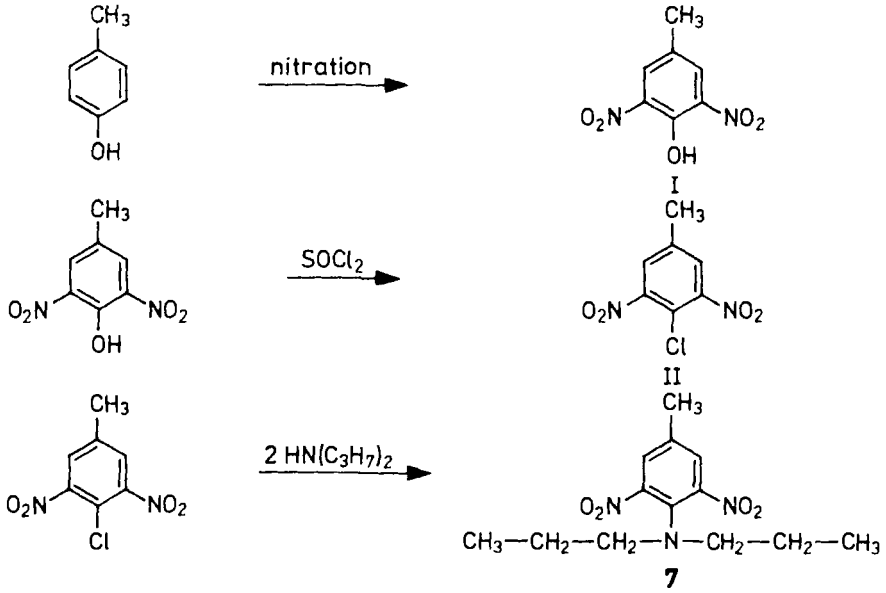
The last method is recommended by Soper (1960b) also for the preparation of benfluralin.

Nitralin is prepared according to the method of Soloway and Zwahlen (1964) by the nitration of 4-chlorophenyl methyl sulfone and the coupling of the 4-chloro-3,5-dinitrophenyl methyl sulfone obtained with dipropylamine.

The starting material of the synthesis is 4-chlorobenzene sulfonyl chloride (I), which is converted into 4-chlorophenyl methyl sulfone (II). This is nitrated in two steps to yield 4-chloro-3,5-dinitrophenyl methyl sulfone (III) (Urenovitch and Dixon, 1971b). Reaction scheme of total synthesis:

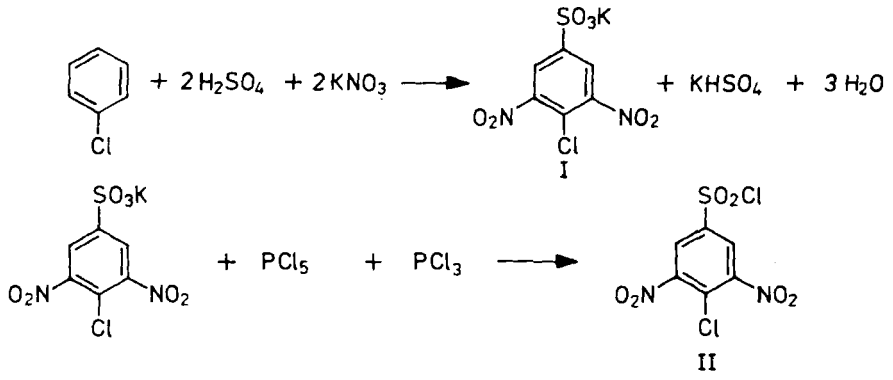


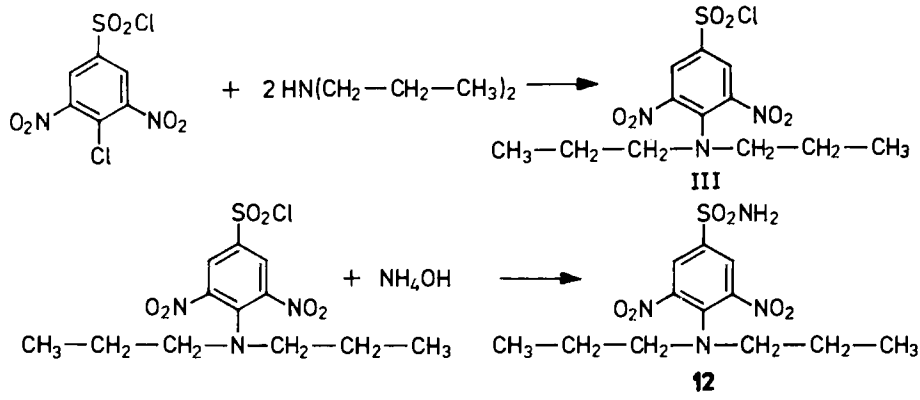
Dipropalin can be prepared starting from *p*-cresol. *p*-Cresol is nitrated, and the dinitro-*p*-cresol (I) obtained is converted with thionyl chloride into 4-chloro-3,5-dinitrotoluene (II). This is then reacted with di-*n*-propylamine to give dipropalin. The reaction scheme is as follows:



Oryzalin is prepared by a different route. Synthesis starts with chlorobenzene, which is nitrated in a single step into potassium 4-chloro-3,5-dinitrobenzene sulfonate (I). This is then converted with phosphorus oxychloride and phosphorus pentachloride into 4-chloro-3,5-dinitrobenzene sulfonyl chloride (II). The reaction of the latter with dipropylamine gives 4-dipropylamino-3,5-dinitrophenyl sulfonyl chloride (III), the reaction of which with ammonium hydroxide yields oryzalin.

The reaction scheme is the following (Urenovitch and Dixon, 1971c):





The main field of application of dinitroaniline herbicides is the control of annual grass weeds. Some annual dicotyledonous weeds are also sensitive to dinitroaniline herbicides in the initial growth stage. All members of the group are fairly volatile, and are hence sprayed before sowing to the soil surface and immediately incorporated to a soil depth of 6–8 cm. Owing to their poor water solubility, they are not absorbed from dry soil in adequate quantity by the plant, so under dry conditions their action is unsatisfactory.

Dinitroaniline herbicides are taken up by the plants through the roots and shoots, from where they are translocated in different ways, depending on the kind of herbicide and plant.

Their action in sensitive plants is general growth inhibition. The growth inhibition of roots is very characteristic in both mono- and dicotyledonous plants. The lateral and secondary roots do not develop. Primary roots become swollen, abnormal multinucleated cells being formed in them.

Of the physiological processes of the plant RNA and DNA synthesis and, thus, protein and nucleic acid levels are reduced by treatment with the herbicides, and carbohydrate synthesis too slows down.

Summarising research results relevant to the activity and mode of action of this group of herbicides, Swanson (1972) concludes that, as with carbamates, the mode of action of dinitroaniline herbicides is the inhibition of mitosis. Dinitroaniline herbicides are thus mitotic poisons.

Unsubstituted dinitroanilines are weakly phytotoxic. Toxicity to annual seedlings depends on the location of the dinitro substitution. 2,6-Dinitroaniline is the most toxic, 2,4- and 2,3-dinitroanilines have progressively weaker action. Alkyl group substituents at the amino nitrogen of 2,6-dinitroanilines increase preemergence activity, but reduce postemergence activity (Soper *et al.*, 1961). Moreover, investigations showed that N-dialkyl substitution and a short-chain substituent in position 4 are needed for good biological activity. Substituents of 2,6-dinitro-N,N-dipropylaniline in position 4 resulted in the following series of decreasing biological activity:

$$CF_3 > CH_3 > Cl > H$$

Indeed, of this group, trifluralin used in agriculture at a rate of 0.5–1.0 kg/ha, is the most efficient herbicide.

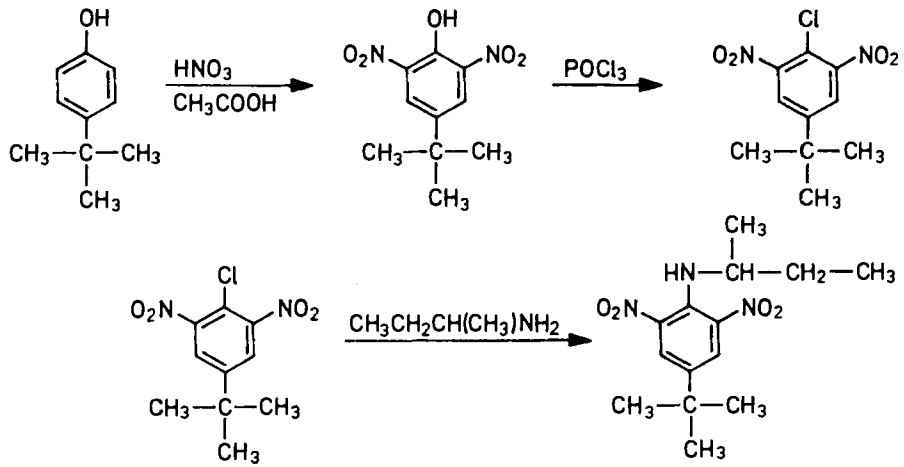
Experiments of Gentner (1966) with mono- and dicotyledonous weeds and crop plants showed that the biological activity of 2,6-dinitro-N,N-dialkylanilines substituted in position 4 with a CH_3 or a CF_3 group decreases if the total carbon atom number of the alkyl chains substituted at the amino nitrogen is more than six.

In the case of analogous dialkyl derivatives, the postemergence activity of the 4-methyl derivative is stronger than that of the 4-trifluoromethyl derivative, while the opposite is true of their preemergence activity.

Malichenko *et al.* (1968) investigated the structure–activity relationships of trifluralin analogues on oat (*Avena sativa*) and radish (*Raphanus sativus*) seedlings. A trifluoromethyl substituted group in the *para* position results in higher activity than if substituted in the *ortho* position. The activity of the compounds increases with increasing carbon atom number of the alkyl chain substituent on the amino group. In the case of dialkyl substitution, preemergence activity on oat increases with increasing chain length, to attain a maximum in the case of the dibutyl analogue. A further increase in carbon atom number gradually reduces the activity of the compounds.

Similarly, Gentner (1970) found in the investigation of nitralin analogues that the highest activity is exhibited by an alkyl substitution involving five or six carbon atoms.

The synthesis of butralin (dibutalin, 3) starts with 4-*t*-butylphenol, the nitration of which with a mixture of nitric acid and acetic acid gives 4-*t*-butyl-2,6-dinitrophenol in a good yield. The dinitrophenol is reacted in dimethyl formamide solution with phosphorus oxychloride to give 1-*t*-butyl-4-chloro-2,6-dinitrobenzene. The reaction of the latter with *sec*-butylamine gives butralin (Bishop *et al.*, 1972).



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Butralin is the sole dinitroaniline derivative in which the amino nitrogen carries only one substituent. It is interesting, on the other hand, that contrary to expectation, the N,N-di-*sec*-butyl derivative exhibits no herbicidal activity.

Butralin is a preplanting selective herbicide to be incorporated into the soil. At a rate of 1–3 kg active ingredient/ha it is selective in cotton, soybean and vegetables. Unlike the other dinitroanilines, it also has a growth-modifying action and is used for the control of tobacco sucker.

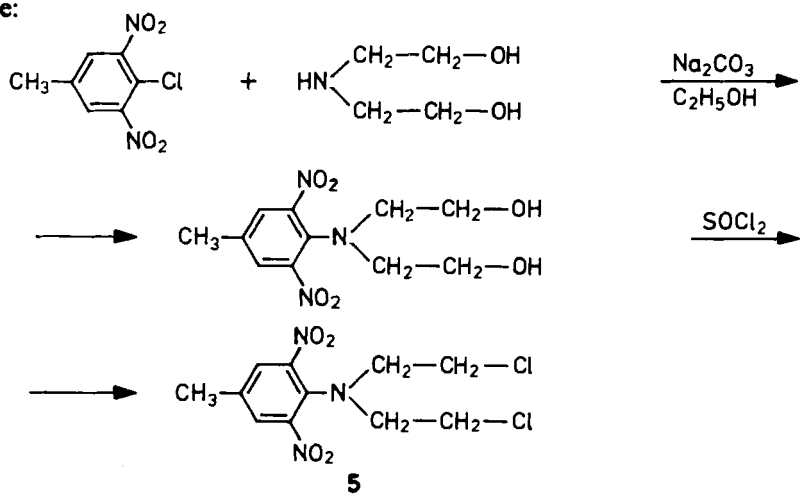
Ashton and Kukas (1974) investigated the phytotoxicity of ten dinitroaniline herbicides to several crops and found butralin to be the least toxic. The decreasing order of phytotoxicity is: oryzalin > dinitramine > nitralin > fluchloralin > trifluralin > profluralin > chlornidin > benfluralin > isopropalin > butralin. Oryzalin was found to be 33 times as toxic as butralin.

Butralin is moderately toxic to mammals, the acute oral LD_{50} of the active substance for rats being 2500 mg/kg. The LC_{50} for fish is 3.4–4.2 ppm.

The herbicidal properties and application of benfluralin (benefin, **2**) are analogous to those of trifluralin, which was developed earlier. It is a preplanting incorporated herbicide used at a rate of 1.0–1.35 kg active ingredient/ha for selective weed control in lettuce and tobacco and alfalfa and other forage crops. It is effective for the control of grass weeds in turf. Its action lasts for 4–5 months; it is microbially degraded in the soil (Probst and Tepe, 1969; Golab *et al.* 1970).

Benfluralin is virtually nontoxic to mammals, its acute oral LD_{50} for rats being 10000 mg/kg active ingredient. It is toxic to fish.

Chlornidin (AN 56477, **5**) is prepared according to the following reaction scheme, (US Patent 3517074) from 4-chloro-3,5-dinitrotoluene and diethanolamine:



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4-Chloro-3,5-dinitrotoluene is prepared from *p*-cresol, which is nitrated in acetic acid medium with nitric acid to give 2,5-dinitro-*p*-cresol. Dinitro-*p*-cresol is chlorinated with thionyl chloride or with phosphorus oxychloride to yield 4-chloro-3,5-dinitrotoluene.

Chlornidin is used as selective preemergence herbicide in cotton and soybean, for the control of *Sorghum halepense, Amaranthus* spp. and *Digitaria* spp. (Talbert, 1972).

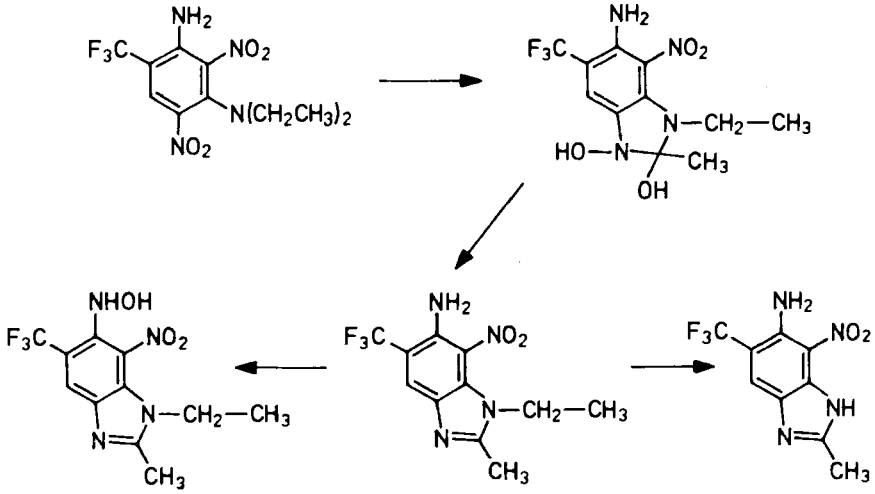
It is moderately toxic to mammals, its acute oral LD_{50} for rats being > 2200 mg/kg, its acute dermal LD_{50} for rabbits > 1640 mg/kg (Anonym, 1970).

Dinitramine (USB 3584, **6**) is made from 2,4-dichlorobenzotrifluoride by nitration, diethylamination and ammoniation (US Patent 3 671 252).

Dinitramine is used mainly for preemergence weed control in cotton and soybean at a rate of 0.4–0.8 kg active ingredient/ha, incorporated into the soil (Stone and Woestemeyer, 1972).

The herbicide taken up through the roots is only slightly translocated to the stem and leaves, the translocated substance consisting mainly of degradation products and metabolites. Its biological action is the inhibition of germination and root growth (Belles and Smith, 1973).

It is strongly adsorbed by soil colloids and is not leached into deeper soil layers. In the soil dinitramine is degraded in 90–120 days by microorganisms (Smith, 1973; Lanio *et al.*, 1973). At the soil surface and in water it is rapidly degraded by photolysis, with the reductive cyclisation of one of the nitro groups and the adjacent N-diethyl group (Newson and Woods, 1973):



Dinitramine is moderately toxic, its acute oral LD_{50}, for rats being 3000 mg/kg, its acute dermal LD_{50} for rabbits 2000 mg/kg. It is not toxic to wild fowl, but is toxic to fish, the LC_{50} for the latter being 3.0–11.0 ppm.

Ethalfluralin (EL 161, **8**) like the other dinitroanilines, is a preemergence incorporated herbicide (Skylakis *et al.* 1974). Applied at rates of 0.9–1.1 kg active ingredient/ha, it controls weeds during their whole growth season in soils containing less than 5% organic matter. It is used in cotton, where nightshade is a problem.

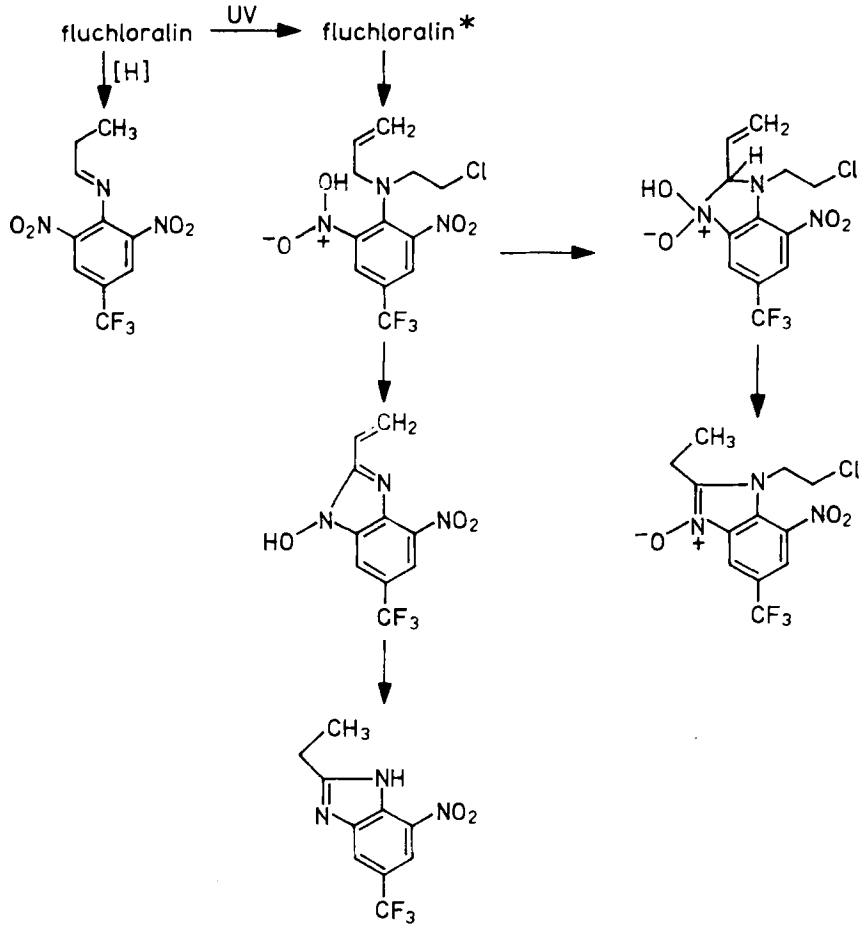
Fluchloralin (BASF 3920 H, 9) is a volatile, selective preplanting herbicide used incorporated in the soil at rates of 0.5–1.5 kg active ingredient (Anonym, 1973). It is very slightly soluble in water (0.001 ppm) and is strongly adsorbed by the soil. It is used for selective weed control in cotton, alfalfa and vegetables.

In the soil it is degraded fairly rapidly into very polar compounds, which are bound by the organic components of the soil. Degradation proceeds in 30 days under aerobic conditions.

The photodegradation of fluchloralin was investigated by Nilles and Zabik (1974) in solution, in thin layers and in soil.

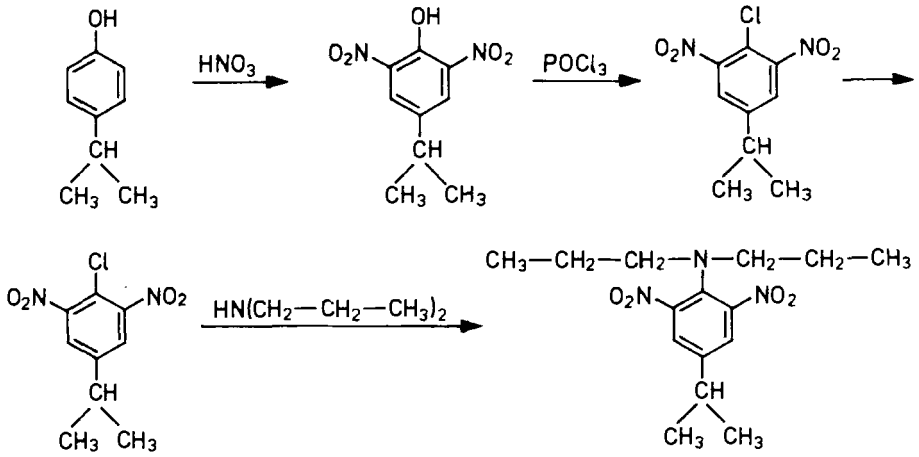
The main pathways of photolysis are photodealkylation, benzimidazole formation and quinoxaline formation. The decomposition of fluchloralin in 5 ppm solution shows zero-order kinetics, with a rate constant of $2.6 \cdot 10^{-7}$ mole/dm^3/min.

The authors propose for the formation mechanism of benzimidazole and its N-oxide, instead of the ionic mechanism assumed by Fielden *et al.* (1970), the following reaction mechanism:



It is moderately toxic, its acute oral LD_{50} for rats being 1500 mg active ingredient/kg. It is very toxic to fish, the LC_{50} (96-hour) being 0.012–0.016 ppm.

Isopropalin (EL 179, **10**) is a preemergence herbicide incorporated in the soil. Its industrial synthesis starts with cumene, which is nitrated with nitric acid to 2,4-dinitrocumene. 2,4-Dinitrocumene is then converted with phosporous oxychloride into 1-chloro-2,6-dinitro-4-isopropylbenzene, the latter giving isopropalin with di-*n*-propylamine (Soper, 1960a and 1960b).



10

In the way usual for dinitroanilines, isopropalin is used preemergence, incorporated on transplanted barley and dark tobacco (Shoop, 1969) and on direct-seeded peppers and tomatoes (Guse, 1969).

It is strongly adsorbed by the soil and presumably undergoes microbial degradation there.

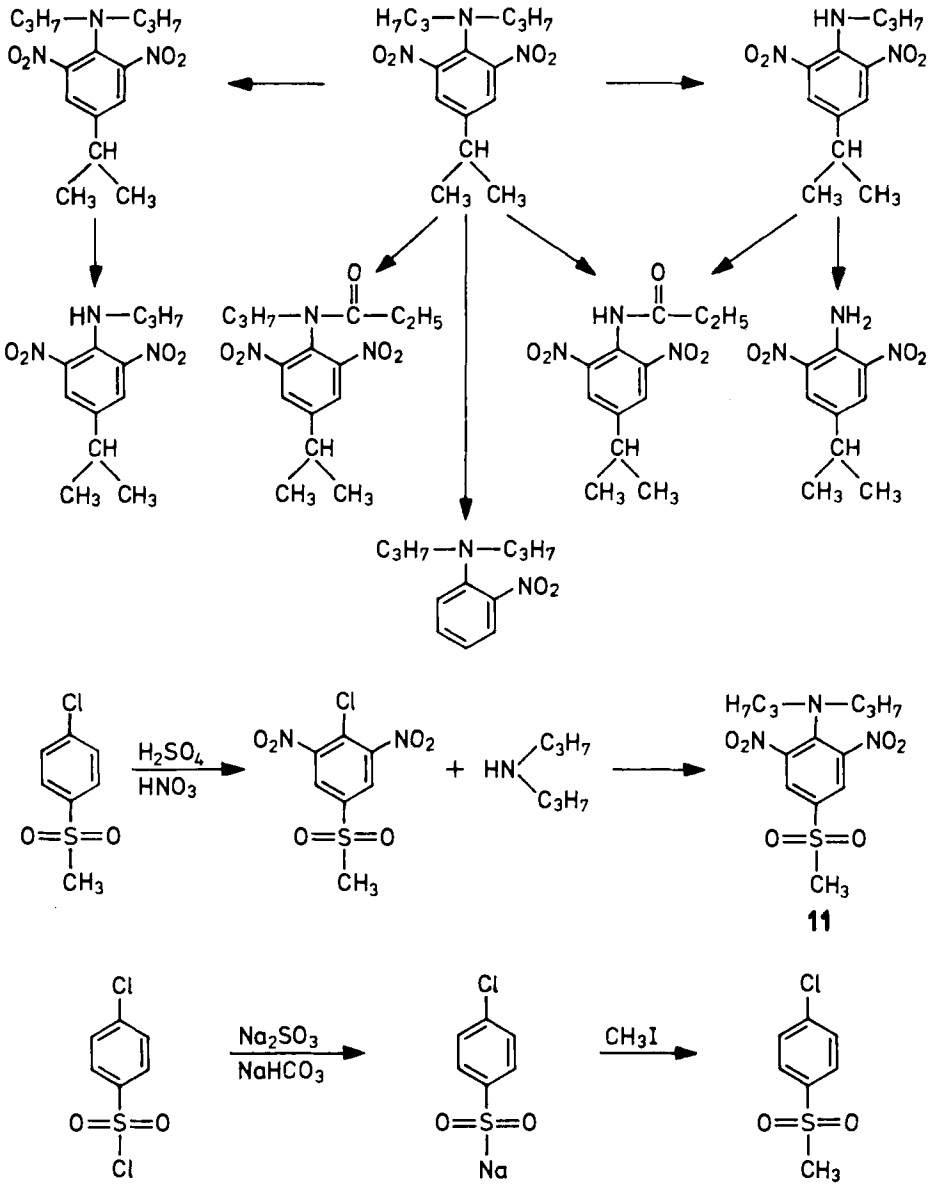
Golab and Althaus (1975) propose, on the basis of the degradation products detected in the soil, the following pathway of degradation:

In warm, humid soil it is degraded in one year.

Isopropalin is nontoxic to mammals and birds, the acute oral LD_{50} for rats being 5000 mg active ingredient/kg. It is toxic to fish (Worth and Arthur, 1970).

The compound nitralin (SD 11 831, **11**) was first described by Soloway and Zwahlen (1966). Its synthesis starts with 4-chlorophenyl methyl sulfone, which is nitrated with a fuming sulfuric acid–fuming nitric acid mixture to the dinitro compound. This then reacts with dipropylamine to give nitralin:

4-Chlorophenylmethyl sulfone can be prepared from 4-chlorobenzene sulfonyl chloride through the sulfonited salt with methyl iodide:



The herbicidal properties of nitralin were first reported by Schieferstein and Hughes (1966). The volatility of the compound is relatively low; thus it requires only shallow incorporation. It is remarkable that in spite of its very slight solubility in water (0.6 ppm), nitralin does not require moisture for the exertion of its action. Depending on the organic matter content of the soil, it is used at rates of 0.5–1.5 kg

active ingredient/ha for selective weed control in cotton, several ploughed land crops and orchards against mono- and dicotyledonous weeds. Applied at doubled rates, it is also suitable for the destruction of the rhizomes of *Sorghum halepense* (McWorther, 1974).

Nitralin inhibits the root growth of sensitive plants by disrupting primary cell wall formation during cell division (Gentner and Burk, 1968). Like trifluralin, it inhibits oxygen consumption and oxidative phosphorylation *in vitro* in the isolated mitochondria of maize, millet and soybean (Negi *et al.*, 1968).

It is strongly adsorbed by the soil and is not leached (Anderson *et al.*, 1968).

The causes of the selectivity of nitralin are not exactly known. Indubitably, one of the causes is biochemical. However, the biochemical tolerance of certain plants is often based on the fact that the roots of tolerant plants develop in the deeper soil layers, which are inaccessible to the herbicide (Cathie, 1969).

Nitralin is moderately toxic to mammals and wild-life, the acute oral LD_{50} for rats being > 2000 mg/kg. Compared to the other dinitroaniline herbicides its toxicity to fish is low, the 96-hour LC_{50} being 27–31 ppm. However, phytoplanktons are sensitive to nitralin, which, at a concentration of 1 ppm, reduces the population by 25% in 24 hours.

Oryzalin (EL 119, **12**) is a preemergence herbicide effective against annual mono- and dicotyledonous weeds in soybean, rice, cotton, tobacco and other crops. Unlike other dinitroanilines, it need not be incorporated into the soil because it is not volatile and is not decomposed by sunlight. It is applied at a rate of 0.75–2 kg active ingredient/ha, depending on the organic matter content of the soil. It can be used on soils of not more than 3% organic matter content. Its action lasts over one growing season. The action of oryzalin can be enhanced by irrigation, since with its poor water solubility it does not act in dry soil (2.5 ppm) (Gramlich, 1969; Fink, 1970; Snell *et al.*, 1975).

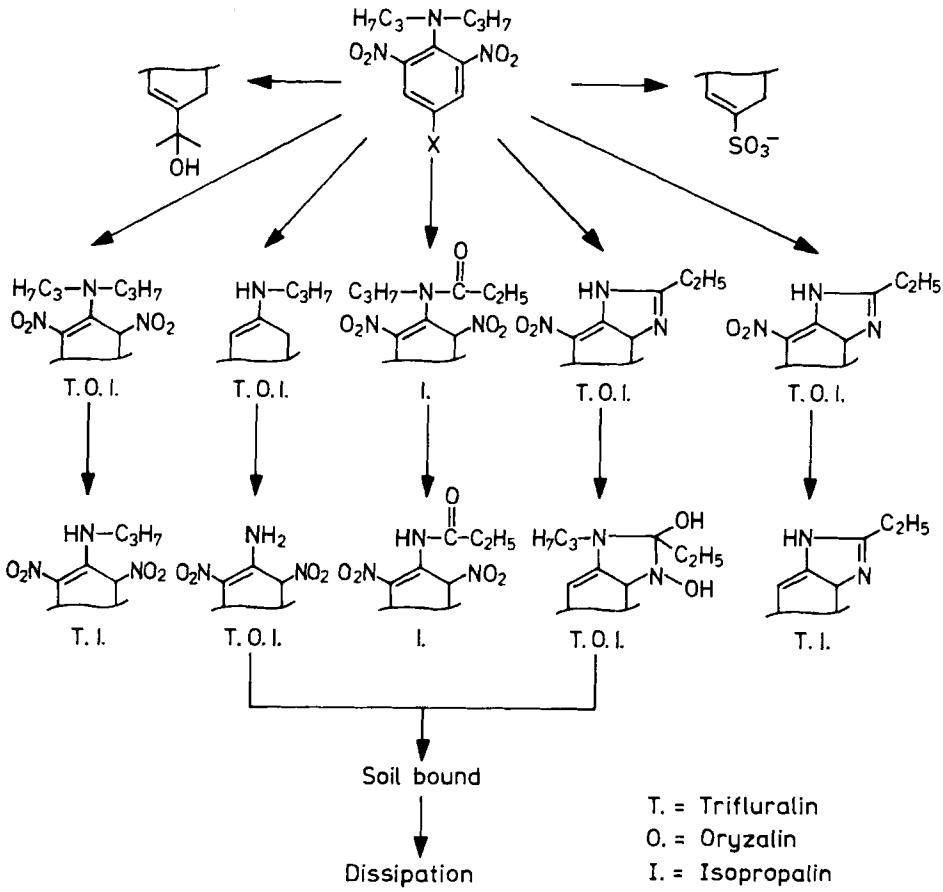
It acts on germinating weeds. Absorbed through the roots it is scarcely translocated. The tolerance of soybean is due to the fact that oryzalin is not absorbed by the plant; neither is it absorbed by wheat following soybean in crop rotation.

The hydrolytic and microbial degradation of oryzalin in the soil is relatively rapid (Golab and Amundsen, 1975; Golab *et al.*, 1975).

The rate of degradation of oryzalin is the same as that of trifluralin and considerably higher than that of isopropalin. The rate of degradation does not depend on the quantity of the herbicides applied.

Several mechanisms are involved in degradation, among them, dealkylation, reduction, oxidation, hydrolysis and combinations of these. Degradation products do not accumulate in the soil, and none of the degradation products are to be found in quantities greater than 4% of the total herbicide initially applied. Nonextractable, so-called "soil-bound" degradation products located in the fulvic acid and humic acid fractions of the soil are formed in substantial quantities.

Golab and Amundsen (1975) propose the following pathway for the aerobic soil degradation of oryzalin, trifluralin and isopropalin:



Crosby and Leitis (1973) found similar photodecomposition products in the decomposition of trifluralin in water.

Oryzalin is not toxic to mammals, its acute oral LD_{50} for rats being > 10 000 mg/kg, nor is it toxic to fish in the permissible prescribed amount in the water (0.7–1.5 kg/ha).

Penoxalin (AC 92 553, **13**) is one of the new dinitroaniline derivatives, the application of which alone or in combination with bladex or atrazine has been investigated in recent years in several crops. Its herbicidal properties were described by Sprankle (1974). This herbicide of the American Cyanamide, first designated by code number AC 92 553 and later by the common name penoxalin, is a preplanting and preemergence soil-acting herbicide for the control of grass weeds and broad-leaved weeds. It can also be used for postemergence treatment for the control of several broad-leaved weeds up the two-leaf stage.

A few weeds such as *Galium*, *Veronica* and *Viola* species, resistant to other herbicides, are particularly sensitive to penoxalin.

Its successful selective preemergence application at rates of 1.5–2. kg active ingredient/ ha has been reported in maize (Wilson and Nzewi, 1974; Roberts *et al.*, 1975), in spring wheat and potatoes (Jorgensen *et al.*, 1975), and in soybean (Ogg *et al.*, 1974; Ogg, 1975). Tolerant vegetables are carrots, parsley and parsnip, while papilionaceous peas and beans (runner bean and broad bean) show medium tolerance.

Penoxalin is slightly volatile and slightly sensitive to photodecomposition. Incorporated into the soil, one year after its application 10–20% of the herbicide is still present in unchanged form. In the soil, alkyl groups are degraded mainly by a nonbiological route first into alcohols, then into carboxylic acids. The same process proceeds in plants and in animal organisms, but at a considerably higher rate. Penoxalin is moderately toxic to mammals, its acute oral LD_{50} for rats being1050–1250 mg/kg, the dermal LD_{50} 5000 mg/kg. It is not toxic to birds but is toxic to fish (Anonym, 1975).

The herbicidal properties of profluralin (CGA 10 832, **14**) were first described by Taylor (1973). It is a selective, preplanting incorporated soil herbicide, applied at a rate of 0.75–1.5 kg active ingredient/ha. At this rate its action lasts for one year, and it is used mainly for the control of annual grass weeds and several broad-leaved weeds. It is well tolerated by cotton, sunflower and peanut. In soybean profluralin is, besides chlornidin, the dinitroaniline herbicide that can be most safely used in overdose amounts (Harvey, 1973), and it is very effective against *Setaria faberi*. It can also be used selectively in several vegetables.

In the soil and in plants its behaviour is similar to that of the other dinitroaniline herbicides. It affects both photosynthesis and respiration in sensitive plants. The degree of its selectivity is related to the lipid content of the plants and their seeds. Profluralin is degraded in tolerant plants to polar metabolites. In the soil it is degraded mainly by the microbial route. At the recommended rates its half-life is 80–120 days, depending on the type of soil.

Profluralin is practically nontoxic to mammals, its acute oral LD_{50} for rats (500 EC) being 2200 mg/kg. It is hazardous to fish (Ciba–Geigy, 1973).

Prosulfalin (EL 131, **15**) is a selective preemergence experimental herbicide effective against annual grass weeds and a few broad-leaved weeds on turf at application rates of 1.5–3.0 kg active ingredient/ha. On established turf it is used 3 weeks before the shooting of the weeds. Bermuda grass is sensitive to prosulfalin. Rain or irrigation is needed for the activation of the herbicide.

Its acute oral LD_{50} for rats is 2000 mg/kg (Thompson, 1975).

Trifluralin (**16**) was the first of the dinitroanilines to be introduced into agriculture (Alder *et al.*, 1960), and even today this compound is the most important member of the group.

During the eighteen years of its use an immense number of scientific publications have dealt with the physical, chemical, biological and application problems of trifluralin, but, in spite of this, even today we have no unequivocal picture of the biochemical mode of action of the compound or of the causes of its selective action.

Trifluralin is a preemergence herbicide which must be incorporated into the soil because of its volatility (vapour pressure at 29.5°C is $1.99 \cdot 10^{-4}$ mm Hg) and its sensitivity to ultraviolet radiation. At application rates of 0.5–1.0 kg active ingredient/ha it can be used selectively against annual grass weeds and several broad-leaved weed species in cotton, potatoes, sunflower, soybean, tomato, many vegetables and orchards. Applied in a double dose in two consecutive years, it kills the rhizomes of Johnson grass (Worther, 1974).

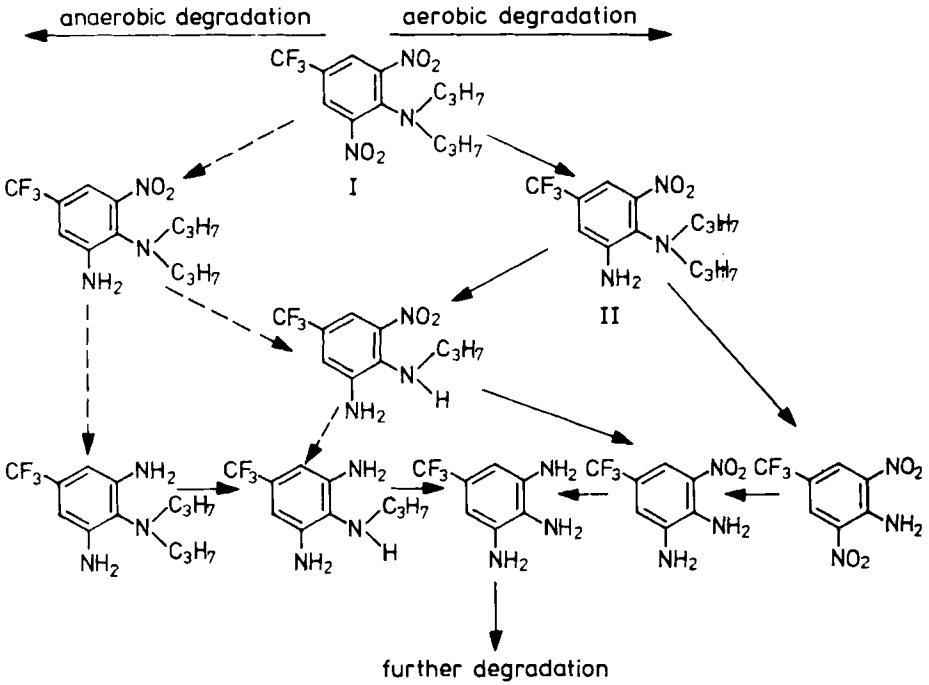
Trifluralin is absorbed by the roots and shoots of germinating plants (Parker, 1966) and, according to most investigations, is not or is scarcely translocated from the site of uptake (Strang and Rogers, 1971).

On the other hand, experiments of Kerchersid *et al.* (1969) on peanuts showed trifluralin absorbed through the roots to be translocated into all parts of the plant, most of it accumulating in the cotyledons.

Research results relevant to the molecular fate of trifluralin in the plant are also contradictory.

Probst *et al.* (1966) conclude from their experiments that trifluralin is not metabolised in soybean and cotton. The same authors, as well as Golab *et al.* (1967), observed in carrots dealkylation, reduction and the oxidation of the trifluoromethyl group into carboxyl, though the major part of trifluralin remained unchanged. Hamilton and Biswas (1967) found in sweet potato and peanut 87% degradation 72 hours after treatment with trifluralin, and in peanut 99% metabolisation.

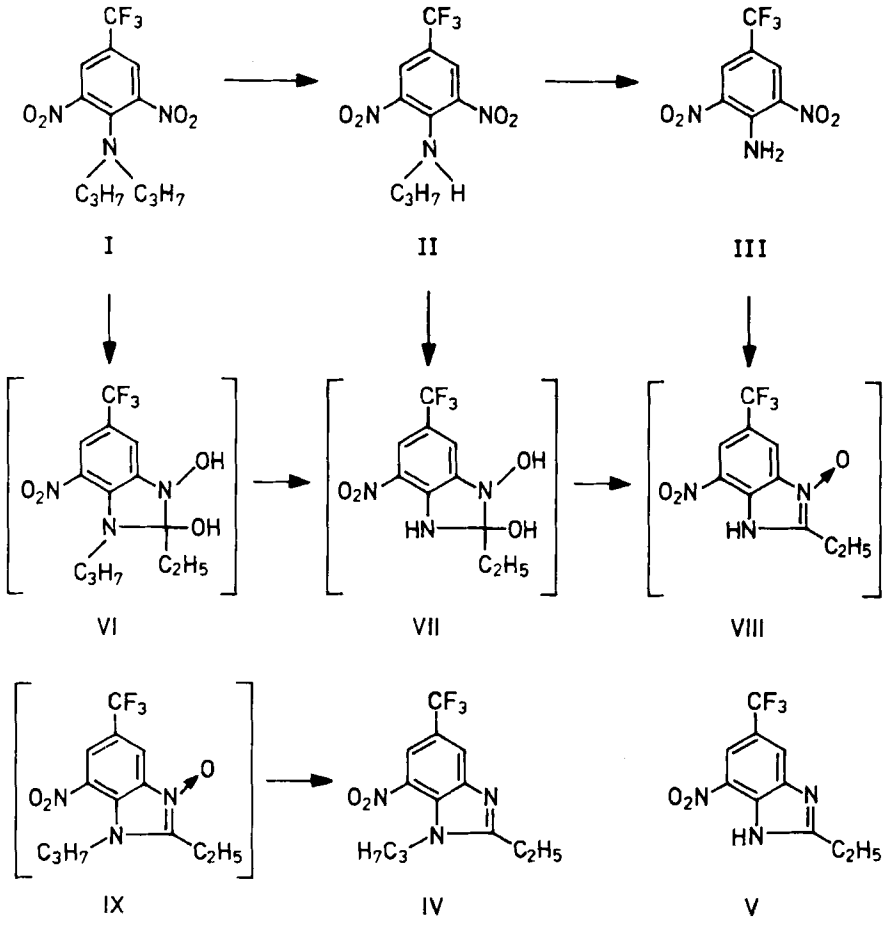
Probst *et al.* (1967) propose the following scheme for the microbial degradation of trifluralin in soil:



Among the degradation end-products of radioactive trifluralin, $^{14}CO_2$, indicating total degradation, has also been identified.

Several investigations have dealt with the photodecomposition of trifluralin (Soderquist *et al.*, 1972; Leitis and Crosby, 1974) under laboratory and field conditions.

Soderquist *et al.* (1972) propose the following vapour phase photolysis scheme:



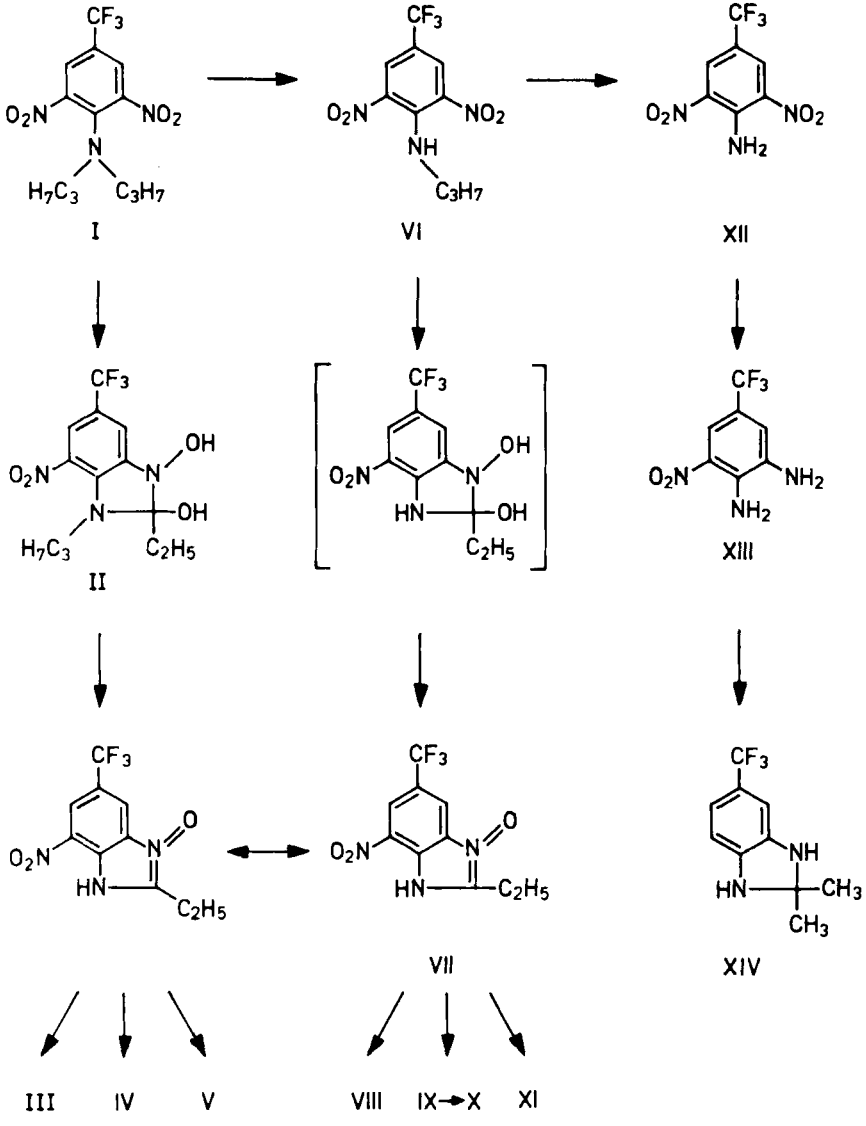
The nitrotoluidine derivatives, II and III and the benzimidazoles, IV and V have actually been detected.

According to the investigations of Leitis and Crosby (1974), trifluralin is rapidly decomposed in water by the action of sunlight. Under acid conditions, a small quantity of dealkylated intermediate and mainly 2-amino-6-nitro-α,α,α-trifluoro-*p*-

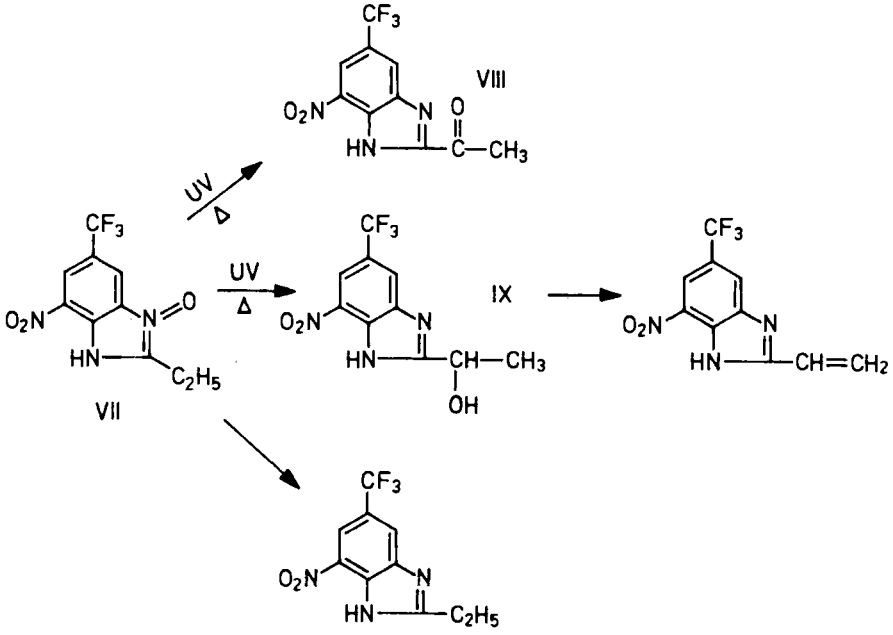
toluidine are formed in 24 hours. In alkaline aqueous medium, 80% of the product is 2-ethyl-7-nitro-5-trifluoromethylbenzimidazole after 24 hours.

As intermediate product the highly polar 2,3-dihydroxy-2-ethyl-7-nitro-5-trifluoromethylbenzimidazole-3-oxide is formed in a large quantity, but this is degraded by further irradiation.

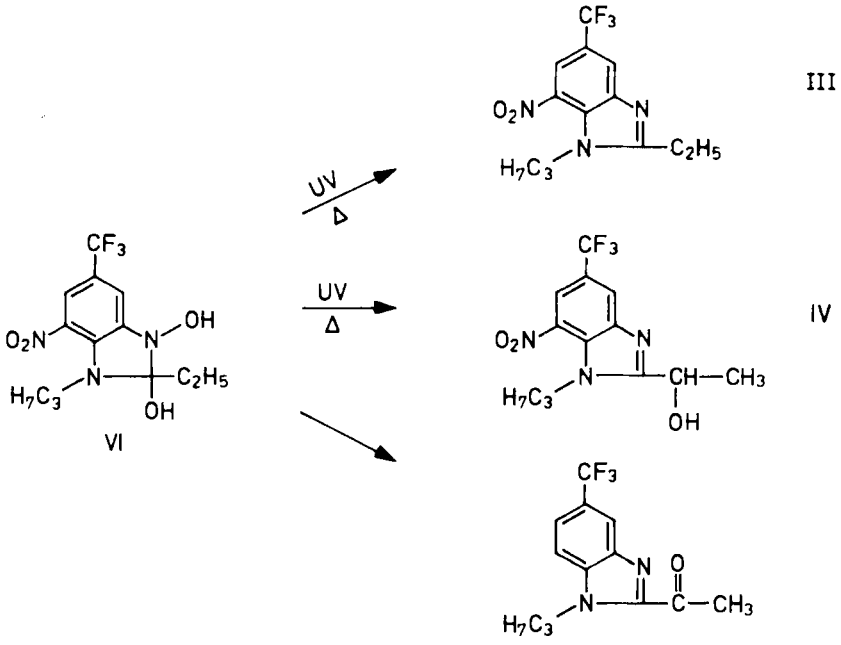
The authors propose the following pathway for the photodecomposition of trifluralin:



Thermal and photochemical decomposition of compound VII:



Thermal and photochemical decomposition of compound II:



Trifluralin is strongly adsorbed by the soil and is not leached by water into the deeper layers. The degree of adsorption depends on the clay content and organic matter content of the soil (Probst *et al.*, 1967).

The persistence of trifluralin in the soil is generally not much influenced by the type of soil or by microbial activity (Anderson *et al.*, 1968; Messerschmith *et al.*, 1971; Grover, 1974). Initial volatilisation loss depends on the method of incorporation and on the depth and time of incorporation (Oliver and Frans, 1968; Robinson and Fenster, 1968; Wiese and Smith, 1970; Smith and Wiese, 1973); the decomposition process in the soil is determined jointly by the moisture content and temperature of the soil.

At normal application rates trifluralin gives 4–6 months of weed control, so that after its application in spring other crops can be sown in the autumn. In cold soils a persistence of longer than 12 months must be taken into account (Menges and Hubbard, 1970).

The herbicidal action of trifluralin is evidently the result of the inhibition of several biochemical processes of the plant. Treatment with trifluralin changes the sugar content and the composition of oils and fats in plants, and the activity of several enzymes is considerably reduced (Dukes and Biswas, 1967; Schweizer, 1970; Ashton *et al.*, 1968; Penner and Meggitt, 1970; Penner, 1970). Treatment with trifluralin also inhibits cell formation and oxidative phosphorylation (Negi *et al.*, 1968) at a concentration of more than 10^{-4} mole/dm^3.

Mitosis inhibition is the most characteristic effect of trifluralin, and the key to its herbicidal action is presumably its interference with RNA and DNA synthesis which upsets the nucleic acid balance of the plant (Dukes and Biswas, 1967).

Trifluralin is not toxic to mammals or birds, its acute oral LD_{50} for rats being > 10 000 mg active ingredient/kg, for chicken more than 2000 mg/kg. The LD_{50} of Treflan EC (4 lb active ingredient/US gal) for rats is 3700 mg/kg, and toxicity is due completely to the solvent system.

Dermal application (2000 mg/kg) produces neither toxic symptoms nor irritation in rabbits.

Two-year feeding tests with rats at 2000 ppm, and with dogs at 400 ppm concentration, produced no symptoms (Worth and Anderson, 1965; Worth, 1970).

Trifluralin is strongly toxic to fish. The LC_{50} for rainbow trout is 0.1 ppm, for bluegill 1.0 ppm, and for black bullhead > 10 ppm (Lawrence, 1966).

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Wilder, M. G. R. (1969): French Pat. 1 253 176. Washington, Monsanto Chemical Co.
Wilson, R. R. and Nzewi, G. I. (1974): *Res. Rep. North Centr. Weed Control Conf.*, **31**, 128.
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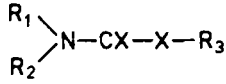
6.10 Carbamates

Carbamic acid derivatives are the group of pesticide compounds with the most varied biological action. They include compounds with insecticidal, fungicidal, and herbicidal action and plant-growth modifiers as well.

Biologically active carbamic acids can be characterised by the chemical formula:



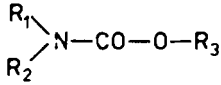
In the formula X can be oxygen or sulfur, R_1 and R_2 are generally organic radicals, but R_1 may be hydrogen. R_3 is an organic radical or metal.

The most important herbicides are carbamic acid esters (urethanes), in which R_3 is an aliphatic or aromatic organic radical.

Carbamates with insecticidal or fungicidal action are discussed in the appropriate chapters of the book.

On the basis of their chemical structure carbamic acid esters can be divided into N-alkylcarbamates and N-arylcarbamates.

N-alkylcarbamates and N-arylcarbamates have with respect to their structural formulae the common feature that in formula R_2=H. Their general formula is the following:



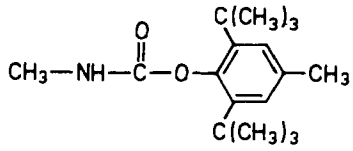
The basic component is a primary or secondary aliphatic, cycloaliphatic or aromatic amine, an aliphatic, aromatic or heterocyclic hydroxy compound, or an oxime of aliphatic, cycloaliphatic or heterocyclic ketones.

6.10.1 N-Alkylcarbamic acid esters

Of the N-alkylcarbamates only the aryl esters of N-alkylcarbamic acid possess herbicidal activity. The herbicidal activity of N-alkylcarbamic acid alkylesters and of the heterocyclic derivatives of N-alkylcarbamic acid is mentioned only in the patents literature, but these latter derivatives have not found agricultural application. Examples are the N-dimethylcarbamic acid enol esters proposed by Whetstone and Kudderna (1959) and the N-methylcarbamic acid pyridine esters proposed by Johnston (1964).

The growth-modifying and herbicidal properties of N-methylcarbamic acid phenylesters and N-methylcarbamic acid naphthylesters were recognised by Gysin and Knüsli (1953), but these compounds did not gain ground in agriculture.

Eleven years later Haubein (1964) applied for a patent for the N-methylcarbamate group of 2,4-6-trisubstituted phenols as selective herbicides. 2,6-Di-*t*-butyl-4-methylphenyl N-methylcarbamate (terbutol, terbucarb, **1**) was introduced in 1964 (Haubein and Hansen, 1965).



1

Terbutol is prepared from 2,6-di-*t*-butyl-4-methylphenol and methyl isocyanate in an apolar solvent in the presence of a tertiary amine as catalyst (Haubein, 1972).

The crystalline active substance is very slightly soluble in water (6–7 ppm), but readily soluble in polar organic solvents. It is weakly adsorbed by the soil, but because of its slight water-solubility it is not leached out.

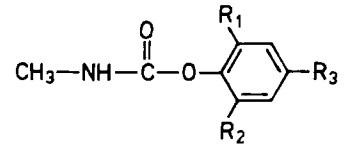
Terbutol is mainly a soil herbicide, but it is also effective postemergence for the control of grass weeds. It has a selective action in cotton, maize, tomato and soybean, and is recommended for the control of crab grass in established turf. It is particularly effective for the control of *Digitaria* spp.

According to the investigations of Moreland (1969) terbutol inhibits the growth of roots and rhizomes at the terminal meristems. Root growth of seedling grass is inhibited—leaves become deformed and do not grow. These symptoms indicate that terbutol, like other carbamates, is a mitosis poison.

It does not inhibit the Hill reaction at a concentration of $3 \cdot 10^{-3}$ mole/dm^3.

It is virtually nontoxic, the oral LD_{50} for rats being 24 600 mg/kg.

Based on the investigations of Haubein and Hansen (1965), Table 6.4 shows the effect of substituents in carbamates of type on biological activity.



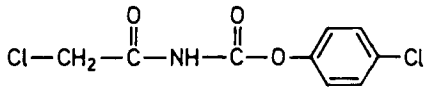
According to the foregoing, the methyl substituent on the phenyl radical can be replaced by a Cl, Br, or CH_3O group without loss in biological activity. A longer alkyl chain substitution, in position 4 reduces activity in proportion to the increase in carbon atom number. On substituting one of the tertiary butyl groups for a methyl group, however, the 4-isopropyl derivative is a compound with activity similar to that of terbutol. The derivative with a methallyl substituent in position 4 is also a very active herbicide. N,N-dimethylcarbamic acid esters are inactive.

Table 6.4
Effect of various substituents in carbamates on biological activity

R_1	R_2	R_3	Efficiency
$(CH_3)_3C$—	$(CH_3)C_3$—	CH_3—	+ + + +
$(CH_3)_3C$—	$(CH_3)_3C$—	Br—	+ + + +
$(CH_3)_3C$—	$(CH_3)_3C$—	Cl—	+ + + +
$(CH_3)_3C$—	$(CH_3)_3C$—	CH_3O—	+ + + +
$(CH_3)_3C$—	$(CH_3)_3C$—	C_2H_5—	+ + +
$(CH_3)_3C$—	$(CH_3)_3C$—	CH_3>CH— CH_3/	—
$(CH_3)_3C$—	$(CH_3)_3C$—	$(CH_3)_3C$—	—
$(CH_3)_3C$—	CH_3—	$(CH_3)_3C$—	—
$(CH_3)_3C$—	CH_3—	CH_3—	+
$(CH_3)_3C$—	CH_3—	CH_3H_7—	+ + +
$(CH_3)_3C$—	CH_3—	CH_3>CH— CH_3/	+ + + +
$(CH_3)_3C$—	CH_3—	CH_2=C(CH$_3$)—CH_2—	
CH_3—	CH_3—	CH_3—	—

+ + + + very good; + + + good; + + satisfactory; + moderately efficient; — inactive

Speziale and Smith (1962) recognised and patented the herbicidal action of N-chloroacetylcarbamic acid aryl esters. An example of this type is 4-chlorophenyl-N-chloroacetylcarbamic acid ester:

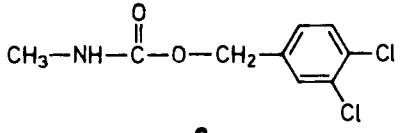


Baskakov (1963) described N-isobutylcarbamic acid 2-chlorophenyl ester as a selective herbicide for the control of *Avena fatua* in cereals.

Herrett and Berthold (1965) synthesised the benzylesters of N-alkylcarbamic acid and found several plant-growth modifiers and compounds with herbicidal action in the group.

According to their investigations only the benzylesters of N-methylcarbamic acid exhibit herbicidal activity, while the N,N-dimethylcarbamic acid esters are inactive.

The most effective derivative is 3,4-dichlorobenzyl N-methylcarbamate (dichlormate, **2**).



2

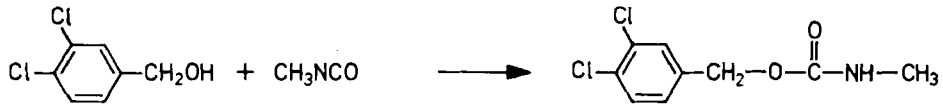
The technical substance is 80% 3,4-isomer and 20% 2,3-isomer.

According to Herrett and Berthold (1967a, b) it is prepared by the reaction of 3,4-dichlorobenzyl alcohol and methyl isocyanate in the presence of dibutyl-tin acetate as catalyst. The reaction is carried out at room temperature in an apolar solvent (Pathway I).

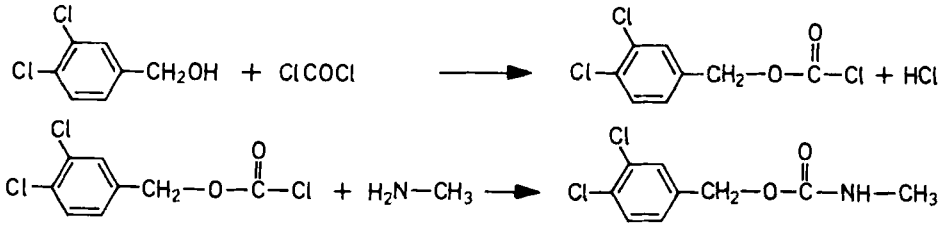
3,4-Dichlorobenzyl alcohol is prepared by the reduction of 3,4-dichlorobenzaldehyde with sodium borohydride.

Another proposed route of synthesis is the reaction of 3,4-dichlorobenzylaldehyde with phosgene, leading *via* chloroformate to the end-product (Pathway II).

Pathway I:



Pathway II:



Used pre- and postemergence, dichlormate kills young sensitive seedlings. After treatment, sensitive weeds show on sprouting extreme chlorotic symptoms and wither because of the inhibition of chlorophyll synthesis.

In the experiments of Burns *et al.* (1971) wheat treated *in vitro* with dichlormate accumulated chlorophyll only in dim light, from which they inferred that, as with aminotriazole and pyrichlor, the primary site of action of dichlormate may be the inhibition of carotenoid synthesis.

Applied preemergence, dichlormate selectively controls mono- and dicotyledonous weeds in cotton, soybean, peanut, potato, garlic and ornamental plants. It can be used postemergence in rice for the control of barnyard grass *(Echinochloa crus galli)* and other annual grass weeds and broad-leaved weeds.

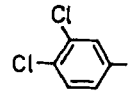
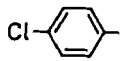
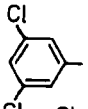
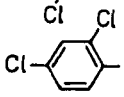
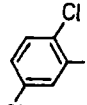
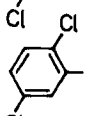
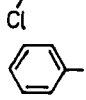
The acute oral LD_{50} for rats is 1870 mg/kg (male) and 2140 mg/kg (female).

Herrett and Berthold (1965) studied the relationships between the different substituents of benzyl-carbamates and herbicidal efficiency.

In the case of N-alkylcarbamic acid benzyl esters, too, those homologues in which only one methyl group was substituted on the N-atom were the most active. An alkyl substituent with longer chain reduced the herbicidal action.

Changing of the substituents of the phenyl group is accompanied by an interesting change in activity, as can be seen from Table 6.5.

Table 6.5
Effect of phenyl substitution on the biological activity of carbamates

	Efficiency			
	preemergence		postemergence	
	mono-	dicotyledons	mono-	dicotyledons
	++++	++++	++	+++
	++	+++	+	+++
	++	++	+	++
	+	+	+	++
	—	—	++	++++
	—	+	—	+
	—	—	—	+
	—	—	—	+
	—	—	—	+

Efficiency markings in the table are the same as in Table 6.4.

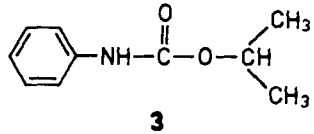
It can be seen that 3,4-dichloro substitution results in the highest herbicidal activity in both pre- and postemergence treatment. The 2,4-dichloro compound is efficient only in postemergence treatment and only for the control of dicotyledons.

With respect to halogen substituents this N-alkylcarbamate group is more similar to the N-aryl-N-alkylcarbamates than to the N-arylcarbamates discussed later.

6.10.2 N-Arylcarbamic acid esters

Friesen reported as early as 1929 on the herbicidal activity of an N-arylcarbamic acid ester, phenyl urethane, however, its action causing abnormal growth on wheat and oats was utilised for practical purposes only 15 years later.

Templeman and Sexton (1945, 1946) found that N-phenylcarbamates are toxic to monocotyledons but not dicotyledons. Of this group the first herbicide used in agriculture was isopropyl N-phenylcarbamate (IPC, propham, **3**).



3

Propham is a selective soil herbicide used preemergence for the control of grass weeds in beet, cabbage, peas and lettuce.

George *et al.* (1954) studied the effect of the alcohol component (R) of N-phenylcarbamic acid esters on herbicidal activity.

β-Chloroethylester has the strongest herbicidal action and the broadest spectrum, but owing to this very fact, its action is not selective. The effect of compounds **2** and **3** is similar.

The selectivity of γ-chloropropylester, chlorpropham (CIPC, **4**) and that of *sec*-butylester correspond to that of IPC.

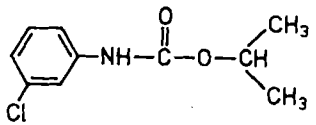
Herbicidal activity decreases with increasing carbon atom number of the alcohol radical. Monosubstitution of the alcohol radical with an alkyl radical in the α-position increases activity (IPC and **5**), but monosubstitution in the β-position (**12**) and disubstitution in the α-position (**16**) reduce activity.

Halogen substitution and the introduction of unsaturated groups (**1,2,3,4**) generally increase herbicidal action.

Even the most active representative of the N-phenylcarbamates contained in the table, propham, is inactive to millet (*Panicum* spp.) and to *Digitaria* spp.

Herbicidal activity can be increased by substitution on the phenyl group, as was shown by the investigations of De Rose (1951) and later of Shaw and Swanson (1953) and Stefanye and De Rose (1959).

Of the IPC analogues isopropyl N-(3-chlorophenyl)carbamate chlorpropham, (CIPC, **4**), is the most active compound.



4

Chlorpropham is effective for the control of several grass weeds (*Digitaria* spp., *Agropyron* spp., etc.) for which propham is ineffective.

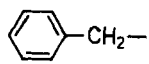
Unlike propham, it is absorbed also through the leaves and is selective also at higher temperatures and lower moisture content.

Chlorpropham is used in soybean, onion, beet, cotton and on perennial crops, usually in combination with other herbicides.

Chlorpropham is also used to inhibit the sprouting of potato tubers during storage.

In the case of N-phenylcarbamic acid esters containing a substituted phenyl group, changing the alcohol component produces similar changes in activity as with N-alkylcarbamic acid esters (see Table 6.6) (Shaw and Swanson, 1953).

Table 6.6
Effect of the alcohol component on herbicidal activity of N-phenylcarbamic acid esters

R	Efficiency	
	mono-	di-
	cotyledons	
$(CH_3)_2CH-$	+ + + +	+ +
$Cl-CH_2-CH_2-$	+ + + +	+ + + +
$CH_2=CH-CH_2-$	+ + + +	+ + +
$CH_2=CH-CH_2-CH_2-$	+ + + +	+ + +
$Cl-(CH_2)_3-$	+ + + +	+ +
$(CH_3)(C_2H_5)CH-$	+ + + +	+
C_2H_5-	+ + +	+ +
H_3C-	+ + +	+
$n\text{-}C_3H_7-$	+ + +	+
$n\text{-}C_4H_9-$	+ +	+ +
$C_5H_{11}-$	+ +	+ +
$C_6H_{13}-$	+ +	+ +
$(CH_3)_2CH-CH_2-$	+ +	—
	+ +	—
	+	—
$C_{12}H_{25}-$	—	—
$(CH_3)_3C-$	—	—

The effect of substitution on the phenyl radical is shown in Table 6.7 based on the investigations of Shaw and Swanson (1953) and Stefanye and De Rose (1959).

The table shows unambiguously that 3-chloro substitution gives the compounds of highest activity. 3-Fluoro, 3-bromo and 3-methyl substitutions, as well as 3,6-dichloro, 3-chloro-6-methyl and 3-chloro-6-methoxy substitutions result in an activity of the same order of magnitude.

3-Iodo, 4-fluoro, 2-chloro and 2-methoxy substitutions lead to compounds of lower activity. 4-Chloro, 3-trifluoromethyl, and 3,5-dichloro substituted de-

rivatives exhibit no herbicidal activity utilizable for practical purposes. Correlations obtained are shown in Table 6.7.

Propham and chlorpropham are absorbed mainly by the coleoptiles of emerging grass seedlings and only to a small degree by the roots. According to the investigations of Knake and Wax (1968) chlorpropham located in the root zone of

Table 6.7
The effect of substitution on the phenyl radical

R	Efficiency	R	Efficiency
3-Cl	+ + + +	2-CH_3—	—
3-Br	+ + + +	4-CH_3—	—
3-F	+ + + +	3-OH—	—
3-CH_3	+ + + +	3-NO_2—	—
3-J	+ + +	4-NO_2—	—
4-F	+ + +	5-Cl—,2-CH_3O—	+ + + +
2-Cl	+ + +	2-Cl—,5-Cl—	+ + + +
2-CH_3O	+ + +	5-Cl—,2-CH_3—	+ + + +
4-Br	+ +	3-Cl—,4-Cl—	+ +
4-J	+ +	2-Cl—,4-Cl—	+ +
4-Cl	+	3-Cl—,5-Cl—	+
3-CF_3	+		

the weeds has a poor efficiency. However, when the herbicide is located in the immediate vicinity of the soil surface, it is very well absorbed through the stem of the seedlings and kills them.

After uptake, propham, chlorpropham and their metabolites are rapidly transported by apoplastic distribution to all parts of the plant.

On foliar application propham and chlorpropham are not translocated basipetally in the plants (Still and Mansager, 1973).

Both herbicides are adsorbed extensively by the organic colloidal components of the soil, but the adsorptive bond is weak, particularly in the case of prophan, so leaching by soil moisture does take place. Adsorption on the clay minerals of the soil is insubstantial (Freed, 1951).

Propham and chlorpropham are not photodecomposed by ultraviolet light. The volatilisation of chlorpropham from dry soil is not great below 35°C. In the case of propham below 25°C there is no vapour loss from dry soil. Dissipation is strongly increased by increased temperature and soil moisture.

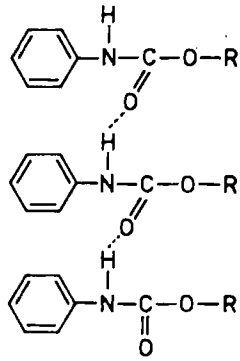
Observable phytotoxic actions of propham and chlorpropham on the intact plant are the inhibition of root and epicotyl growth and reduction of transpiration and respiration. Symptoms found at the cellular level are absence of spindle development; abnormal root cell growth; inhibition of messenger RNA, protein and amylase synthesis and inhibition of photosynthesis and oxidative phosphorylation (Ennis, 1948; Moreland and Hill, 1959).

Absorption and translocation of propham and chlorpropham do not differ considerably in resistant and in sensitive plants. Selectivity can be attributed to the

fact that in resistant plants chlorpropham is split into water-soluble metabolites, while this process does not take place in sensitive plants.

To elucidate relationships between structure and action, Moreland and Hill (1959) investigated on isolated chloroplasts the photolytic activity of a series of alkyl N-phenylcarbamates. The following order of activity was established; *sec*-butyl > *n*-butyl > *n*-propyl > isopropyl > *n*-amyl ester. On substituting the imino hydrogen for an ethyl, phenyl or benzyl radical, the inhibiting effect decreased. Similarly, on replacing carbamyl oxygen with sulfur, activity considerably decreased.

The authors propose the possible formation of a hydrogen bond between the carbonyl group of the carbamate molecule and the imino group of another carbamate molecule and increased action by the associating molecules.



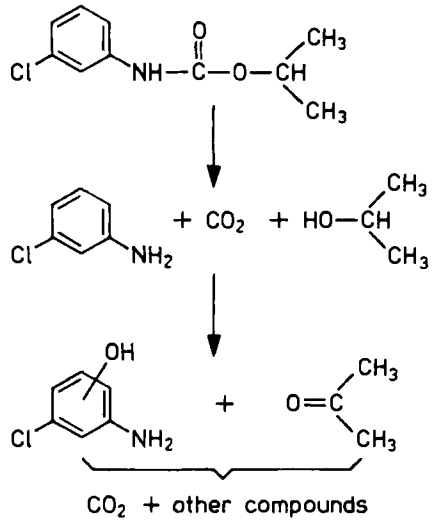
The biochemical action is produced by the formation of a hydrogen bond between the carbonyl group of the carbamate molecule and the imino group of the protein molecule.

The authors explain the inhibition of the Hill reaction by carbamates by the formation of a hydrogen bond by the imino hydrogen with some active electronegative component of the chloroplast. This assumption seems to be completely supported by the observation that compounds in which the imino hydrogen is substituted do not inhibit the Hill reaction. Chlorine substituted in the *ortho* position on the phenyl ring has a similar effect. Such derivatives are biologically inactive, because the chlorine substituent in the *ortho* position, forming an intramolecular hydrogen bond with the imino hydrogen of the molecule, forms a chelate, thus inhibiting the formation of a hydrogen bond with the electronegative group of another molecule.

Propham and chlorpropham are easily degraded by the microorganisms of the soil. Chlorpropham is more persistent in the soil than propham. During microbial degradation aniline is formed by enzymatic hydrolysis along with 3-chloroaniline, carbon dioxide and isopropyl alcohol. Subsequently, aniline is hydroxylated, the

ring is split and carbon dioxide, together with other unidentified compounds, is formed (Kaufmann, 1967).

The reaction scheme proposed by Kaufmann for the microbial degradation of chlorpropham is the following:



Depending on the rate of application and on soil and climatic conditions, the activity of the two herbicides lasts from three weeks to a few months (Burschel and Freed, 1959; Burschel, 1963; Sheets and Harris, 1965).

Pseudomonas striata, a *Flavobacterium* sp., an *Agrobacterium* sp. and an *Achromobacterium* sp. can live on propham and chlorpropham as their sole carbon source (Kaufmann and Kearney, 1965; Kaufmann and Blake, 1973).

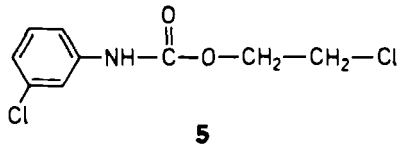
Propham and chlorpropham are rapidly metabolised in plants (Gard and Reynolds, 1957; Gard *et al.*, 1959; Baskakov and Zemskaya, 1959; Zemskaya and Rakitin, 1969; Schütte *et al.*, 1971).

During metabolism polar compounds and their conjugates are formed. For example Still and Mansager (1972, 1973) found that in soybean 2-hydroxypropham is formed, which is then conjugated as a glucoside. The same authors investigated the metabolism of (^{14}C)propham in alfalfa. Propham taken up through the roots could not be detected 7 days after the treatment either in the root or the stem; 73% of the radioactivity was to be found in the stem, 27% in the roots, mainly in the form of polar and insoluble residues. The polar metabolite was mainly the glucoside conjugate of 4-hydroxypropham, while a smaller part was 2-hydroxypropham. The metabolism of chlorpropham under the same conditions gave 2-hydroxychlorpropham and 4-hydroxychlorpropham.

The main difference between the metabolites of the two herbicides is that about three times as much of the propham metabolites is bound by the insoluble plant fractions as of the chlorpropham metabolites.

2- and 4-methyl, 3-hydroxy, and 3- and 4-nitro derivatives are completely inactive.

Of the derivatives of N-(3-chlorophenyl)carbamic acid, 2-chloroethyl-N-(3-chlorophenyl)carbamate (CEPC, **5**) was used for a time as an experimental herbicide (George *et al.*, 1954).



5

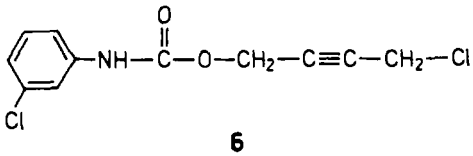
CEPC is a preemergence selective soil herbicide for the control of mono- and dicotyledonous weeds.

Later the selective herbicidal action of two alkynyl esters of N-(3-chlorophenyl)carbamic acid was discovered.

4-Chlorobut-2-yn-yl-N-(3-chlorophenyl)carbamate (barban, **6**) is a specific foliage herbicide.

Used postemergence in sugar beet and cereals it selectively kills monocotyledonous weeds. It is particularly effective for the control of wild oats (*Avena fatua*) (Brown, 1958; Hopkins *et al.*, 1958).

1-Methylprop-2-yn-yl-N-(3-chlorophenyl)carbamate (chlorbufam, BiPC, **7**) is a more selective and effective preemergence herbicide than chlorpropham.



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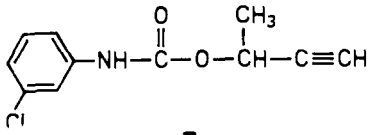

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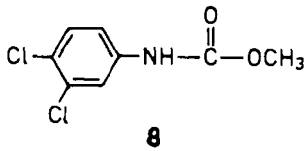


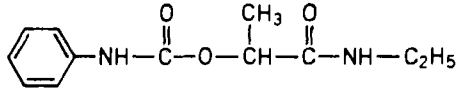
8

It can be used for the selective control of mono- and dicotyledonous weeds in onion, sugar beet, flower gardens and nurseries. It is used in combination with cycluron and pyramin (Fischer, 1960).

Table 6.6 showed a moderate herbicidal action for isopropyl N-(3,4-dichlorophenyl)carbamate. However, by changing the alcohol component, a compound has been developed which is less active than CIPC, but more selective (Hudgins, 1963). This compound is swep, methyl N-(3,4-dichlorophenyl)-carbamate (**8**).

Swep is a selective preemergence soil herbicide, effective mainly against monocotyledonous weeds in rice, soybean and peanut.

Desmoras *et al.* (1963) described the herbicidal properties of the D-isomer of N-ethyl 2-(phenylcarbamoyloxy)propionamide, prepared by the condensation of phenyl isocyanate with N-ethyl lactamide (carbetamide, **9**).



9

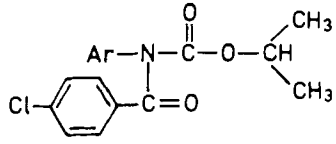
Carbetamide is a crystalline substance fairly soluble in water (3.5 g/l) and readily soluble in polar solvents. Owing to its relatively good water solubility, it does not require soil incorporation. It is a selective soil herbicide; absorbed through the roots it is effective mainly against sprouting grass weeds and some broad-leaved weeds. Its activity is higher in cold weather than in warm. It is used in alfalfa, red clover, crucifers, chicory, rape, sunflower and endive. Under normal soil conditions it is active for 2 months. It is nontoxic, its acute oral LD_{50} for rats being 11 000 mg/kg.

In three-month feeding experiments rats fed at 3200 ppm and dogs fed at 12 800 ppm were unaffected.

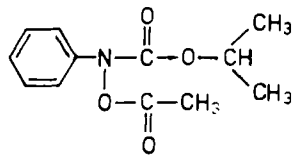
In the last ten years, patents have been obtained for several new N-arylcarbamate derivatives. However, up to the present they have not actually been introduced into agriculture.

N-acylated urethanes can be considered as N-arylcarbamates with retarded action.

Compounds of type are converted after hydrolysis into active phenylcarbamic acid esters.

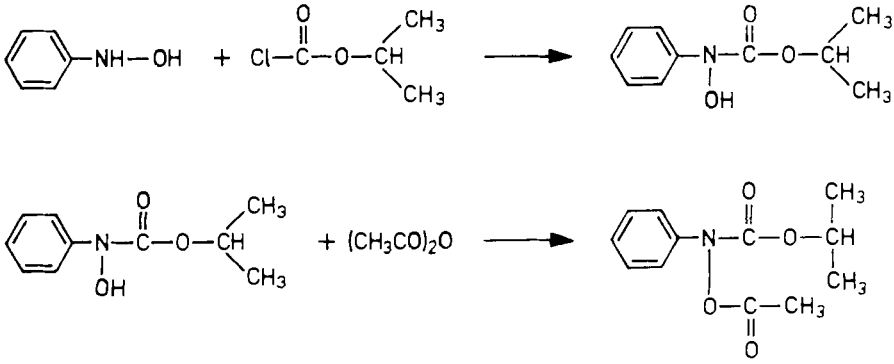


A similar compound is acylate, isopropyl N-acetoxy-N-phenylcarbamate (**10**), which was developed in the USSR (Melnikov, 1971).



10

Acylate is prepared from phenyl hydroxylamine according to the following reaction scheme (Melnikov, 1971):

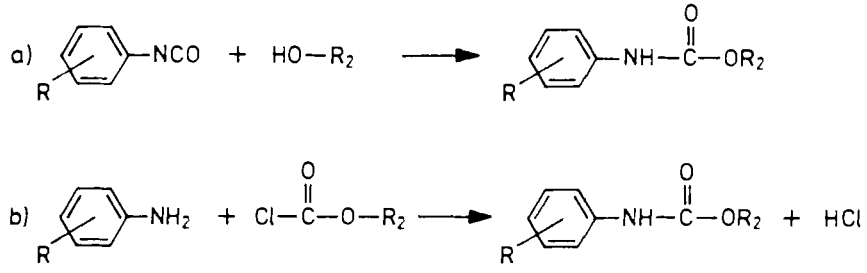


The crystalline substance, slightly soluble in water and readily soluble in organic solvents, is a soil herbicide. It is effective against annual grass weeds in sugar beet and legumes at a rate of 6–8 kg/ha. The LD_{50} for rats is 3000 mg/kg.

For the industrial manufacture of N-arylcarbamates one of the following two methods is generally used:

(a) reaction of aromatic isocyanates and hydroxy compounds,

(b) reaction of aromatic amines with chloroformic acid esters.



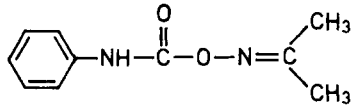
Both types of reaction are carried out in apolar organic solvents, such as benzene, toluene or chlorinated hydrocarbons. For the enhancement of the reaction of isocyanates with hydroxy compounds, metal salts or tertiary amines are used as catalyst. In the case of reaction *(b)* the hydrochloric acid liberated is bound with a tertiary amine (pyridine, triethylamine).

6.10.3 Oxime carbamates

Of the oxime carbamates, the herbicidal action of one derivative, O-(N-phenylcarbamoyl)propanon oxime (proximpham, **11**) meets practical requirements.

The herbicidal activity of this group was recognised by Kühle *et al.* (1957). Jumar and Grünzel (1966, 1968) continued the investigation of the relationships between

structure and biological activity by changing the phenol substituents and the oxime group. They established that arylcarbamoyl oximes generally exhibit substantial herbicidal activity.

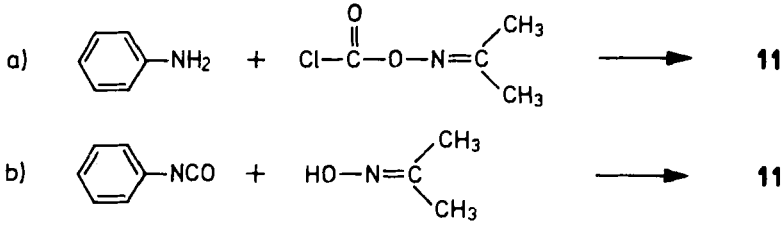


11

The biological activity of the phenylcarbamoylpropanone oxime group is substantially influenced by the substituent on the phenyl group. The 3-chlorophenyl derivative is the most efficient, but the 4-bromo compounds are also very efficient. Surprisingly, of the dihalogen derivatives, 2,6-substitution and not 3,4-substitution is the more efficient. Derivatives with three or more halogen substituents are of low activity. Compounds with methyl, methoxy and methylmercapto substituents are active, particularly if the groups are substituted in the *meta* position.

Enlargement of the oxime group reduces activity; however, halogen substitution in the dimethyloxime group results in a compound with good activity.

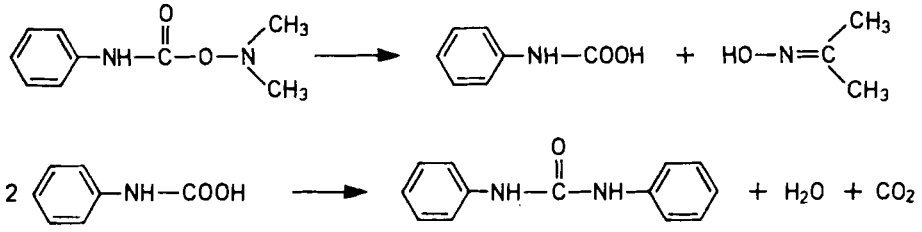
The two possible methods of proximpham synthesis are shown by the following reaction schemes:



Proximpham is a selective soil herbicide, but it is absorbed also through the leaves. It is used in beet, onion, vegetables and ornamental plant cultures for the control of *Compositae, Labiatae* and *Cruciferae* weeds, which are tolerant to the other phenylcarbamates.

It is rapidly decomposed in the soil by hydrolysis and microbial degradation. Its half-life is 7–10 days.

It is converted by hydrolysis in acid and neutral media into aniline and diphenylurea, and in alkaline media into diphenylurea and alkalicarbanylate (Spengler and Jumar, 1969).

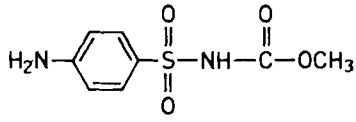


The acute oral LD_{50} of the active substance for rats is 1540 mg/kg. In 90-day feeding experiments the no-effect level was 100 ppm.

Proximpham taken up by beet is rapidly (12 days) metabolised. The main metabolite is the glucoside of the hydroxylated active substance.

6.10.4 Sulfonyl carbamates

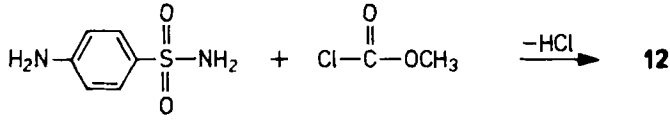
Cottrell and Heywood (1965) were the first to describe the herbicidal action of benzene sulfonyl carbamates. The most active member of this group is asulam, methyl 4-aminophenylsulfonyl carbamate **(12)**.



12

Asulam is readily soluble in polar solvents and slightly soluble in water (5 g/l). Its alkali and alkaline earth metal salts are readily soluble in water. The sulfonyl and ester groups enhance the acidity of the imino group so that it forms stable water-soluble salts with alkali hydrogen carbonates. Thus it is formulated as an aqueous solution of the sodium salt (400 g asulam per litre).

Asulam is prepared from 4-aminobenzenesulfonamide and methyl chloroformate in the presence of an acid-binding agent. The amino group must be protected before the reaction. Reaction scheme:



Asulam is used pre- and postemergence as a selective herbicide. In plants it is translocated mainly basipetally with the nutrient stream. Absorption through the leaves can be considerably increased with surfactants.

It is effective primarily against weed grasses. Of the annual and perennial weed grasses it controls also rhisomatic weed grasses, such as *Agropyron* and *Sorghum halepense*, reaching the resting buds and destroying them.

It is important in its action against deep-rooted grass weeds in the foat that asulam is only slightly adsorbed by the soil colloids and, because of its high water solubility is easily leached into the deeper layers of the soil.

Some of the problem dicotyledonous weeds, such as common lambsquarters *(Chenopodium album)*, pigweed *(Amaranthus retroflexus)* and Russian thistle *(Salsola kali)*, are resistant to asulam. On the other hand, as a postemergence herbicide asulam is effective against *Rumex* spp., *Avena fatua* and *Pteridium aquilinum*.

It can be used for selective and total weed control at a rate of 1–7 kg active ingredient/ha. Sugar beet is particularly tolerant to asulam.

At lower rates it is used as an experimental herbicide in several crops, in pastures, established alfalfa, banana plantations, orchards, forests, rubber plantations, flax and hemp.

Its action on plants develops slowly (in 2–4 weeks), the visible symptom being chlorosis.

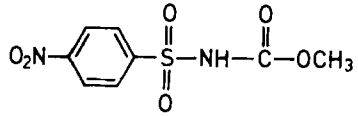
Under the climatic conditions of the temperate zone at average rates of application it remains active for 4–6 weeks in the soil.

Asulam is a moderately toxic herbicide. The acute oral LD_{50} of its potassium salt for rabbit, mouse and rat is 2000 mg/kg, and the LD_{50} for fowls is similar. It is not toxic to fish, LC_{50}-values being > 5000 mg/l.

Derivatives carrying an NH_2—, CH_3NH—, CH_3CONH—, CH_3— and/or NO_2 group in position 4 are biologically active. Derivatives halogenated in position 3 and unsubstituted in position 4 are inactive. On replacing the SO_2 group by an SO or S, herbicidal action is considerably reduced. The amino group in position 4 cannot be substituted, thus, for example, it cannot form part of an urea group.

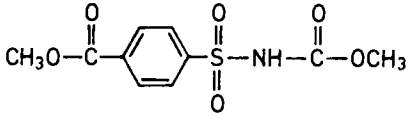
To attain good activity, the sulfamide group must contain a hydrogen.

The 4-nitro analogue of asulam is methyl (4-nitrophenylsulfonyl)carbamate (nisulam, MB 8882, **13**).



13

This compound has a rather similar herbicidal spectrum to that of asulam, the main difference being that it is better tolerated by dicotyledonous crops (alfalfa, peas, potatoes).



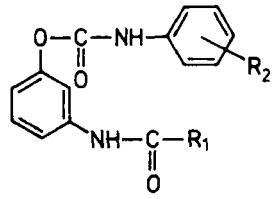
14

A further experimental herbicide belonging to this group is an N-acyl derivative, methyl {N-(4-methoxycarbamoyl)phenylsulfonyl}carbamate (carbasulam, MB 9555, **14**).

6.10.5 Carbamic acid esters with two carbamate groups or with an urea group

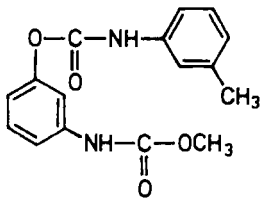
All of the carbamates discussed so far in this chapter have contained only one carbamate group. Doubling the functional group carrying the biological activity generally does not result in a doubling of biological efficiency. An exception to this rule is the group of biscarbamate compounds, developed by Arndt and Kötter (1967).

These novel biscarbamates are described by the following general formula:



where the R_1 group represents an alkoxy radical and R_2 a hydrogen, halogen or alkyl radical.

Two compounds of this group have been developed into commercial herbicides: first phenmedipham, methyl (3-*m*-tolylcarbamoyloxy-phenyl)carbamate (**15**), and two years later desmedipham, ethyl (3-phenylcarbamoyloxy-phenyl)carbamate (**16**) (Arndt and Boroschewski, 1969).



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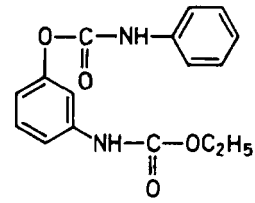
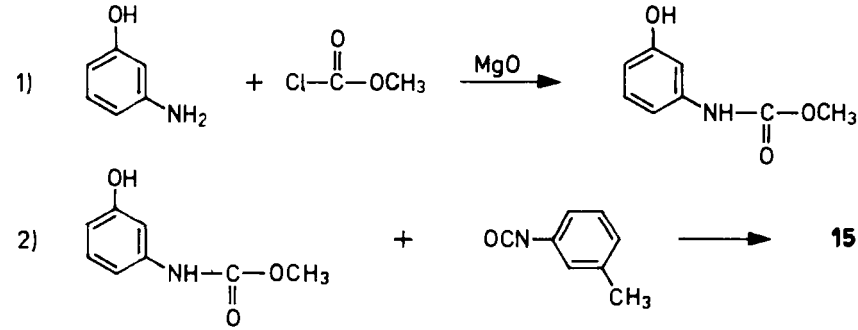


16

Phenmedipham is manufactured in two synthesis steps. First, *m*-aminophenol reacts with methyl chloroformate in the presence of MgO as acid binder. The 3-methoxycarbonylaminophenol obtained is then condensed with *m*-tolyl isocyanate to give phenmedipham. For the acceleration of the latter reaction a tertiary amine catalyst may be used.



The same reaction route is followed for the synthesis of desmedipham, except that ethyl chloroformate and phenyl isocyanate are used as coupling components to *m*-aminophenol.

Phenmedipham is a crystalline compound moderately soluble in water and organic solvents. It is formulated as an emulsifiable isophoronic solution of 157 g active ingredient/l concentration. It rapidly hydrolyses in alkaline aqueous solution. In buffer–methanol solution (95 : 5) its half-life at pH 4 is about 135 days, at pH 7 about 5 hours, and at pH 9 about 10 minutes (Schering, 1968).

Phenmedipham and desmedipham are selective postemergence herbicides effective in beet crops, particularly sugar beet, at rates of 1 kg active ingredient/ha against several weeds, particularly against dicotyledons, in the 2–4-leaf stage.

Resistant weeds are *Matricaria* spp., *Anthemis* spp., *Centaurea cyanus, Vicia hirsuta, Amaranthus retroflexus, Mercurialis annua, Galium aparinae, Polygonum aviculare, Convolvulus arvensis* and most of the monocotyledonous weeds.

Desmedipham has basically the same selectivity as phenmedipham but it also controls *Amaranthus retroflexus* and is thus used combined with phenmedipham (Schweizer, 1974).

Plants absorb both herbicides mainly through the leaves. Absorbed compounds are transported by the transpiration stream in the plant. Light and heat increase herbicidal action; however, when applied at temperatures above 25°C, they are not detrimental to the yield, sugar content, nitrogen content or soluble ash content of sugar beet (Schering, 1968, 1973).

Phenmedipham applied to the soil remains predominantly in the upper 5 cm of soil. On the basis of field experiments carried out on soils of several types, the half-life of the herbicide is 25–48 days, depending on the type of soil (Sellke and Kossmann, 1968).

End-products of degradation are 3-methylaniline, 3-aminophenol and 3-hydroxycarbanylic acid methyl ester (Kossmann, 1969, 1970).

The phenmedipham and desmedipham taken up by plants are metabolised to essentially the same end-products as those from microbial metabolism in the soil (Kossmann, 1971).

When applying phenmedipham at a normal rate (1 kg/ha) in sugar beet, less than 0.1 ppm residue, including 3-methylaniline, is found at harvest time.

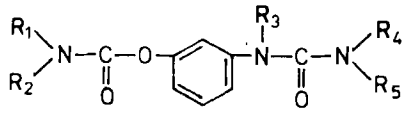
Phenmedipham and desmedipham are moderately toxic, their acute oral LD_{50} for rats being 8000 and 9600 mg/kg, respectively. The MTL (4-day value) for fish is 4–14 mg/l.

Sonowane and Knowles (1971) investigated the metabolism of phenmedipham in rats. 91.1% of (*m*-aminophenyl-^{14}C) phenmedipham administered orally was eliminated in 72 hours in the urine and 8% in the feces.

From the rat urine 42.2 to 68.5% of the ^{14}C could be extracted with ethyl acetate. Of the ^{14}C-labelled material in the extract 0.2–1.9% was the parent compound and 36.4–66.2% the methyl N-(3-hydroxyphenyl)carbamate. In the hydrolysate of the polar phase obtained after extraction with ethyl acetate, methyl N-(3-hydroxyphenyl)carbamate, 3-aminophenol, 3-hydroxy acetanilide and two or more unknown ^{14}C-labelled compounds could be detected.

Sonowane and Knowles (1971) obtained similar results in their investigation of the metabolism of desmedipham.

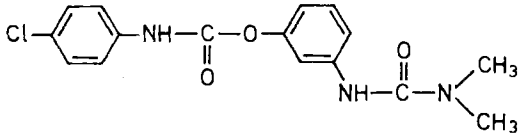
Hermann and Fischer (1967) described the selective herbicidal activity of a new group of compounds, the substituted phenylcarbamic acid ureidophenylesters. The new group of compounds has the following general formula:



In the formula R_1 represents a phenyl group with a halogen atom, or nitro, methoxy, carboxy, short-chain alkyl or short-chain halogenalkyl substituent, or a cycloaliphatic group containing 3–7 carbon atoms.

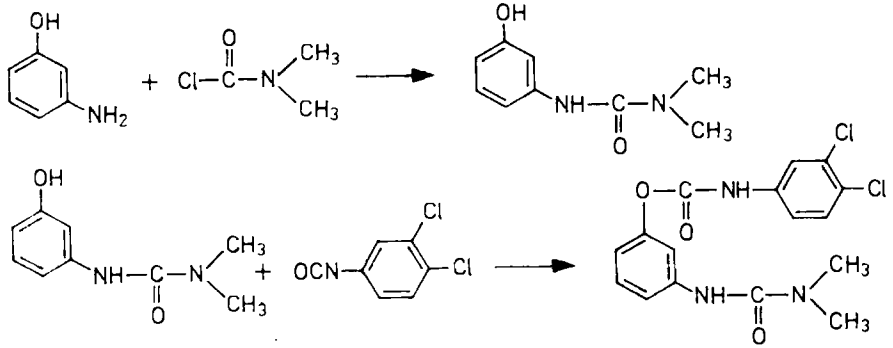
R_2, R_3, R_4 and R_5 represent a hydrogen atom, a methoxy group, a saturated or unsaturated aliphatic group or a phenyl group.

Compounds of the group are pre- and postemergence herbicides, effective against mono- and dicotyledonous annual weeds. They seem promising in monocotyledonous crops such as barley, wheat, maize and beet. Examples of efficient compounds are 3-(N,N-dimethylureido)phenyl N-(4-chlorophenyl)carbamate

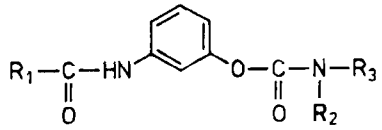


and 3-(N,N-dimethylureido)phenyl N-(3,4-dichlorophenyl)carbamate.

The synthesis scheme of the latter is as follows:



Arndt and Boroschewski (1975) described ureidocarbamic acid esters of the following general formula:



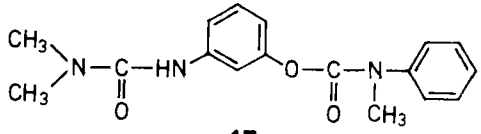
where R_1 represents a methoxy or a dimethylamino group, R_2 an alkyl group and R_3 a hydrogen or a phenyl group.

Of the group three derivatives have been developed as experimental herbicides:

3-(N,N-Dimethylureido)phenyl (N-methyl-N-phenyl)carbamate (SN 40624, **17**) is a selective postemergence herbicide in cereals. At rates of 1–2 kg active ingredient/ha it is effective against *Alopecurus, Apera, Lamium, Matricaria, Stellaria* and *Veronica* species and annual grasses in the cotyledon first-leaf stage.

It can be used preemergence in peanut, beans, soybean, orchards and forest. Its half-life in the soil is 20–30 days.

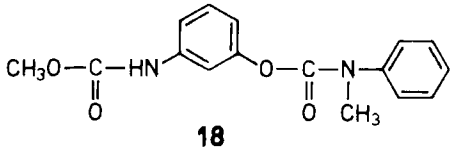
It inhibits the Hill reaction: P_1 value = 6.6.



17

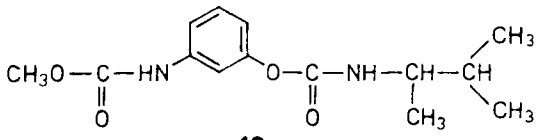
3-(Methoxycarbonylamino)phenyl (N-methyl-N-phenyl)carbamate (SN 40454, **18**) is a broad-spectrum pre- and postemergence herbicide effective primarily against broad-leaved weeds. Used preemergence at a rate of 2–4 kg active ingredient/ha, it is selective in peanut, cotton and soybean. In postemergence application at a rate of 1.5 active ingredient/ha it is effective for directed spray treatment in cotton and soybean.

SN 40454 inhibits the Hill reaction: P_1-value = 6.6.



18

3-(Methoxycarbonylamino)phenyl N-(3-methylbut-2-yl)carbamate (SN 45311, **19**) is also a pre- and postemergence herbicide having essentially the same selectivity as SN 40454. Its P_1-value is 6.4.



19

6.10.6 Physiological and biochemical action of carbamates

The carbamate herbicides discussed in the foregoing differ considerably from one another, with respect to both the skeleton of the molecule and the substituent groups.

On the basis of these differences it is reasonable to expect differences in physiological and biological action. Indeed, the members of the group show a wide variability in the mode of uptake (root, stem, leaf), the measure and rate of absorption and translocation, and their distribution and metabolism within the plant. All of these differences indicate that in spite of their chemical relationship, the biological mode of action of the individual active substances is different, as well as the detoxication mechanism of the herbicides in the plants of different sensitivity, the latter phenomenon being responsible for their selectivity.

Almost all of the carbamate herbicides inhibit photosynthesis, as has been shown by the investigations of Moreland and Hill (1959). Asulam and terbutol do not inhibit photosynthetic electron transport *in vitro*, while the other carbamates do only in high concentrations not occurring *in vivo*. The conclusion of Corbett (1974), that the inhibition of photosynthesis is only a side-effect of these compounds, therefore seems justified.

The general and primary action of carbamate herbicides is their inhibiting effect on mitosis, as has been shown by several workers in hundreds of experiments. Of the biochemical reactions of plant cells, carbamate herbicides inhibit oxidative phosphorylation and the synthesis of ATP, RNA and protein. As a result of these processes abnormal cells with anomalous nucleotides are formed in sensitive plants, which finally leads to the destruction of the plant.

On the basis of numerous experiments, the selective action of carbamate herbicides can be attributed primarily to the fact that compounds taken up are rapidly metabolised by tolerant plants into harmless derivatives, while in sensitive plants their metabolism is slower, so that the plants are permanently injured by the unmetabolised herbicides.

Carbamate herbicides are rapidly degraded in the soil and in plants. The primary pathway of metabolic degradation is hydrolysis, during which carboxylic acid and amine are formed generally through a water-soluble adduct (Herrett, 1969).

From the point of view of environmental pollution and crop rotation, carbamate herbicides can be considered nonhazardous substances at normal application rates.

Their tolerated residue in crops is 0.05–0.2 ppm.

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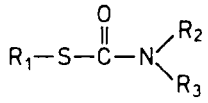
6.11 Thiocarbamates

The inhibiting effect on grass growth of propham, the first active representative of the chemically related carbamate compounds was recognised as early as 1941, but the herbicidal action of the thiocarbamate group was discovered much later.

The first thiocarbamate herbicide was described by Hannah (1959); further development of this group of compounds followed, in the course of which several selective herbicides were introduced.

This group of herbicides is characterised by the general formula:

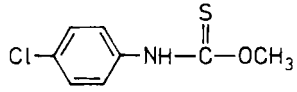


In the general formula, the substituent groups are as follows for the commercially available herbicides:

R_1 is an alkyl, dichloro- or trichloroalkyl, or a 4-chlorobenzyl group;

R_2 and R_3 are the same or different alkyl, methylcyclohexyl or azepine groups.

The isomers of these thiol esters are the thione carbamates. So far the only example worth mentioning is 3,4-dichlorothiocarbanylic acid O-methylester (**1**), the postemergence foliage herbicide of the Monsanto, code number CP 43 797.

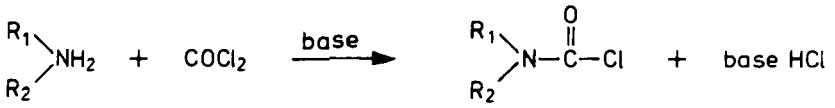


1

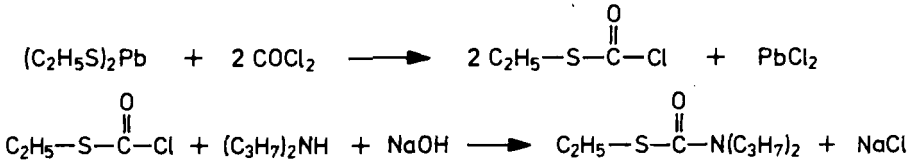
Thiocarbamate herbicides can be prepared by the following reaction routes:

(1) Reaction of metal mercaptide with dialkylcarbamoyl chloride in anhydrous, nonreactive solvent (Tilles and Antognini, 1956):

The metal mercaptide can be prepared by the reaction of alkylmercaptan with sodium metal in an organic solvent (e. g. xylene). Carbamoyl chloride is prepared by the reaction of the amine with phosgene in the presence of an acid binder (e.g. *t*-amine) according to the following scheme:

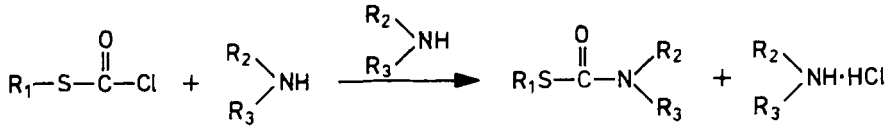


(2) According to Riemschneider and Lorenz (1953) the respective chloroformic acid thiolester is prepared in the first step from metal mercaptide and phosgene; this then reacts with the respective amine in the presence of alkali. The following example reaction scheme shows this method for S-ethyl N,N-dipropyl-thiocarbamate:

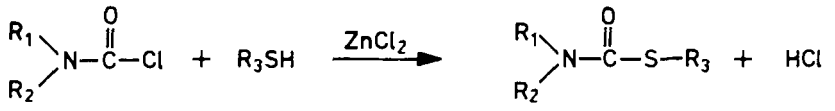


This method is less suitable for industrial use.

(3) The reaction of chlorothiolformates with amines can be used on an industrial scale for the preparation of thiol carbamates. The reaction is carried out in a solvent, and the excess of amine binds the acid (Tilles and Antognini, 1965). The yield varies between 79 and 96%.



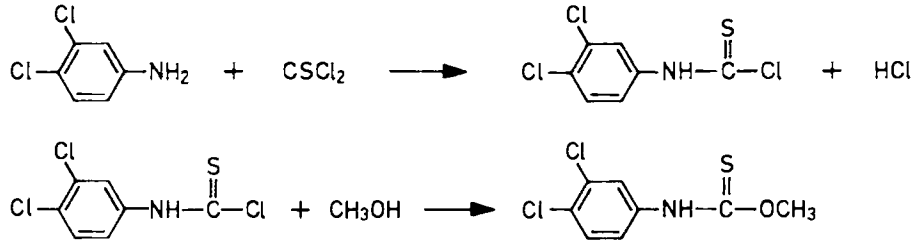
(4) According to the process of Campbell and Klingmann (1961) thiolcarbamic acid esters can be prepared with a good yield (90%) by the reaction of carbamoyl chlorides with alkyl mercaptans in solvent-free medium, in the presence of anhydrous zinc chloride as catalyst. The reaction is the following:



The reaction can be carried out at temperatures of 20–160°C. Mercaptan is used in excess; at the end of the reaction it is distilled from the system and recovered.

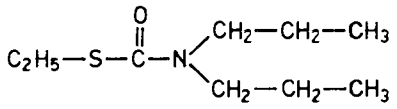
Carbamic acid thionesters can be prepared by the reaction of amines, thiophosgene and alcohols. CP-43 797 (**1**), for example, can be synthesised by the

esterification with methanol of 3,4-dichlorothiocarbamoyl chloride, prepared from 3,4-dichloroaniline and thiophosgene.



1

Of the dialkyl thiocarbamate group of herbicides first EPTC, S-ethyl N,N-dipropylthiocarbamate (**2**), was developed by the research workers of the Stauffer Co. (Tilles and Antognini, 1956; Antognini, 1957).



2

EPTC (**2**) is a liquid with an aromatic odour, miscible with organic solvents. Its solubility in water at 20°C is 365 mg/l, and it is relatively volatile, particularly in humid soils. This is why results obtained in its preemergence application varied widely until incorporation techniques were developed. It is also incorporated into the soil by irrigation immediately after application. This is made possible by the fact that, while strongly adsorbed by dry soil, it can be easily displaced by water.

EPTC is a selective preemergence herbicide effective against several mono- and dicotyledonous weeds in many crops, in orchards and in vineyards, particularly against grass weeds (*Agropyron* spp., *Sorghum halepense* and *Cyperus* spp.). It is effective against dicotyledonous weeds in the germinating state. Its usual rate of application is 3–6 kg active ingredient/ha, in the form of an emulsifiable concentrate or granules.

EPTC is easily absorbed by the plants through the roots, from where it is translocated into the stem and the leaves (Yamaguchi, 1961; Prendeville *et al.*, 1968). On foliar application EPTC is also symplastically translocated, though this is of little significance in view of its customary preemergence application.

EPTC treatment does not directly affect either the germination of seeds or the growth of roots.

On treatment broad-leaved weeds first develop cupped leaves, and subsequently necrotic symptoms appear at the edges of the leaves.

In mono- and dicotyledonous tolerant crop plants symptoms caused by EPTC are similar though milder, but tolerant plants outgrow the injury in the later stages of growth.

As with the other thiocarbamates, EPTC considerably inhibits wax deposition on the external leaf surface (Gentner, 1966; Still *et al.*, 1970; Wilkinson and Hardcastle, 1969).

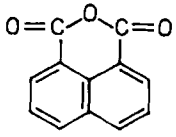
The excellent grass weed controlling action of EPTC could not be appropriately utilised in selective weed control because maize, one of the most important crops, was not satisfactorily tolerant to it in higher doses. Particularly in rainy spring weather preemergence EPTC application distorts the growth of maize — the more sensitive hybrids are even destroyed. In any case, the yield is reduced.

In the 1970s compounds were developed which eliminated these harmful effects on the growth of crop plants. They can be applied for the treatment of the seeds or admixed with EPTC in a quantity of 5–10%. These antidotes or safener substances presumably exert their action by stimulating the functioning of the EPTC-detoxicating enzyme of crop plants, of glutathione-S-transferase. This theory is supported by the observation that sensitive and tolerant plants absorb and translocate EPTC to essentially the same extent, but in tolerant plants the active substance is rapidly metabolised oxidatively to sulfoxide, then to biologically inactive sulfon derivatives, while in sensitive plants this process is slower and the plant meanwhile dies.

The antidotal EPTC preparation, called "Eradicane-GE®" (Stauffer), contains 6 lb EPTC and 0.5 lb of N,N-diallyl-2,2-dichloroacetamide (R-25 788) per gal.

The antidote "Protect", 1,8-naphthalic anhydride (**3**) is used for the seed treatment of maize and rice at a rate of 5 g/kg to counteract the harmful effects of EPTC, butylate (**5**), ethiolate (**6**) and vernolate (**7**) (Hoffmann, 1969; Wicks and Fenster, 1971; Parker and Dean, 1976).

Further systematic research at the Stauffer Chemical Company produced many new analogues of R-25 788. The most promising new compound developed so far is 3-dichloroacetyl-2,2-dimethyl oxazolidine (R-29 148, **4**) (Gray *et al.*, 1982).



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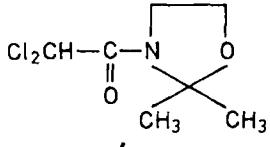


4

R-29 148 exhibits safener activity comparable to R-25 788 when tank-mixed with thiocarbamates.

Several excellent summarising reports and a book have been published on the safeners (Blair *et al.*, 1976; Pallos *et al.*, 1978; Stephenson and Ezra, 1982; Parker, 1982).

The biochemical site of action of EPTC, as is the case with the other thiocarbamates, is not exactly known.

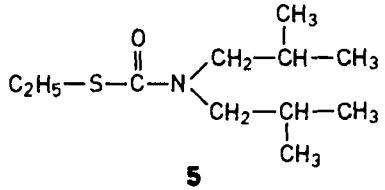
According to the investigations of Ashton (1963), Moreland *et al.* (1969), and Gruenhagen and Moreland (1971), it affects several biochemical processes of the plant. It inhibits photosynthesis only at high concentrations, and since it acts in a

growth stage in which photosynthesis is not yet important, it is unlikely that this would be essential from the point of view of biological action. EPTC at a concentration of $6 \cdot 10^{-4}$ mole/dm^3 reduced protein synthesis by 24% in soybean hypocotyl sections and inhibited RNA synthesis. With respect to total effect, EPTC, can be considered as a mitosis poison.

EPTC is rapidly degraded in the plants and soil. In higher plants it is degraded to CO_2, and its nitrogen is incorporated into the amino acids (Nalewaja *et al.*, 1964; Fang, 1969). In the soil it is degraded mainly by the microbial pathway; in loam soil of normal moisture content the half-life of EPTC is 1 week.

EPTC is moderately toxic, its acute oral LD_{50} for rats being 1652 mg/kg, its acute dermal LD_{50} for albino rabbits 10 000 mg/kg. The LC_{50} (7-day feeding) for bobwhite quail is 20 000 ppm. The MTL (median tolerance limit) (48 hour) on killifish is more than 10 mg/l, the 96-hour MTL on bluegill and sunfish 27 mg/l, and on rainbow trout 19 mg/l.

In the aliphatic thiocarbamate group the compound most closely related chemically to EPTC is butylate, S-ethyl di-isobutylthiocarbamate (**5**), the herbicidal properties of which have been described by Gray (1962). Butylate is a liquid, less volatile than EPTC by one order of magnitude, its solubility in water is also much lower.



5

Incorporated to a depth of 6–10 cm in the soil immediately prior to sowing, butylate, is used at an average rate of 4 kg/ha for the control of the grass and broad-leaved weeds of maize. The effective rate is about half of that of EPTC, but butylate also depresses yield in maize. To prevent this effect, as in the case of EPTC, an antidotal formulation has been put on the market. The product, with the trade name "Sutan Plus 6 EC" contains 6 lb of Sutan and 1/4 lb of R-25 788 (N,N-diallyl-2,2-dichloroacetamide), and is used for weed control in field maize, sweet corn and silage maize.

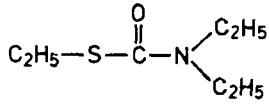
Applied at normal rates butylate is active for 4–6 weeks in the soil and is thus not harmful to the next crop. For a broader range of action it is also used in combination with atrazine.

In plants, butylate is rapidly metabolised to CO_2, di-isobutylamine, fatty acids, conjugates of amines and fatty acids, and natural plant components (amino acids, proteins).

The toxicity of butylate to mammals is lower than that of EPTC. The acute oral LD_{50} of the technical product for rats is 4000–4660 mg/kg.

The aliphatic thiocarbamate herbicide on a symmetric diamine base, ethiolate, S-ethyl N,N-diethylthiocarbamate (**6**), was developed in 1968 by the research workers of the Gulf Oil Co. (Anonym, 1974).

This selective preplanting herbicide with a range of action similar to that of the two preceding thiocarbamates is used combined with cyprazin, and incorporated in the soil for the control of grass and broad-leaved weeds and maize. Its rate of application is 2–3 kg ethiolate/ha. The trade name of the combination is Prefox®.

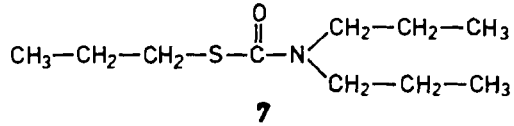


6

Its use may be limited by the fact that the combined preparation strongly irritates the skin, eyes and mucous membranes.

The acute oral LD_{50} of ethiolate for rats is 400 mg/kg, of Prefox® 542 mg/kg.

The thiolpropylester analogue of EPTC is vernolate, S-propyl dipropylthiocarbamate (**7**).



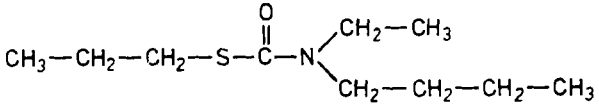
7

This herbicide developed simultaneously with EPTC (Tilles and Antognini, 1956) is, like the other alkylthiocarbamates, a preemergence herbicide effective, incorporated in the soil at an application rate of 1.5–3.0 kg active ingredient/ha for the control of sprouting broad-leaved and grass weeds.

Crops show a higher tolerance to vernolate than to EPTC. It is used in soybean, tobacco, sweet potatoes and peanut. Investigations of Bourke and Fang (1968) showed that the selective applicability of vernolate in soybean can be attributed to the fact that it is rapidly metabolised to inactive compounds in soybean and other tolerant dicotyledonous crops. Its half-life in moist clay soil is approximately 1.5 weeks.

It is moderately toxic, its acute oral LD_{50} for rats being 1780 mg/kg. Its toxicity to fish and wild fowl is similar to that of EPTC.

Pebulate (**8**), S-propyl butylethylthiocarbamate, is a thiocarbamic acid ester containing an asymmetric amine. Its herbicidal properties have been described by Burt (1959).



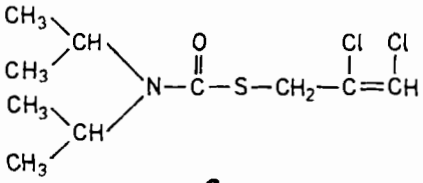
8

Pebulate is a preplanting herbicide for the control of grass and broad-leaved weeds. Like the other volatile thiocarbamates, it must be incorporated in the soil. It is tolerated by a wider range of crops than EPTC. It is used in sugar beet, tomatoes and transplanted tobacco at a rate of 4–6 kg active ingredient/ha. Its action lasts for

6–8 weeks (Batchelder and Patchett, 1960; Hughes and Freed, 1961; Antognini and Reed, 1960).

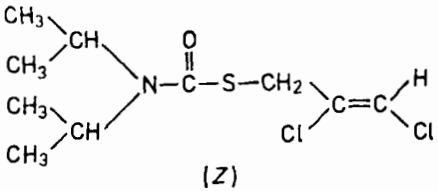
Its toxicity to mammals, fish and wild fowl is about the same as that of EPTC.

The halogen alkenyl thiocarbamate herbicide diallate, S-2,3-dichloroallyl di-isopropylthiocarbamate **(9)**, was first described by Hannah in 1959:

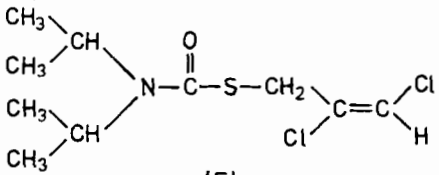


9

According to the investigations of Rummens (1975), diallate is a mixture of the *cis* (*Z*) and *trans* (*E*) isomers:



(*Z*)

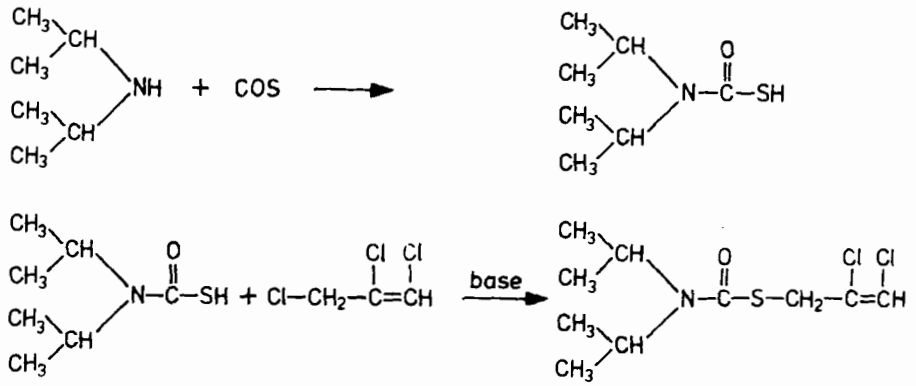


(*E*)

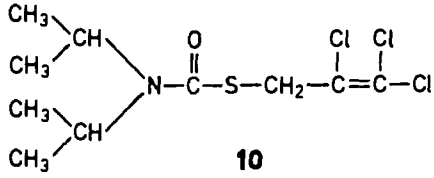
The biological activity of the two isomers is also different, the herbicidal action of the *trans* isomer on *Avena fatua* being 65% less than that of the *cis* isomer. A mixture containing 42% of *cis* and 58% of *trans* isomer is 2.6 times less effective than the pure *cis* isomer. The commercial active substance, an amber-coloured liquid, is a mixture of the *Z*- and *E*-isomers.

The synthesis of diallate and triallate differs from the general thiocarbamate synthesis routes described. Diallate is prepared from di-isopropylamine, carbonyl sulfide and 1,2,3-trichloropropene, and triallate from di-isopropylamine, carbonyl sulfide and 1,1,2,3-tetrachloroprop-1-ene in the presence of a base.

The synthesis scheme of diallate:



The herbicidal properties of triallate S-2,3,3-trichloroallyl di-isopropyl-thiocarbamate **(10)**, were described by Friesen in 1960. This compound differs by a single chlorine atom from diallate:



10

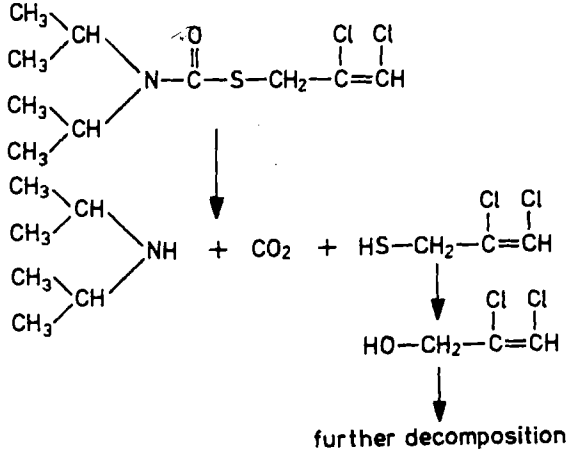
Both diallate and triallate active substances are liquids of medium vapour pressure; they must therefore be incorporated into the soil to a depth of about 5 cm to attain a satisfactory herbicidal effect. They are absorbed mainly through the developing coleoptile, and are used at a rate of 1.5–4 kg active ingredient/ha for the control of wild oat *(Avena fatua)* and black grass *(Alopecurus mysuroides)*. Crops tolerant to diallate are root crops, sugar beet, fodder beets, maize, leguminous plants and fruit trees; triallate is selective in cereals, wheat and barley (Monsanto, 1972).

All that is known of their mode of action is that in sensitive plants they inhibit cell growth and division in the early growth period (Fang, 1969; Banting, 1970).

Moreover, it is known from several investigations that thiocarbamate herbicides generally inhibit drastically the wax synthesis of plants. Still *et al.* (1970) found that diallate inhibits the synthesis of the primary alcohol components of waxes. However, it is unlikely that this action would cause the destruction of the plants, because sensitive plants are already destroyed before their emergence.

Diallate remains active in clay soils for 3–4 months, and in humic soils for 4–5 months, while the herbicidal action of triallate is longer by 1–2 months (Linden, 1964).

Diallate and triallate are completely metabolised in the plants in 1–2 weeks. In the soil degradation takes place by the microbial pathway. According to Kaufmann (1967), diallate is degraded in the soil by the following reaction scheme:

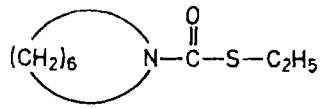


As can be seen from the proposed reaction scheme, 2,3-dichloroallyl alcohol is formed during decomposition, which is assumedly strongly phytotoxic, the strong phytotoxicity of unsubstituted alkyl alcohols being well known. The actual formation of this hypothetical intermediate is supported by the observation that the phytotoxic action of the herbicide incorporated into the soil increases after a time, then disappears gradually in a few weeks (Kaufmann, 1967).

The microflora of the soil are inhibited for a brief time by the two herbicides, but the normal population density is reestablished during the vegetation period (Fletcher, 1967). Diallate and triallate herbicides are not toxic to bees (Beran, 1970).

Diallate is toxic to mammals, triallate moderately toxic, the acute oral LD_{50} of diallate for rats being 395 mg/kg, that of triallate 1675–2165 mg/kg. The acute dermal LD_{50} for rabbits are 2000–2500 mg/kg and 2225–4050 mg/kg, respectively. Diallate may cause irritation to the skin and mucous membranes; triallate does not.

The R_2 and R_3 substituents in the general formula given at the beginning of the chapter may form a heterocyclic amine by ring closure with the nitrogen of the carbamate molecule. Compounds of this type have been described by Tilles and Curtis (1961) and by Curtis and Tilles (1961). Of this group of compounds one herbicide, molinate, S-ethyl N,N-hexamethylenethiocarbamate (in C. A. usage, S-ethyl hexahydro-1H-azepine-1-carbothioate) **(11)** has so far been introduced as a commercial product.



11

Molinate, prepared by the reaction of ethyl chlorothiolformate and hexamethyleneimine, is a clear liquid of relatively high vapour pressure. Of the thiocarbamates discussed, molinate is the most soluble in water, but it is also miscible with organic solvents.

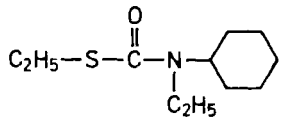
Molinate is a selective pre- and postemergence soil herbicide mainly for the control of grass weeds and particularly for *Echinocloa* spp. (Smith and Fox, 1965). It is applied either before planting to water-seeded or shallow soil-seeded rice, or post flood on other types of rice culture. Applied at its recommended rate of 2–4 kg active ingredient/ha, its action lasts over the whole crop period (Swain, 1974).

Owing to its high volatility, molinate must be immediately incorporated into the soil after its application. Plants rapidly absorb molinate through their roots, from where it is translocated to the leaves. In the leaves of rice it is rapidly metabolised to CO_2 and naturally occurring plant constituents, while in weeds this metabolism is slower. In the soil it is degraded by the microbial pathway. Its mode of action is unknown. At low rates it inhibits the development and growth of leaves. It presumably inhibits protein synthesis, as do the other thiocarbamates.

It is moderately toxic, its acute oral LD_{50} for male rats being 720 mg/kg. It is rapidly metabolised in rats, 50% to CO_2, while 25% is excreted in 3 days in the

urine, 7–20% in the feces. Its dermal toxicity is low, the LD_{50} for rabbits being more than 10 000 mg/kg. At the recommended rate it is not hazardous to wildlife or fish (Deuel, 1975).

The herbicidal action and application of cycloate, S-ethyl cyclohexylethylthiocarbamate **(12)**, known by the code number R-2063, were first described by Tilles and Antognini (1957a,b). The details of application were later described by Riggleman (1964).



12

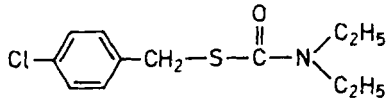
Cycloate is a clear liquid of substantial vapour pressure, poorly soluble in water, but miscible with organic solvents. Cycloate selectively controls germinating mono- and dicotyledonous weeds in sugar beet and in spinach. It is incorporated preplanting into the soil to a depth of 5–8 cm. Cycloate is easily absorbed through the roots by the plants and is translocated to the leaves. It is readily absorbed also through the leaves, but this is of no particular importance in preemergence application. It is more strongly adsorbed by soil colloids than the other thiocarbamate herbicides, but the adsorbed cycloate is desorbed by water and leached into deeper soil layers. It is leached to a smaller extent than pebulate or EPTC.

Cycloate is rapidly metabolised in the roots and leaves of sugar beet—3 days after treatment no unchanged compound can be detected. Metabolic degradation results in amines, CO_2, amino acids, sugars and other naturally occurring plant constituents. In sensitive plants this metabolism is slow, presumably it is the main reason for selectivity. Cycloate is rapidly degraded in the soil by the microbial pathway. At normal rates of application it is degraded in 3–6 weeks.

Rats excreted 81.8–83% of orally administered cycloate in the urine in 96 hours, and 12.3–17.8% in the feces, while 0.0–0.6% was exhaled (Antognini *et al.*, 1970).

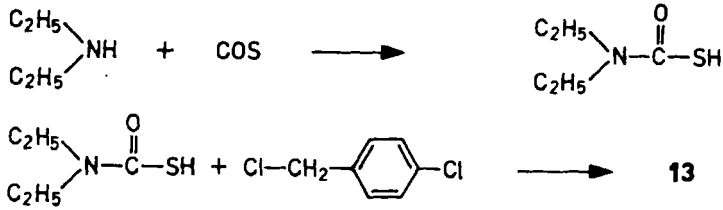
Cycloate is moderately toxic, the acute oral LD_{50} of the active substances for rats being 2000–3190 mg/kg. The dermal LD_{50} for rabbits is more than 4640 mg/kg. The ninety-day no-effect level in dogs is more than 240 mg/kg per day. In 7-day feeding tests the LC_{50} for bobwhite quail was more than 56 000 ppm. The ninety-six hour MTL value for rainbow trout is 4.5 mg/l.

The first herbicide containing within the thiocarbamate molecule an aromatic mercapto group was developed in 1965 in Japan. The selective herbicide benthiocarb, S-(4-chlorobenzyl) diethylthiocarbamate **(13)** was introduced under the code number B-3015.



13

Benthiocarb is prepared by the reaction of carbonyl sulfide with diethylamine and the condensation of the diethylthiocarbamic acid obtained with 4-chlorotoluene:



Benthiocarb is a selective herbicide in rice, but it seems promising for weed control in cotton, soybean, tomatoes, potatoes, peanut, beet and beans as well. It is effective against annual grass and broad-leaved weeds in the germinating stage; it is also effective in postemergence application against *Echinocloa* spp. up to the two-leaf stage.

For direct seeded rice benthiocarb is applied at a rate of 3–6 kg active ingredient/ha to the surface of the water 3–5 days before seeding or 5–10 days after seeding, for transplanted rice at the same rate 3–10 days after transplanting.

Herbicide combinations developed for paddy rice are "Saturn-S", containing benthiocarb and simetryne, and "Saturn-M", containing benthiocarb and 4-nitrophenyl 2,4-6-trichlorophenyl ether.

Benthiocarb inhibits the Hill reaction in isolated chloroplasts but does not inhibit photosynthesis either in intact rice or in intact barnyard grass (Ishii, 1975).

Eastin (1975) found that benthiocarb is rapidly absorbed by the rice plant through the roots and is translocated and uniformly distributed in the whole plant. Benthiocarb applied on the foliage is only slightly mobile. After treatment, the absorbed benthicarb is rapidly degraded, so that after 4 days only about 10% of the unchanged compound is to be detected, mainly in the roots. The nonextractable fraction increases with time, indicating that benthiocarb and/or its metabolites form complexes with natural plant constituents.

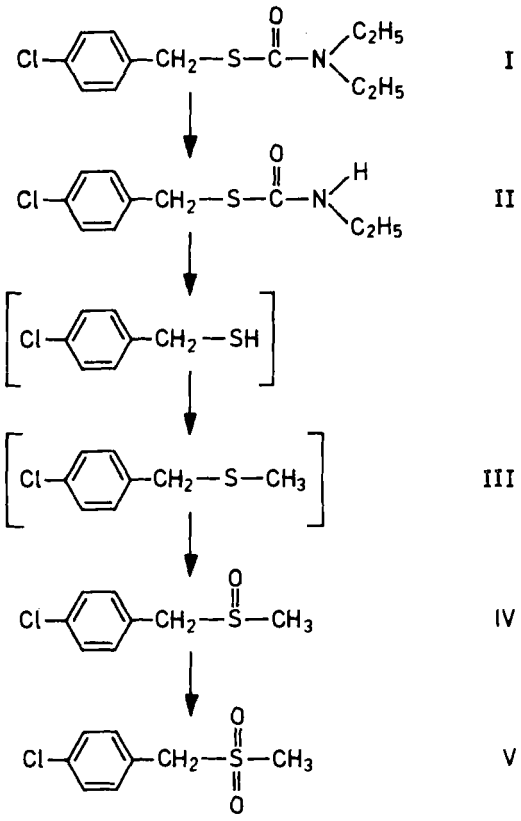
Benthiocarb remains active for 30–40 days in the soil (Gross and Bayer, 1974).

Ishikawa *et al.* (1976) investigated the persistence and degradation of radiolabelled benthiocarb in sandy clay loam soil. Twenty radioactive decomposition products were detected, the major products being desethyl benthiocarb, benthiocarb sulfoxide, 3-chlorobenzoic acid, 2-hydroxybenthiocarb and 4-chlorobenzylmethyl sulfon, while 4-chlorobenzylmethyl sulfoxide and 4-chlorobenzyl alcohol were detected in small amounts.

According to the investigations of Ishikawa *et al.* (1976) more than 80% of the benthiocarb administered orally to mice was excreted within 48 hours in the urine, 5% in the feces and less than 1% exhaled in the form of decomposition products. Benthiocarb is also rapidly degraded by liver homogenates.

Of the eight or more products metabolised with liver homogenates N-deethyl benthiocarb, bis(4-chlorobenzyl) mono- and disulfides and 4-chlorobenzoic acid could be identified.

According to the investigations of Ishii (1975) carp kept in a tank tolerated a benthiocarb concentration of 60 ppm for 24 hours and recovered from toxic symptoms when they were transferred to clean water. The benthiocarb content of water seeping from rice fields treated with benthiocarb decreased to 3 ppm in two weeks. For the rapid metabolism in carp the authors suggest the following pathway:



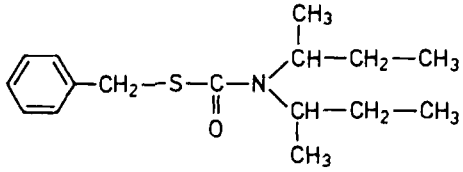
Crayfish accumulated benthiocarb from water in 2–30-fold amount, but when they were transferred to fresh water the quantity of benthiocarb accumulated was reduced by 50% in 10 days. Other invertebrates show a similar uptake. In 24 hours fish lose 50% of the quantity accumulated in fresh water (Harris and Eschmeyer, 1975).

Benthiocarb is moderately toxic to mammals, the acute oral LD_{50} for rats being 1300 mg/kg, for mice 560 mg/kg, and the acute dermal LD_{50} for rats 2900 mg/kg; but benthiocarb can, however, cause eye irritation.

The MTL (48-hour exposure) for carp is 3.6 mg/l. The acute oral LD_{50} of the technical active substance for bobwhite quail is 7800 mg/kg, for mallard duck 10 000 mg/kg.

In a 90-day subacute test the no-effect level of the active substance for rats and dogs was 660 ppm.

Thiocarbaryl, S-benzyl di-*sec*-butylthiocarbamate **(14)**, a patented herbicide of the Montedison has been developed for the control of grass weeds in rice (Caracalli *et al.*, 1973).



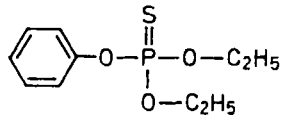
14

Thiocarbaryl formulated as an emulsifiable concentrate (70% active ingredient), applied either as seed dressing or as pre- or postemergence treatment selectively controls the *Echinocloa* spp. in flooded paddy fields (Corradini *et al.*, 1975). Field trials conducted in Italy from 1979 to 1981 showed that thiocarbaryl can be used in sugar beet too against grass weeds, specially against *Echinocloa* spp. as a postdrilling, preemergence treatment. Its recommended dose is 4 kg active ingredient/ha. In tank-mixture with chloridazone (8 kg active ingredient/ha), complete weed control has been achieved (Gelmetti *et al.*, 1982).

Thiocarbaryl is practically nontoxic to mammals and birds. Acute oral LD_{50} is 10 000 mg/kg.

Recently a new concept was born in extending the weed control activity of the thiocarbamate herbicides (Miaullis *et al.*, 1982). *In vitro* experiments have shown that the persistence of EPTC and molinate may be extended by addition of a known thiophosphorus ester (code number R-33 865) to the formulation.

R-33 865 **(15)** has been described by Fukuto and Metcalf (1956). Its chemical name is O,O-diethyl-O-phenyl phosphorothioate.



15

R-33 865, is inactive as an insecticide and is of moderate mammalian toxicity. Acute oral LD_{50} for rats is 740 mg/kg.

Trials were carried out in maize with 120 g/l R-33 865 added to the standard EPTC and molinate formulations. The addition of R-33 865 resulted in delayed soil degradation and therefore in prolonged and enhanced herbicidal effect. This improvement was the greatest in the control of late germinating annual grasses, such as *Digitaria sanguinalis*, *Panicum dichotomiflorum* and in improved suppression of perennial grass weeds such as *Cynodon dactylon*, *Sorghum halepense* and *Agropyron repens*.

Several earlier studies have shown that R-33 865 does not interfere with the microbiological breakdown of EPTC. Miaullis (1982) postulates that R-33 865 may block the secondary breakdown pathways of EPTC without affecting its herbicidal activation to sulfoxide and sulfone.

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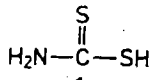
6.12 Dithiocarbamates

Dithiocarbamic acid (**1**) can be derived from carbamic acid by substituting its two oxygen atoms with two sulfur atoms.

Substituted dithiocarbamic acid derivatives have a broad range of biological action, the salts and thiuram compounds exhibiting mainly fungicidal action (see the section on fungicides).

Two dithiocarbamates, sodium methyldithiocarbamate (metham, SMDC, **2**) and 2-chloroallyl diethyldithiocarbamate (sulfallate, CDEC, **3**) have been introduced as herbicides. These compounds were developed before the thiocarbamate herbicides discussed in the preceding chapter.



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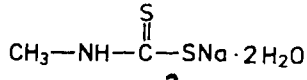

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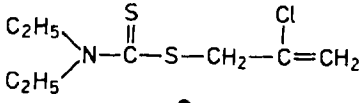

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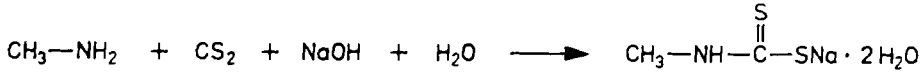
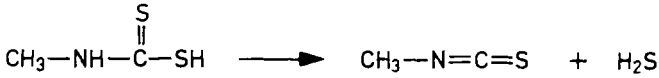
The soil-disinfecting action of metham and its homologues was recognised by Dorman and Lindquist (1954). Metham is prepared from methylamine, carbon disulfide and NaOH.



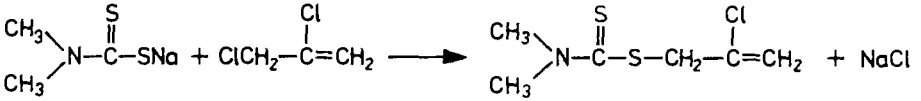
Metham is very readily soluble in water, while the solid compound and its dilute aqueous solution decompose rapidly, a 20–40% solution is stable (Dorman and Lindquist, 1955), hence it is available on the market as a 32.7% solution. The decomposition of the compounds is enhanced by heavy metals, acids and the soil. During the decomposition of metham toxic gaseous methyl isothiocyanate is formed, and this exerts the biological action (Read *et al.*, 1961).



Metham is used for general soil disinfection, in greenhouses and under field conditions at a rate of 11 litres of the 32.7% solution per 100 m^2. At this rate it kills all plants and seeds, thus the planting of crops must be delayed for about 2 weeks after treatment. The termination of the phytotoxicity of treated soil must be checked by the cress-seed tests.

Metham is an irritant to the skin and eyes. Inhalation of the gases formed in the decomposition must be avoided. Its acute oral LD_{50} for male rats is 820 mg/kg, for mice 285 mg/kg. The acute dermal LD_{50} for rabbits is 2000 mg/kg.

The herbicidal properties of sulfallate (3) were described by Harman and D'Amico (1952), as well as its preparation by the transesterification of sodium dimethyldithiocarbamate with 2,3-dichloropropene:



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Sulfallate is a liquid of low vapour tension, slightly soluble in water. In the absence of water it is completely stable at room temperature. It hydrolyses in acid and alkaline media, its half-life being 47 days at pH 5 and 30 days at pH 8.

Sulfallate is a translocating herbicide, applied preemergence at rates of 3–6 kg active ingredient/ha at the soil surface or incorporated into the soil, against annual grass weeds and a few broad-leaved weeds, mainly on vegetable crops and ornamental plants.

It is irreversibly adsorbed by the soil (Upchurch, 1958), and is easily absorbed through the roots of the plants, while it is not absorbed through the leaves.

Sulfallate does not accumulate in the plants; in sensitive weeds it is degraded more slowly, in tolerant plants it is rapidly metabolised to diethylamine. It is

degraded hydrolytically in the soil. At rates of 4 kg/ha it remains active for 3–6 weeks.

As like the other carbamate herbicides, sulfallate is a mitosis poison. Of the biochemical processes of plants inhibition of protein and RNA synthesis has been demonstrated experimentally (Moreland *et al.*, 1969). It seems certain that sulfallate forms a chelate with tyrosinase and cytochrome oxidase (Anonym, 1974).

Sulfallate is moderately toxic to humans and is somewhat irritating to the skin and eyes.

Its acute oral LD_{50} for rats is 850 mg/kg, its acute dermal LD_{50} for rabbits is 2000–2800 mg/kg.

It is virtually nontoxic to wild fowl. The acute oral LD_{50} for pheasants is more than 15.4 g/kg. The TLM for rainbow trout is 9.6 ppm.

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6.13 Urea herbicides

Urea herbicides form, along with phenoxy derivatives and triazines, the most important agricultural herbicide group. Since their discovery almost thirty years ago several tens of thousands of urea derivatives have been synthesised in research laboratories, and almost all of the major pesticide manufactures have marketed herbicides with a urea derivative as the active substance.

Most of the urea derivatives are compounds with herbicidal activity, although some of the aliphatic guanidine derivatives have a fungicidal action and some of the aromatic thioureas a rodenticidal action.

The first compound with significant herbicidal action discovered among aliphatic urea derivatives, N-butyl-N',N'-dimethylurea (Searle, 1954) was never put on the market. Others, for example, halo and polyhaloallyl-N,N-dimethyl ureas, also have herbicidal properties, while symmetric tetraalkyl-ureas are inactive.

Of the aliphatic urea derivatives a single compound, dichloral urea (DCU), has attained some practical importance (King, 1950), combined with Pyramin® it is used in Hungary for weed control in sugar beet.

Almost all of the urea compounds with good herbicidal action are trisubstituted ureas, containing a free imino hydrogen. According to the receptor theory, this hydrogen plays a role in the formation of the hydrogen bond (for details see the section on the mode of action).

Recently, however, tetrasubstituted urea compounds, for example N-acyl-N-aryl-N′,N′-dialkylureas, have been discovered, which also exhibit good herbicidal activity, though it is assumed that these compounds exert their herbicidal action after the splitting off of the acyl group, that is, in the trisubstituted form, containing free imino hydrogen.

Urea herbicides with cycloaliphatic substituents may contain several kinds of cycloalkyl and cycloalkenyl radicals, but only those in which two methyl groups are the substituents on N 1 are of satisfactory activity. A longer alkyl chain reduces herbicidal efficiency, this is also true for aryl urea derivatives.

The most important and most active compounds of the urea group are the N-aryl-N′,N′-dialkyl ureas. In these compounds the aryl group carries not more than two substituent groups, and none of these can be in the *ortho*-position. The monosubstitution (in *meta*- or *para*-position) and the disubstitution (in 3,4-positions) are most favourable.

The N′-substituted alkyl, alkenyl and alkynyl groups may contain a total of five carbon atoms. Herbicidal action decreases rapidly with the lengthening of the carbon chain. N′,N′-dimethyl derivatives are the most active members. N′-monoalkyl derivatives have no noteworthy herbicidal action. The substitution of one of the methyl groups with a methoxy group reduces the herbicidal action slightly, while simultaneously selectivity suddenly increases and persistence decreases.

The phenyl group can carry one or more halogen substituents of the following decreasing order of activity; Cl > Br > I, and alkyl, cycloalkyl, halogen alkyl alkoxy or phenoxy carbamate groups. The favourable positions of the substituents are the *para* and *meta* positions.

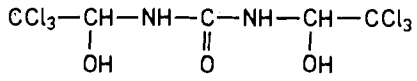
Diaryl and triaryl or naphthyl carbamates exhibit low herbicidal activity. The substitution of the aryl radical for a heterocyclic radical gives heterocyclic alkyl and dialkyl ureas, of which many examples have been prepared in recent years. The herbicidal activity of urea derivatives containing a heterocyclic radical, such as benzthiazole, thiazole, thiadiazole, oxadiazole and pyridine, is favourable if one or two methyl groups are substituted at the N′-nitrogen. The carrier of total or selective action in these derivatives is presumably the heterocyclic part of the molecule. More recently several new groups of compounds have become known, mainly in the patent literature, for which the structure–activity on relationships are still to be elucidated.

Compared to the respective urea derivatives, thiourea derivatives usually have a weaker herbicidal action. According to our present knowledge, this is attributed to the fact that unlike urea derivatives the thiourea derivatives do not exert their action by the inhibition of photosynthesis, but by another still unknown means.

6.13.1 Aliphatic urea derivatives

Of the aliphatic derivatives of urea, one compound, dichloral urea (DCU, **1**), 1,3-bis(2,2,2-trichloro-1-hydroxyethyl)urea, has attained some importance (King, 1950).

Prepared from chloral and urea by condensation catalysed with HCl, it is a crystalline compound insoluble in water and stable to acids. In alkaline medium it is decomposed into dichloroacetic acid and urea. In the soil it yields trichloroacetic acid by oxidative decomposition. According to Melnikov (1971a) these reactions



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explain its selective action for the control of weed grasses. It is also effective for the control of certain crucifer dicotyledon weeds that are difficult to kill.

It irritates the mucous membranes and is hazardous to fish, but is otherwise nontoxic. Its acute oral LD_{50} for rats is 6800 mg/kg.

DCU is a soil herbicide used at rates of 2–50 kg active ingredient/ha for pre-emergence treatment in sugar beet, cotton, oil flax, potato, carrots and medicinal herb cultures. In Hungary it is used in combination with Pyramin for weed control in sugar beet (Ubrizsy and Gimesi, 1969).

It is nonpersistent, even when used at high rates, being broken down in the soil in one growing season.

6.13.2 Cycloaliphatic urea derivatives

The research laboratories of the BASF and the Bayer Corporations in Europe and the Hercules in the USA were active in the development of this family of compounds.

The weed-killing properties of cycluron, 3-cyclooctyl-1,1-dimethylurea (**2**) were first reported by Fischer (1960).

It was developed as an experimental herbicide in 1958 by the BASF. Relationships between the structure and biological activity of cycloaliphatic urea derivatives were summarised first by Scheurer and Fischer (1962).Three routes are described in the patent literature for the synthesis of cycluron (Fischer *et al.*, 1958; Fischer, 1959; Steinbrunn and Fischer 1959).

(1) Cyclooctyl isocyanate is reacted with dimethylamine:

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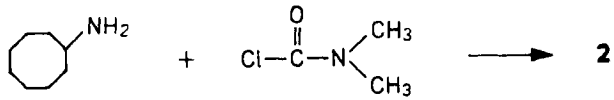
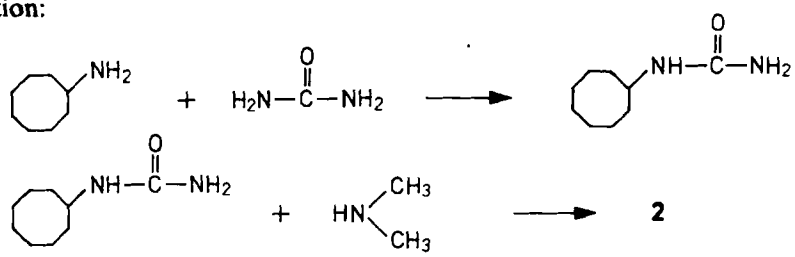
(2) Dimethylcarbamoyl chloride is reacted with cyclooctyl amine in the presence of an acid acceptor:



(3) Cyclooctyl amine, urea and dimethylamine are reacted in a two-step reaction:



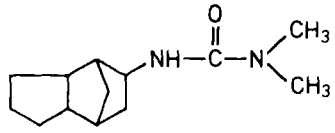
The acute oral LD_{50} of cycluron for rats is 2600 mg/kg, for mice 300 mg/kg. It does not irritate the skin.

It is effective mainly for the control of monocotyledonous germinating annual weeds as a preemergence herbicide at rates of 0.8–2 kg/ha. Its effect is unsatisfactory in dry weather. Its action lasts for over one growing season.

Cycluron is generally used in a 3 : 2 combination with chlorbufam (1-methyl-prop-2-yn-yl-N-(3-chlorophenyl)carbamate) for weed control in sugar beet at 2–2.5 l/ha (Alipur®, BASF). It is not recommended in monogermical sugar beet sowings because the plant can be damaged.

Like the other urea herbicides, cycluron inhibits photosynthesis. *In vitro,* it inhibits the Hill reaction at a-concentration of 5.6 mole/dm³ (Moreland, 1969).

Noruron, 3-(hexahydro-4,7-methanoindan-5-yl)-1,1-dimethylurea **(3),** is a bicyclo-aliphatic urea herbicide.



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Noruron was introduced in 1962 by Hercules Inc. in the USA under the trademark Herban®. The herbicidal effect of the compound was first described by Bunting (1963); its manufacturing process is protected by the patent of Diveley and Pombo (1964).

It is produced by the condensation of tetrahydrodicyclopentadienyl isocyanate with dimethylamine or by the reaction of tetrahydrodicyclopentadienyl amine with dimethylcarbamoyl chloride.

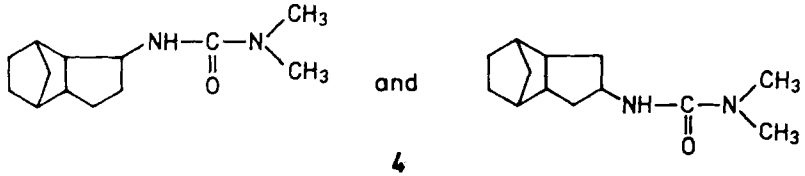
Noruron is a selective preemergence herbicide used at rates of 0.75–4 kg of active ingredient/ha on cotton, sugar cane, soybeans and potato. In combination with other herbicides, it enhances their grass weed killing effect.

Its acute oral LD_{50} for rats is 1476 mg/kg, for dogs 3700 mg/kg.

Moreland and Hill, in an earlier investigation (1963) of the photochemical activity of several polycyclic ureas, found that noruron has the strongest 50% Hill reaction inhibiting effect, $4.0 \cdot 10^{-6}$ mole/dm³. The Hill reaction inhibition of diuron is $3.3 \cdot 10^{-7}$ mole/dm³, thus being somewhat higher than that of cyclic ureas.

Moreland and Hill attribute the weaker inhibiting effect of polycyclic ureas to their higher lipophilicity, their less favourable special configuration, and to the absence of resonance interaction between the ring system and the amino nitrogen.

Another bicyclo-aliphatic urea, isonoruron (**4**), an isomer of noruron, has been developed in the research laboratory of the BASF AG (Fischer, 1967).



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Noruron is a mixture of 3-(hexahydro-4,7-methanoindan-1-yl)-1,1-dimethylurea and 3-(hexahydro-4,7-methanoindan-2-yl)-1,1-dimethylurea.

Isonoruron in 1 : 1 combination with bromopyrazon or in 2 : 3 combination with buturon is used as a selective preemergence and postemergence herbicide. The first combination is used for the control of grass weeds (*Alopecurus myosuroides, Apera spica venti*) and broad-leaved weeds in winter cereals under the name Basanor®, while the second combination (Basfitox®) is used in potatoes.

The acute oral LD_{50} of isonoruron for rats is more than 500 mg/kg: it has no dermal ill effects. The formulations are moderately toxic to fish (Sipos, 1968).

6.13.3 Aryl urea derivatives

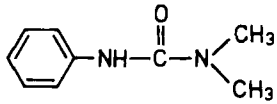
In terms of chemical structure, this group of herbicides is characterised by an aryl or substituted aryl radical as substituent on one of the N-atoms of urea, while two methyl groups are attached to the other urea nitrogen.

The first active member of this group, 3-(4-chlorophenyl)-1,1-dimethylurea (monuron, **6**) was prepared in 1951 (Bucha and Todd, 1951).

In the subsequent years intensive research work was carried out for the further development of the herbicidal compounds of this group by various substitutions of the phenyl group. This work continues today. A few new derivatives with higher selectivity and safer application than earlier compounds have been developed. On the basis of the patent literature, the introduction of further new compounds is to be expected. It is noteworthy that mainly European firms have excelled in the further development of this type.

The most important substances of this group are: 1,1-dimethyl-3-phenylurea (fenuron, **5**); 3-(4-chlorophenyl)-1,1-dimethylurea, (monuron, **6**); 3-(3,4-dichlorophenyl)-1,1-dimethylurea (diuron,**7**); 1,1-dimethyl-3-(α,α,α-trifluoro-*m*-tolyl)urea (fluometuron, **8**); 1,1-dimethyl-3-(α,α,α-trifluoro-*p*-tolyl)urea (parafluron, **9**); 3-(3-chloro-*p*-tolyl)-1,1-dimethylurea (chlortoluron, **10**); 3-(3-chloro-4-methoxyphenyl)-1,1-dimethylurea (metoxuron, **11**); 3-[(4-chlorophenoxy)phenyl]-1,1-dimethylurea (chloroxuron, **12**); 3,4-(4-methoxyphenoxy)phenyl-1,1,-dimethylurea (difenoxuron, **13**); 3-(1′1′2′2′-tetrafluoroethoxyphenyl)-1,1-dimethylurea (fluor-

etoxuron, **14**); 3-(3-chloro-4-difluorochlorothiomethylphenyl)-1,1-dimethylurea (thiochloromethyl, **15**); 3-(4-cyclopropylphenyl)-1,1-dimethylurea (isoproturon, **16**); 3-(4-cyclopropylphenyl)-1,1-dimethylurea (PH-40-51, **17**) and 3-[3-(N-*t*-butylcarbamoyloxy)phenyl]-1,1-dimethylurea (karbutilate, **18**).



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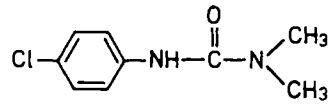

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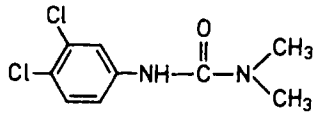

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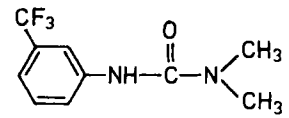

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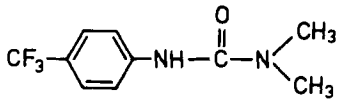

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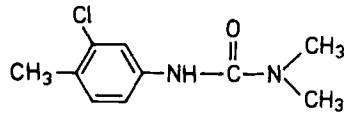

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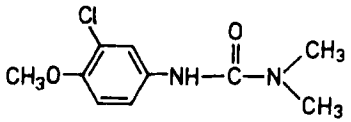

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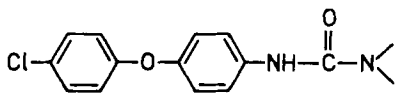

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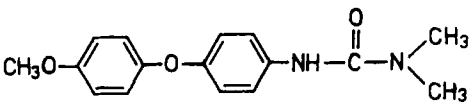

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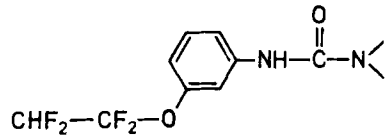

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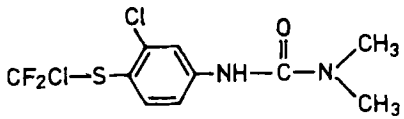

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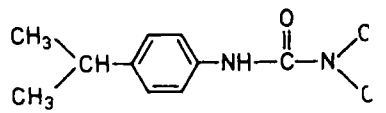

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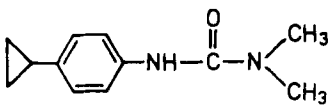

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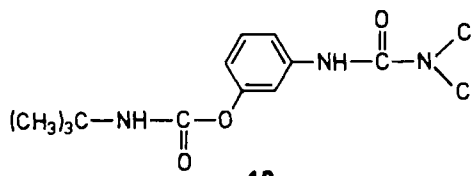

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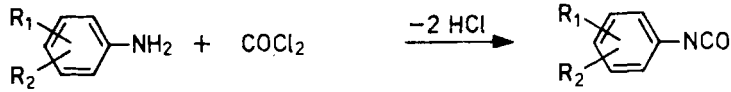
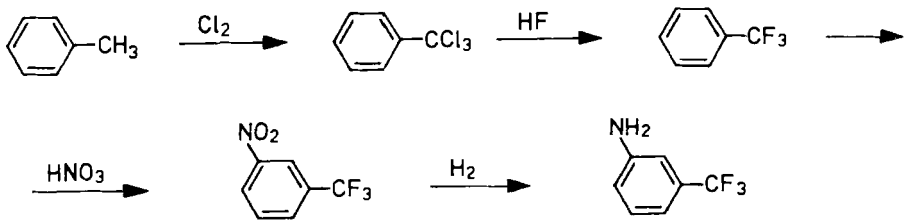
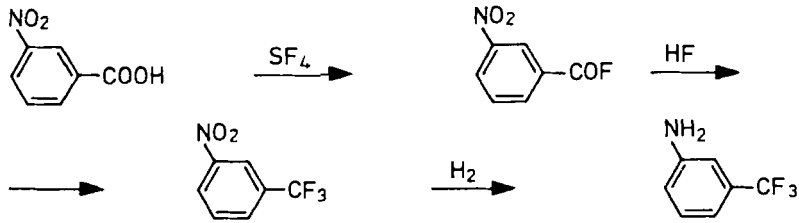
Aryl isocyanates are prepared by acylation with phosgen:



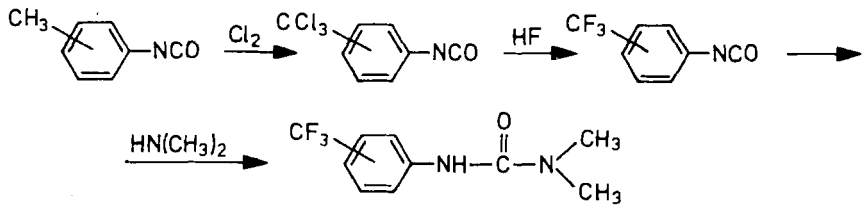
Simpler aryl amines can be prepared easily by the reduction of the respective nitro compounds using standard methods. The intermediate of fluometuron **(8)**, 3-trifluoromethylaniline, is prepared in a different way, because the substitution of the strongly electron-attracting CF_3 group can be realised only by indirect synthesis, involving the following steps (Wegler, 1970):



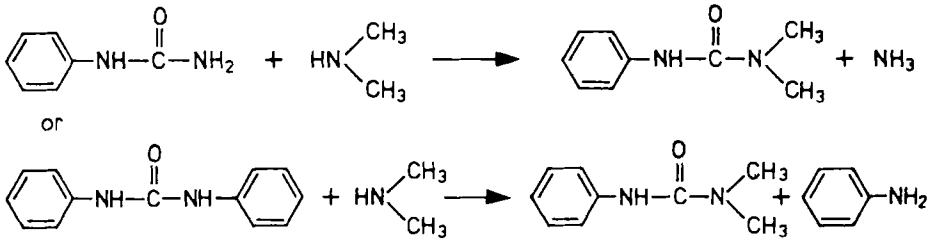
Jagupolski *et al.* (1971) recommend an alternative possibility starting from 3-nitrobenzoic acid:



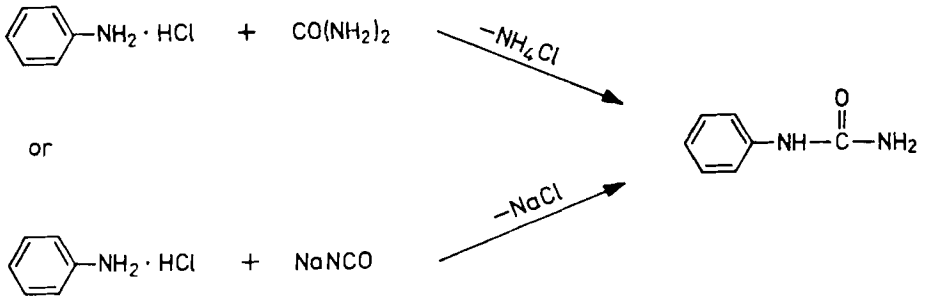
Eue *et al.* (1975) recommend for the introduction of the trifluoromethyl group the chlorination and subsequent fluorination of the tolyl isocyanates and the obtaining of the end-product by coupling with dimethylamine:



Another synthesis route of N-aryl dialkylamines, proposed by Melnikov (1971b), is the reaction of aryl- or diarylureas with diamines in solvents of high boiling point (e. g. in trichlorobenzene) at the boiling point of the solvent:

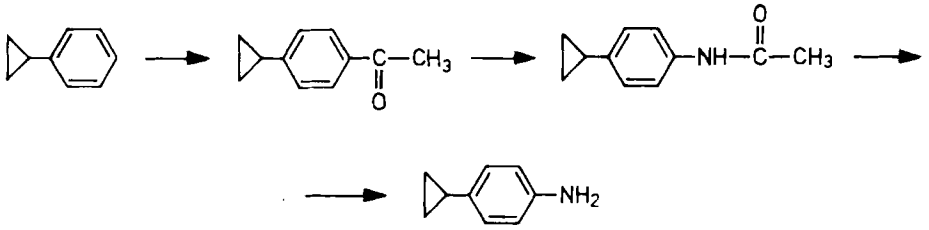


The second route yields an end-product of lower purity. The aryl urea intermediate can be prepared at a good yield by the reaction of aniline hydrochloride with urea or of aniline hydrochloride with alkali metal isocyanates:

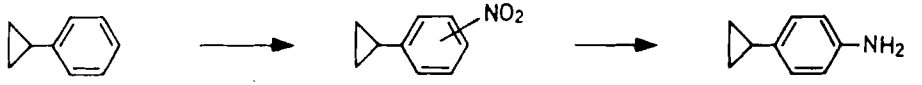


Three synthesis routes can be used for the preparation of the aromatic intermediate of PH 40–51, of 4-cyclopropyl aniline:

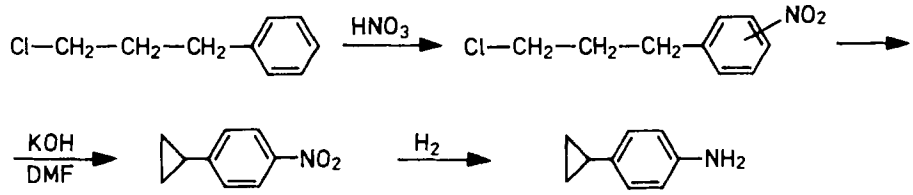
(1) According to one of the methods, the starting material is cyclopropyl benzene, which is acetylated, and the 1-acetyl-4-cyclopropyl benzene obtained being converted by Schmidt rearrangement into 4-cyclopropyl acetophenone. The hydrolysis of the latter yields 4-cyclopropyl aniline:



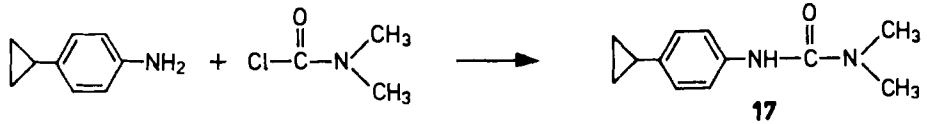
(2) The nitration and subsequent reduction of cyclopropyl benzene similarly gives 4-cyclopropyl aniline, though at a poor yield:



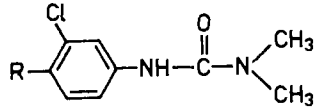
(3) According to another method, an *o*- and *p*-isomer mixture is prepared from 1-chloro-4-phenylpropane by nitration. The *o*-nitro compound is removed by treatment with alkali, and 1-nitro-4-cyclopropyl benzene is obtained by ring closure; this gives 4-cyclopropyl aniline on reduction:



PH 40–51 is obtained by the condensation of 4-cyclopropyl aniline with dimethylcarbamoyl chloride:



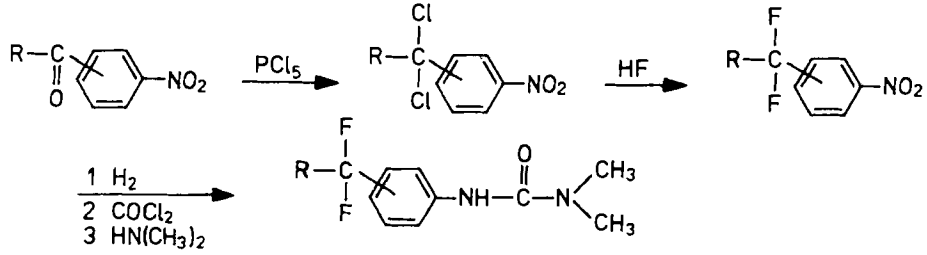
Eue *et al.* (1975) reported on experimental phenylurea derivatives of the following type:



where R is CF_3, OCF_3, SCF_3 or SCF_2Cl.

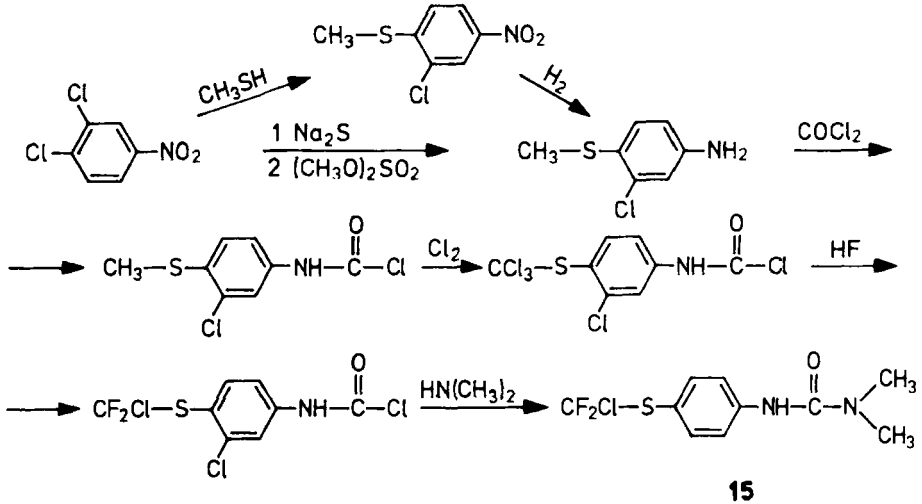
The CF_3 derivative is selective in cotton and cereals, the OCF_3 derivative in cotton, the SCF_3 and SCF_2Cl derivatives in rice.

One of the methods recommended for the synthesis of difluoromethyl derivatives is the following:



R = H, CH_3, C_6H_5

Two routes have been proposed for the industrial synthesis of thiochloromethyl: 3,4-dichloronitrobenzene is either reacted with methyl mercaptan and then reduced to 3-chloro-4-methylmercaptoaniline, or it is reduced in a single step with sodium sulfide and methylated with dimethylsulfate into the desired aniline derivative. Next, the aniline is reacted with phosgen chlorinated, partially fluorinated and finally coupled with dimethylamine to give the desired product.



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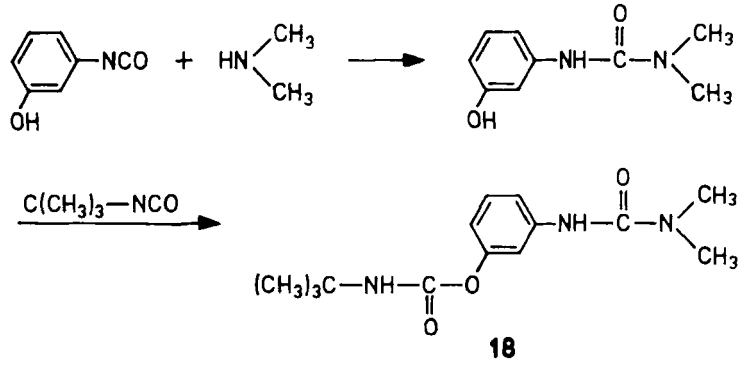
The preparation of karbutilate **(18)**, which contains a *m*-urethan group, proceeds according to a different type of synthesis route (Wilson and Hill, 1965).

3-Hydroxyphenyl isocyanate is condensed with dimethylamine to give 3-(3-hydroxyphenyl)-1,1-dimethylurea, which is reacted with *t*-butyl isocyanate to yield karbutilate:



18

Of all the urea derivatives the herbicide fenuron **(5)** has the highest solubility in water and is the least adsorbed by the soil. Owing to its good water solubility, it is easily washed into the deeper layers of the soil. Absorbed through the roots it kills deep-rooted grass and broad-leaved weeds. It is also effective for the control of

woody plants and trees. It is used pre- and postemergence, and by basal application, at a rate of 2–30 kg/ha (Bucha and Todd, 1951; Sharp *et al.*, 1953; Crafts, 1960).

Fused in equimolar ratio with trichloroacetic acid it forms a complex readily soluble in water, the complex (Urab®, Allied Chemicals) combines the action of the two herbicides and is used for total weed killing.

The acute oral LD_{50} of fenuron for rats is 6400–7500 mg/kg, that of fenuron-TCA 400 mg/kg (Bayley and White, 1965).

Introduced in 1951 by du Pont in the USA monuron (CMU, **6**) was the first urea herbicide. Diuron (DCMU, **7**) was introduced by the same company in 1956.

The two closely related urea herbicides take the form of stable crystalline compounds slightly soluble in water. Owing to their high chemical stability, their strong adsorption to the soil and their poor water solubility, they remain in the upper few centimeters of the soil and are very persistent. Diuron is the most persistent herbicide apart from simazine.

Both herbicides are used at a rate of 0.6–4.8 kg active ingredient/ha for selective weed control in sugar cane, cotton, citrus and orchards.

Applied at rates of 10–30 kg active ingredient/ha they provide total weed control on non-crop areas. At these rates, they remain active for 2 years in the soil, so that no crops should be sown in the treated areas.

Monuron TCA, prepared by the reaction of monuron with trichloroacetic acid, is also a total herbicide with foliar action and can therefore also be used post-emergence at rates of 10–15 kg/ha. Owing to its acid character, it is incompatible with alkaline substances.

The acute oral LD_{50} of monuron for rats is 3400 mg/kg, that of diuron 3600 mg/kg. The no-effect levels for rats and dogs are 250 and 500 ppm, respectively. Monuron is nontoxic to bees, diuron mildly toxic (Beran, 1970).

Fluometuron (**8**) was introduced in 1961 under the code number Ciba 2059. Its herbicidal properties have been described by Aebi (1965) (see also Ciba, 1965).

It is applied pre- and postemergence at a rate of 1–4 kg active ingredient/ha for the control of annual grass and broad-leaved weeds in cotton and sugar cane.

It is of medium persistence, with a half-life of 60–75 days depending on soil conditions. Several crop plants are very sensitive to fluometuron; thus, within 6 months of treatment only cotton can be planted in the area treated. After doses of more than 4 kg, no sensitive plants can be planted even after a year (Darding, and Freemann, 1968).

The acute oral LD_{50} for rats is more than 8000 mg/kg, for dogs and rabbits more than 10 000 mg/kg. A dermal treatment of 400 mg/kg caused no ill effects in rabbits. In twelve month feeding tests the no-effect level for rats is 10 mg/kg, for dogs 15 mg/kg.

Fluometuron is moderately toxic to fish and to animals consumed by fish. The LC_{100} limit for rainbow trout *(Salmo irideus)* is more than 60 ppm, for water flea *(Gommarus pulex)* 60 ppm. Exposure of killifish *(Orysias latipes)* to 25 ppm of fluometuron for 25 hours caused a mortality of 6.7% to 50 ppm a mortality of 100% (Ciba, 1966; Brade, 1968).

Fluometuron is not toxic to bees. The experimental herbicide parafluron is the 4-trifluoromethyl analogue of fluometuron. Its field of application will probably be similar to that of fluometuron.

The herbicidal properties of chlortoluron (C 2242, **10**) were first described by l'Hermite *et al.* (1969), and later by Flemming (1970).

It is effective against mono- and dicotyledonous weeds, particularly against black grass *(Alpecurus myosuroides)* in cereals. On winter cereals it is used at a rate of 1.5–3 kg active ingredient/ha immediately after sowing or in spring postemergence, from the three-leaf stage of the cereal up to tillering. On spring wheat and barley, rates of 1–2 kg active ingredient/ha are recommended pre- or postemergence. Against some weeds that are difficult to control, such as *Galium, Veronica* and *Papaver* spp., the herbicidal action can be improved by mixing with bromofenoxim (1 kg/ha) or with mecoprop (1.2 kg/ha).

The acute oral LD_{50} for rats is more than 10 000 mg/kg, the dermal LD_{50} for rats more than 2000 mg/kg. For guppies *(Lesbistes reticulatus)*, the LC_{100} of the 80% formulated product is 40 ppm. It is not toxic to bees.

In temperate climates, its half-life in a soil application of 6 kg active ingredient/ha is 30–40 days.

It is remarkable that the herbicidal properties and the persistence of chlortoluron, so similar in composition to diuron, should be so different.

Metoxuron **(11)** was developed by the Sandoz Ltd. (Berg, 1968).

This selective compound, absorbed through the roots and the leaves, is used in cereals and carrots, mainly against grass weeds but also against many annual broad-leaved weeds, at early preemergence and late postemergence. Most winter wheat and winter barley varieties show a good tolerance in preemergence application at a rate of 2.4–3.2 kg active ingredient/ha. All carrot varieties are tolerant at pre- or postemergence application rates of 2.1–4.3 kg active ingredient/ha, depending on the type of soil. The persistence of metoxuron is low, the half-life varying between 10 and 30 days according to soil type.

The acute oral LD_{50} for rats is 3200 mg/kg, the acute dermal LD_{50} 1600 mg/kg. In ninety-day feeding tests, daily levels of 50, 250 and 1250 ppm fed to dogs produced nontoxic symptoms. Chickens fed at daily levels of 50, 250 and 1250 ppm showed no abnormalities.

Bees suffered no ill effects from a spray of 4.8 kg of metoxuron/ha.

The herbicidal properties of crystalline chloroxuron **(12)** were described by Aebi and Ebner (1961). It is absorbed by the roots and the leaves and is used for the pre- or postemergence control of annual grass and particularly of broad-leaved weeds. Owing to its poor water solubility and to its strong bonding to soil colloids, it remains near to the soil surface, and in dry weather the area treated must be irrigated to attain adequate herbicidal action.

Applied at a rate of 3–5 kg active ingredient/ha preemergence or postemergence up to the 2–5 cm stage of the weeds, it can be used as a herbicide in strawberries, fodder turnips, soybeans, potatoes, vegetables and ornamentals.

Chloroxuron is of brief persistence, its action lasting for a few weeks. After treatment at the rate recommended it is degraded in 3–4 months into nonphytotoxic compounds.

The acute oral LD_{50} for rats is 3000 mg/kg, for mice 1000 mg/kg. It does not cause skin irritation. The no-effect level for rats in a four-month feeding test is 10 mg/kg per day, for dogs in a ninety-day feeding test 15 mg/kg per day. In a concentration of 15 ppm, no ill effects were produced in killifish *(Orysias latipes)* during 48 hours, the LC_{50} for killifish being 30 ppm.

It is not hazardous to bees.

The herbicide difenoxuron **(13)** is closely related to metoxuron **(11)**. It is absorbed through both the roots and the leaves. Its range of selectivity is narrow; it is recommended mainly for postemergence weed control in onion seedlings. Its other properties are similar to those of metoxuron.

The acute oral LD_{50} for rats is more than 7750 mg/kg, and the acute dermal LD_{50} for rats more than 2150 mg/kg.

Fluoretoxuron **(14)** has been developed in the research laboratories of Hoechst (Scherer *et al.*, 1972). Its herbicidal properties have been described by Langeldücke and Schulze (1972).

The 50% Hill reaction inhibiting concentration of fluoretoxuron on *Chlorella* algae is $1.4 \cdot 10^{-5}$ mole/dm^3. In preemergence application it is a better weed-killer than linuron or fluometuron.

At 0.5–5 kg active ingredient/ha it is selective in cotton. Sugar cane tolerates 4 kg applied preemergence, and 3 kg applied postemergence.

At higher dosage it is effective over the whole growing season against some weeds that are difficult to combat, in particular *Agropyron repens* and *Agrostis alba*.

Fluoretoxuron is not easily leached out of the soil; applied at a rate of 0.62 kg, it is completely degraded in 3 months, and at 1.25 kg it is decomposed to 60% in 5 months.

The acute oral LD_{50} for rats is more than 6000 mg/kg. The dermal LD_{50} for rabbits (at five consecutive treatments) is more than 5800 mg/kg. In subchronic toxicity feeding tests of 90 days the no-effect level for rats is 2000 ppm, for beagles 200 ppm.

Isoproturon (Hoe 16 410; **16**) is a closely related analogue of monuron **(6)**, containing an isopropyl group instead of the Cl atom of monuron in position 4. A period of 21 years separates the development of the two herbicides. This long time is indicative on the one hand of the difficulties of "molecule development", and on the other hand of the fact that by changing the molecule of a well-known total herbicide, another herbicide of surprisingly new selectivity can be obtained.

The herbicidal properties and toxicology of isoproturon have been described by Thizy *et al.* (1972), Hewson (1974) and Schwerdtle and Schumacher (1975).

Isoproturon can be used both pre- and postemergence in winter cereals. Applied preemergence at an average rate of 2.0 kg active ingredient/ha, or postemergence at 1.5 kg/ha, it is an effective weed-killer, particularly against grass weeds, and is not toxic to cereals. Of the grass weeds it is particularly effective against *Alopecurus*

myosuroides and *Avena* spp., *Galium aparine*, *Lamium* spp., *Veronica* spp. and *Viola arvensis* are resistant to isoproturon. Against these weeds, the use of dinoseb acetate and/or CMPP and tank mixtures are recommended.

The acute oral LD_{50} for rats is 1826 mg/kg.

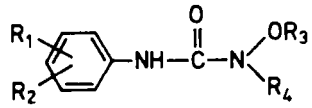
Karbutilate (**18**) is a total herbicide. Against sensitive annual weeds rates as low as 2–5 kg active ingredient/ha are sufficient, at 12–24 kg active ingredient/ha it kills all vegetation.

It is used for weed control on non-crop land, highways and industrial areas (Williams, 1965; Dawson, 1967; Fisons, 1969).

The acute oral LD_{50} for rats is 3000 mg/kg; it is not irritating to the skin, and is only slightly toxic to fish (LC_{50} for trout is more than 135 ppm).

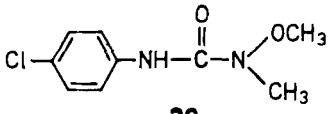
6.13.4 Arylalkoxy urea derivates

The compounds of the 3-aryl-1-alkoxy-1-alkylurea group, closely related to the 3-aryl-1,1-dialkylureas, can be derived from the oxyureas:



They have a lower biological activity and persistence than the aryl-dialkyl ureas discussed above, but their selectivity is greater. These derivatives can safely be used as selective weed killers in sensitive crops.

Of the many variants four compounds found so far have received widespread application in agriculture: monolinuron, 3-(4-chlorophenyl)-1-methoxy-1-methylurea, (**20**); linuron, 3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea, (**21**); metobromuron, 3-(4-bromophenyl)-1-methoxy-1-methylurea, (**22**); chlorbromuron, 3-(3-chloro-4-bromophenyl)-1-methoxy-1-methylurea (**23**).



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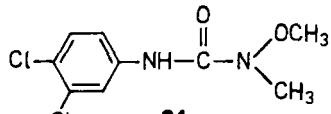

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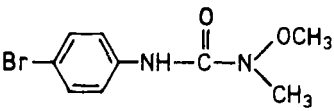

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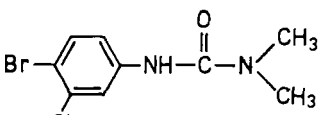

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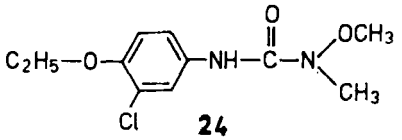
Three other experimental herbicides belonging to this group are: 3-(3-chloro-4-ethoxyphenyl)-1-methoxy-1-methylurea (**24**), 3-(3-chlorodifluoromethylphenyl)-1-methoxy-1-methylurea (**25**), and 3-(4-fluorophenyl)-1-carboxymethoxy-1-methylurea (**26**).



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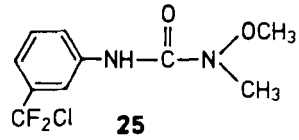

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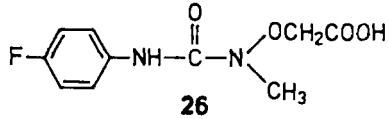

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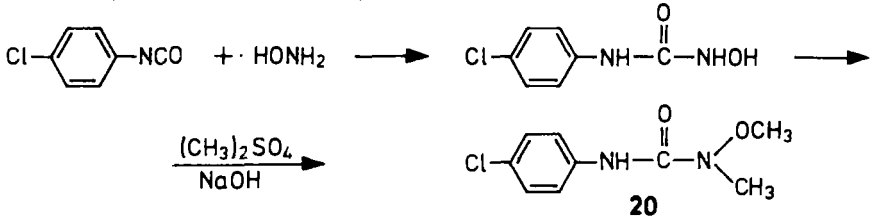
3-Aryl-1-alkoxy-1-alkylureas can be synthesised by various methods. For example, for the synthesis of monolinuron the following reaction routes have been used:

(1) By the reaction of the respective isocyanate with hydroxylamine 3-aryl-1-hydroxyurea is made, which is then methylated with dimethyl sulfate (Scherer and Heller, 1958); Scherer *et al.*, 1963):



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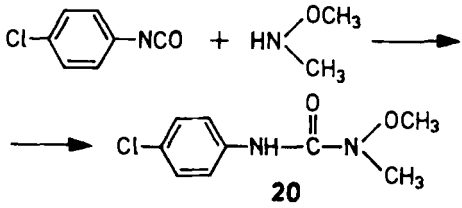
(2) The condensation of aryl isocyanate and O,N-dimethylhydroxylamine gives the pure end-product at the very good yield of 95% (Scherer and Heller, 1960):



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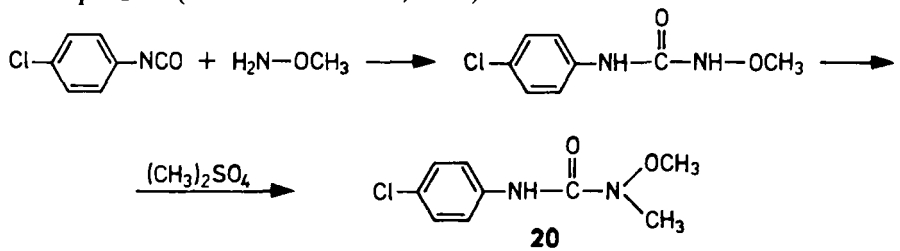
(3) Aryl isocyanate reacts in the first step with O-methylhydroxylamine, giving 3-aryl-1-methoxyurea, which is then methylated with dimethyl sulfate to yield the desired product (Scherer and Heller, 1960):



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For industrial synthesis the first reaction route is the most economical.

Monolinuron **(20)**, developed in 1958 simultaneously by the Farbwerke Hoechst and the Du Pont, was the first methoxyurea derivative to be introduced (Haertel, 1962).

It decomposes slowly in acid and alkaline media and in moist soils. Owing to its relatively high volatility, it also penetrates the plants in the form of vapour.

It is used as a preemergence herbicide at a rate of 1.5–7 kg active ingredient/ha for the control of weeds in potatoes, medicinal plants, vineyards and orchards. It is ineffective for the control of deep-rooted and perennial weeds, probably because it does not reach the depth of their root zone in toxic quantities. A certain degree of natural resistance to monolinuron is also possible (Brian, 1965; Couturier, 1963; Börner *et al.*, 1969).

Certain crop plants, such as beans and peas are species-sensitive to monolinuron, and phytotoxic injuries may occur also when application is followed by heavy precipitation, the herbicide being washed down to the root zone of the crop plant (Heichler, 1965; Lichte, 1965; Weiler, 1965; Bryner and Meyer, 1966).

Monolinuron is nonpersistent, in soil it is degraded within three months to 5.6%, within ten months to 0.2% (Börner, 1965a).

The acute oral LD_{50} for rats is 2250 mg/kg, for dogs 500 mg/kg. In ninety-day feeding tests rats suffered no ill effects up to a daily dose of 500 ppm; above this value they showed a decrease in weight compared to the control animals, but no histological changes developed even when they were fed doses of 2500 ppm.

Linuron, **(20)** developed at the same time as monolinuron, was placed on the market in 1960 (Haertel, 1962).

The crystalline compound has a solubility in water less by almost one order of magnitude than that of the closely related monolinuron. Vapour tension and solubility in organic solvents are also considerably lower than those of monolinuron. The stability of linuron is the same as that of monolinuron, but it is more strongly adsorbed by the soils. Adsorption is enhanced in soils rich in organic matter (Hilton and Yuen, 1963; Hance, 1965).

Because of its lower solubility in water and stronger adsorption by the soil, it is leached more slowly into the deeper soil layers than monolinuron, and its decomposition is also slower (Börner, 1965).

It can be used for pre- and postemergence treatment because it is absorbed through both the roots and the leaves. Preemergence application is more advantageous because of its acropetal translocation. Depending on the humus content of the soil and on the crop species, it is used at rates varying between 1 and 3.5 kg active ingredient/ha against annual weeds in potatoes, cotton, maize, carrots, other vegetable crops and orchards. In sandy soils it may cause phytotoxic injuries, and the crop also can be damaged after heavy rainfall.

It is nonpersistent; four months after application at the usual rates sensitive crops can be sown. Its half-life is 1–2 months, depending on weather conditions.

Less toxic than monolinuron, it is virtually nonhazardous. Its acute oral LD_{50} for rats is 4000 mg/kg, for dogs 500 mg/kg. In two-year feeding tests, the no-effect level

for rats was found to be more than 125 ppm, for dogs more than 25 ppm. It is not toxic to bees.

The herbicidal properties of metobromuron **(22)** introduced by Ciba under the code number 3126, have been described by Schuler and Ebner (1964) and by Würzer (1966).

The compound has a solubility in water lying between that of monolinuron and linuron. It is very soluble in organic solvents. Its chemical stability is lower than that of monolinuron; it is decomposed by ultraviolet light with demethylation (Rosen *et al.*, 1969).

Metobromuron taken up through the roots is translocated into the transpiration system. The compound taken up through the leaves also flows basipetally, unlike monolinuron (Voss and Geissbühler, 1966).

Metabromuron is used preemergence at rates of 1.5–2 kg active ingredient/ha for the control of annual seedling grass and broad-leaved weeds. In general, it is more effective against the latter. It is ineffective for the control of perennial weeds. It is used on potatoes, beans, tobacco before transplanting, peanuts, soybeans, sunflowers and flax.

It is degraded rapidly by microbes in the soil. This degradation is more rapid than that of monolinuron but slower than that of linuron (Majumdar, 1969).

The acute oral LD_{50} for male rats is 2700 mg/kg, for female rats 3000 mg/kg. In ninety-day tests dermal application of 2000 mg/kg had no effect on rabbits. The no-effect level in two-year feeding tests on rats was more than 250 ppm, on dogs more than 100 ppm. The lethal dose for wild fowl ranges from 18 000 to 24 000 ppm. At ninety-six-hour exposure, the LC_{50} for goldfish and trout was 71–85 ppm. It is not toxic to bees, the LD_{50} being 160μg/bee (Heim *et al.*. 1966).

Chlorbromuron **(23)** was introduced as an experimental herbicide under the code number C 6313 by the Ciba Geigy AG in 1961 (Green *et al.*, 1966).

The areas of application are similar to those of metabromuron. It is used as a pre- and postemergence herbicide against annual weeds in potatoes, peanuts, soybeans, peas and vegetables at a rate of 0.70–1.5 kg active ingredient/ha.

It is nonpersistent, its half-life in sandy soils being 40 days.

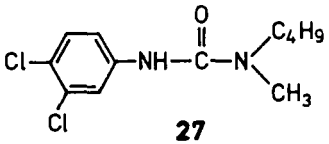
Its acute oral LD_{50} for male and female rats is higher than 5000 mg/kg. The LD_{50} value cannot be established for dogs, because at a dose higher than 1000 mg/kg they throw up the active substance. Acute dermal LD_{50} for rabbits is higher than 10 g/kg. In three-month feeding tests on male rats and dogs the no-effect level was higher than 316 ppm.

Chlorbromuron is moderately toxic to wild fowl and fish. The subacute LD_{50} in feeding tests for 10 consecutive days on wild ducks, pheasants and bobwhite quails was more than 10 250 ppm.

The four-day TL_m (medium tolerance limit) values have been determined for fish. According to experiments on young fish, 5–10 cm long, the TL_m of chlorbromuron for rainbow trout *(Salmo gardineri)* is 0.56 ppm, for channel catfish *(Ictalurus punctatus)* 11 ppm, and for bluegill *(Lepomis macrochirus)* 7.5 ppm. In comparative tests, the TL_m values of DDT varied between > 0.01 and < 0.05 ppm (Industrial Bio-Test Laboratories, 1965–1967).

6.13.5 Other 3-aryl-1-substituted urea derivatives

By varying the aryl substituent and the 1-substituents of 3-aryl ureas several effective herbicides have been prepared, such as neburon, 1-butyl-3-(3,4-dichlorophenyl)-1-methylurea **(27)**; trimeturon, 3-(4-chlorophenyl)-O,1,1-trimethylisourea **(28)**; buturon, 3-(4-chlorophenyl)-1-methyl-1-(1-methylprop-2-ynyl)urea **(29)** and Proban®, 3-(3,4-dichlorophenyl)-1-isopropyl-1-(2-propynyl)-urea **(30)**. Those containing unsaturated side-chains include siduron, 1-(2-methylcyclohexyl)-3-phenylurea **(31)**, and methazole, 2-(3,4-dichlorophenyl)-4-methyl-1,2,4-oxadiazolidine-2,5-dione **(32)**.



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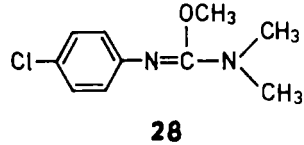

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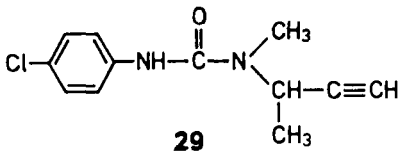

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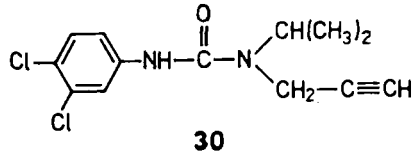

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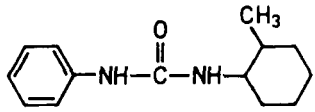

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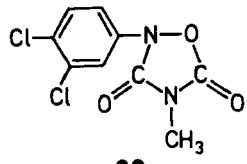

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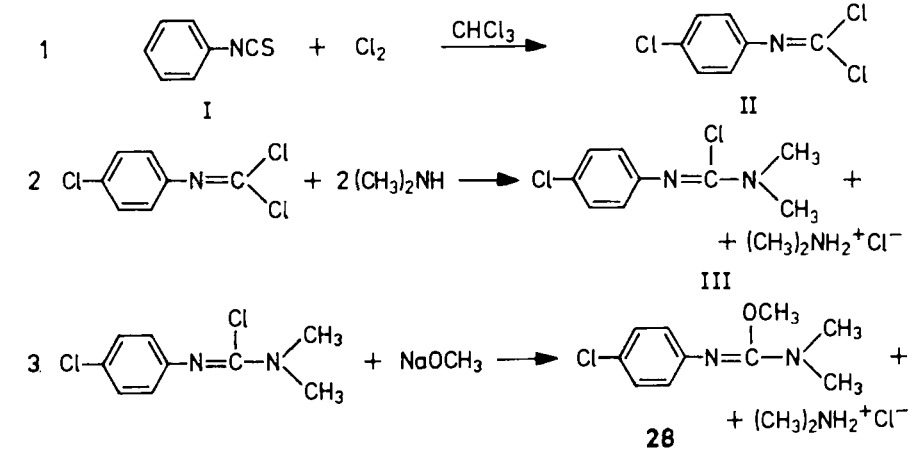
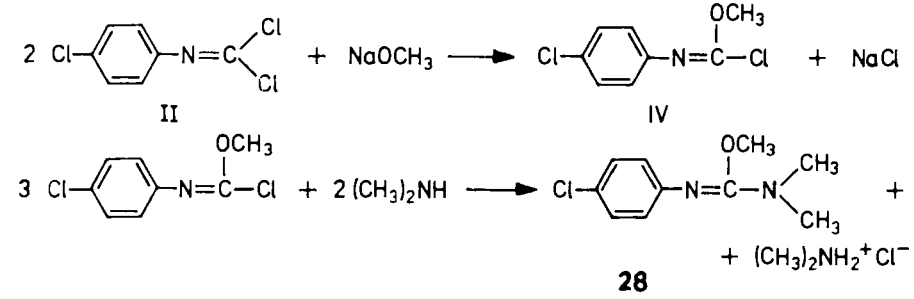
According to British Patent 904 706, trimeturon can be synthesised by the following routes:

(A) Phenyl isocyanate (I) is chlorinated in chloroform, and the *p*-chlorophenylcarbonimidoyl dichloride (II) obtained is reacted with dimethylamine to give *p*-chlorophenylimino chlorocarbonic acid dimethylamide (III). This is treated with

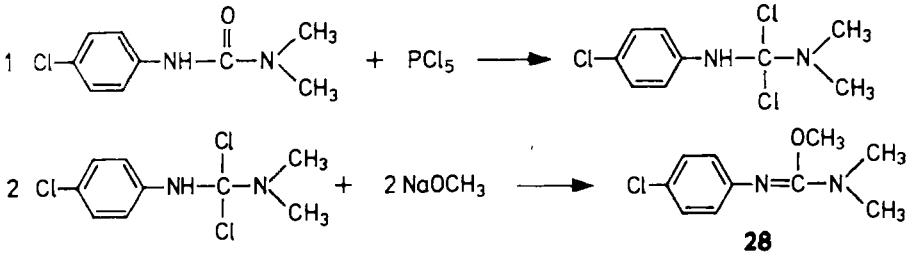
sodium methylate solution in benzene to yield 3-(4-chlorophenyl)-O-1,1-trimethylisourea, trimeturon:



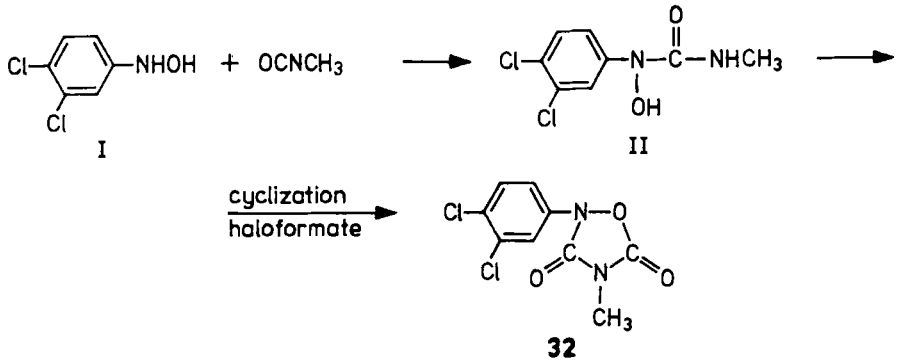
(B) The first step of this synthesis route is the same as that of route *A*. In the second step, *p*-chlorophenylcarbonimidoyl dichloride (II) reacts with sodium methylate; *p*-chlorophenylimino chlorocarbonic acid methyl ester (IV) is formed, which is reacted with dimethylamine to give trimeturon:



(C) According to the third synthesis route, the end-product is obtained from 3-(4-chlorophenyl)-1,1-dimethylurea (monuron) in two steps. In the first step 3-(*p*-chlorophenyl)-1,1-dimethylurea dichloride is prepared with phosphorus pentachloride, which, with sodium methylate gives trimeturon.



Methazole (**32**) is prepared from N-(3,4-dichlorophenyl)hydroxylamine in two steps. In the first step, reaction with methyl isocyanate gives 3-(3,4-dichlorophenyl)-1-hydroxy-1-methylurea, which is cyclised by reaction with a haloformate to give methazole:



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Bucha and Todd described the herbicidal properties of neburon (**27**) together with those of monuron, fenuron and diuron as early as 1951, but neburon, introduced only in 1955, did not gain widespread use.

It is recommended for the preemergence control of annual weeds in nursery plantings of ornamental trees and shrubs at a rate of 2–5 kg active ingredient/ha. It is used with good results for the control of grass weeds in winter cereals (Poignant *et al.*, 1965; Rognon, 1966; Schneider *et al.*, 1968).

It is more strongly adsorbed by the organic components of soils than monuron or diuron, and is therefore of poor efficiency in soils with high humus content, particularly under dry weather conditions. Low doses are persistent in the soil for 3–6 months, high doses for as long as 2 years. It is a nontoxic substance.

Buturon (**29**) was developed by the BASF and introduced in 1966 (Fischer, 1964). In the soil, a dose of 1–2 kg/ha is microbially decomposed in 12 weeks. Buturon is effective as a pre- or postemergence herbicide against annual, shallow-root mono- and dicotyledonous weeds. An application rate of 1 kg/ha active ingredient is recommended in cereals, and 5 kg/ha on berry fruits and vine. The acute oral LD_{50} for rats is 3000 mg/kg. It has no skin-irritating effect.

Siduron (**31**) synthesised from phenylcarbamoyl chloride and 2-methylcyclohexylamine, was developed in 1964 under the code number "Du Pont 1318" (Varner *et al.*, 1964). It is used preemergence at 2–12 kg active ingredient/ha. The acute oral LD_{50} for rats is 7500 mg/kg.

Methazole (**32**) was developed in 1968 by the Velsicol Chemical Corp. under the code number VCS-438 (Furness, 1970).

Of all the urea herbicides this compound has the lowest solubility in water. It is readily soluble in isophoron (300 g/l).

It is used as a selective herbicide for the preemergence treatment of cotton, garlic, flower bulbs and potatoes at rates of 2–6 kg active ingredient/ha. Applied

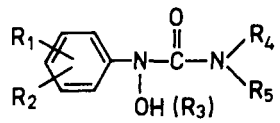
postemergence as a directed spray at 5–10 kg active ingredient/ha, it is used as a selective herbicide on cotton, fresh growth of alfalfa, orchards and vines.

The acute oral LD_{50} for rats is 1350 mg/kg; the acute dermal LD_{50} for albino rabbits more than 1200 mg/kg. It is mildly irritating to the skin and the eyes. It is toxic to fish, the LC_{50} (96-hour exposure) for goldfish and rainbow trout being 3 ppm. In ninety-day subacute feeding tests rats and dogs suffered no ill effects up to 500 ppm.

6.13.6 3-Aryl-3-hydroxy-1-alkyl urea derivatives

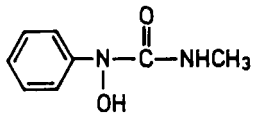
From this group of compounds Soviet research workers developed herbicides with selective action (Baskakov, 1966, 1967, 1973).

Though the hydroxyl group attached to the nitrogen of the aryl group reduces somewhat the biological activity of the derivative, at the same time it increases considerably its selectivity. Baskakov (1960) investigated the group of compounds characterised by the following general formula:



where R_1 and R_2 = H or halogen; R_3 = alkyl; R_4 = H or CH_3 and R_5 = CH_3.

The most effective derivative introduced in the agriculture as a selective herbicide is meturin, 1-phenyl-1-hydroxy-3-methylurea (**33**).



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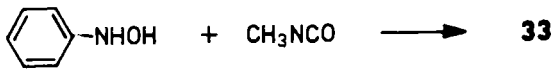
Meturin developed in 1958 in the USSR (Baskakov, 1960), is prepared by the reaction of phenylhydroxylamine with methyl isocyanate:



It is a herbicide of selective action, used preemergence at a rate of 4 kg active ingredient/ha against annual weeds in cotton and potatoes. Its herbicidal action lasts for 2–3 months.

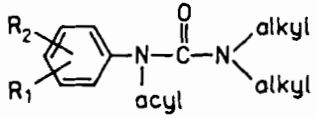
It is moderately toxic to mammals, the acute oral LD_{50} for rats and white mice being about 5000 mg/kg.

Its mode of action differs from that of the other known urea herbicides in that it does not inhibit photoreactions I and II *in vitro*. *In vivo*, however, weeds are killed

and show symptoms characteristic of photosynthesis-inhibiting herbicidal action (chlorosis of leaves). Thus, meturin is a herbicidal precursor compound, which is converted within the plant by metabolic processes into a compound with herbicidal activity (Stonov *et al.*, 1974).

6.13.7 3-Acyl-3-aryl-1,1-dialkyl urea derivatives

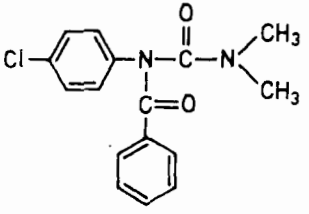
The herbicidal properties of this group of compounds were described by Poignant *et al.* (1965). Of the large number of compounds prepared derivatives benzoylated at the nitrogen adjacent to the phenyl group proved to be the most active. Their general formula is:



where R_1 and R_2=H or halogen.

Owing to their different steric configuration, the absorption of acylureas by plants is different from that of the other urea herbicides, which may partly explain their different selectivity. Presumably, these compounds exert their action after hydrolysis of the acid group.

Derivatives are: monomarc, 3-benzoyl-3-(4-chlorophenyl)-1,1-dimethylurea **(34)**; phenobenzuron, 3-benzoyl-3-(3,4-dichlorophenyl)-1,1-dimethylurea **(35)** and methoxymarc, 3-(4-methoxybenzoyl)-3-(4-chlorophenyl)-1,1-dimethylurea **(36)**.



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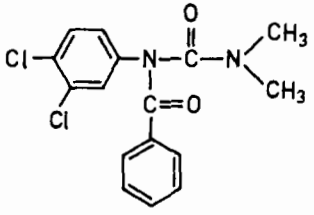

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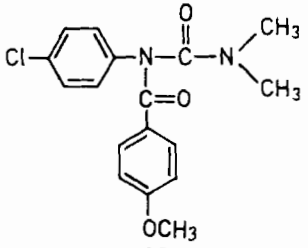

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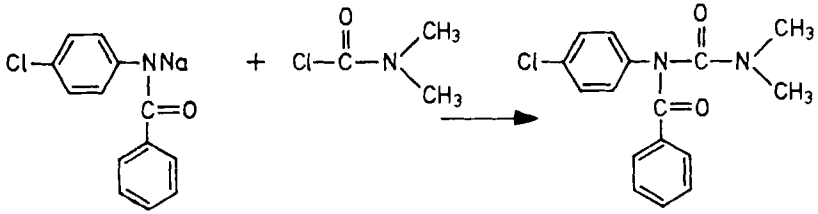
They are prepared by the condensation of dimethylcarbamoyl chloride with the sodium salt of the respective substituted benzanilide, (Poignant, 1960; Pillon and Poignant, 1965).



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Phenobenzuron (**35**) is a crystalline compound very slightly soluble in water and readily soluble in acetone and ethanol.

Applied at a rate of 2–3 kg active ingredient/ha it is a selective herbicide in rice, cotton, soybean, flax and perennial cultured plants, as in orchards and vineyards.

The 4-chlorophenyl analogue (monomarc, **34**) is selective in wheat, the 3,4-methoxybenzoyl-3-(4-chlorophenyl) analogue (metoxymarc, **36**) in flax.

Phenobenzuron and its analogues, applied at the recommended rate, are persistent for 10–12 months in the soil.

Phenobenzuron is nontoxic, its acute oral LD_{50} for rats being 5000 mg/kg, its acute dermal LD_{50} for guinea-pigs more than 4000 mg/kg.

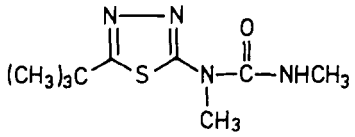
The selectivity of these compounds can be attributed to several factors. Because of their acyl group, their mode of penetration into the plants differs substantially from that of the other urea herbicides. The acyl group is slowly split off in the soil, resulting in diuron and monuron, and they exert their action in these forms. Owing to their poor solubility in water and strong adsorption on the soil, they remain in the upper 10 cm of the soil, and are not toxic to deep-rooted crop plants.

6.13.8 Urea derivatives containing a heterocyclic group

It stood to reason that the substitution of one of the nitrogens of urea for a heterocyclic group would result in new active urea derivatives. As far back as 1955 a patent application was made for the use of thiazolyl urea derivatives as herbicides. Since then various urea derivatives with heterocyclic group substituents have been prepared and investigated for their herbicidal action. Of the 1,2- and 1,3-thiazolyl, the thiadiazolyl and isothiazolyl, the thiadiazolinyl, pyridyl, benzthiazolyl and benzimidazolyl urea compounds, only two groups, 1,3,4-thiadiazolyl- and benzthiazolylureas, have been used so far in agriculture, partly as experimental herbicides.

Of the 1,3,4-thiadiazole derivatives already approved for agricultural use, tebuthiuron, 1-(5-*t*-butyl-1,3,4-thiadiazol-2-yl)-1,3-dimethylurea (**37**); thiazafluron, 1,3-dimethyl-1-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)urea (**38**) and sul-

fadiazole, 1,3-dimethyl-1-(5-ethylsulfonyl-1,3,4-thiadiazol-2-yl)urea (**39**) should be mentioned.



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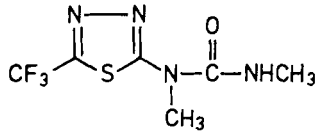

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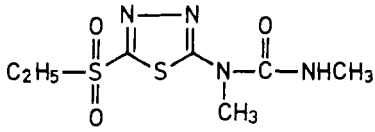

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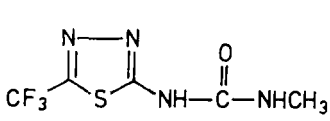
3-Methyl-1-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)urea (MC 2692, **40**), 3-(β,β-dimethoxyethyl)-1-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)urea (HCS 3438, **41**) and 3-(β,β-dimethoxyethyl)-3-methyl-1-(5-*t*-butyl-1,3,4-thiadiazol-2-yl)urea (HCS 3510, **42**) are experimental herbicides of this group. This group contains both total and selective herbicides.

Of the urea derivatives containing the benzothiazolyl group as substituent two compounds are used in agriculture: benzthiazuron, 1-(benzothiazol-2-yl)-3-methylurea (**43**) (Hack *et al.*, 1966) and methabenzthiazuron, 1-(benzothiazol-2-yl)-3,3-dimethylurea (**44**) (Searle, 1956; Hack *et al.*, 1967; Hack, 1968). The former is selective in sugar beet and spinach, the latter in cereals, pea, bean and other crops.



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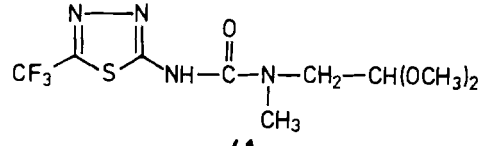

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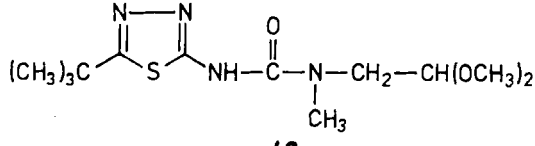

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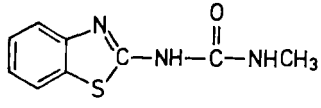

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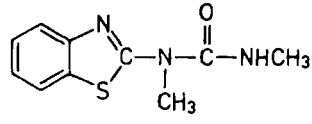

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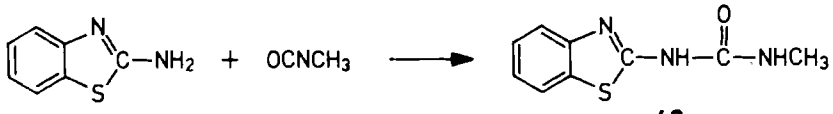
Benzthiazuron and methabenthiazuron are prepared by the condensation of 2-aminobenzothiazole and 2-methylaminobenzothiazole, respectively, with methyl isocyanate (Hack *et al.*, 1966, 1967):



43

Tebuthiuron (**37**) was developed by the Elanco Prod. Co., in the period 1972–1974 (Schwer, 1974).

Applied at rates of 0.58 kg active ingredient/ha it kills all annual grass and broad-leaved weeds. At low rates it is used for selective weed control on sugar cane, pineapple and pastures, while at higher rates it provides total weed control on non-crop areas, highways and industrial areas. High doses also kill woody weeds. *Cyperus* spp. are resistant to tebuthiuron.

Owing to its low water solubility and strong adsorption by the soil, its vertical movement in the soil is slow. It does not move laterally, thus it is used in spot treatment for the control of woody weeds on pastures.

Tebuthiuron is a persistent herbicide, its half-life in the soil being 12–14 months.

A moderately toxic substance, its acute oral LD_{50} for rats and mice is 600 mg/kg, for dogs, cats, chickens and wild fowl more than 500 mg/kg. The dermal LD_{50} for rabbits is 200 mg, without any irritating effect. In thirty-day feeding tests at a level of 1000 ppm chickens did not show toxic symptoms. In three-month feeding test the no-effect level for rats and dogs was 1000 ppm.

The LC_{50} (TL_m) for trout and bluegill is 144 and 112 ppm, respectively; thus, tebuthiuron is not toxic to fish.

In feeding experiments with up to 1800 ppm, no teratogenic effect was observed in rats.

Thiazafluron (GS 29 696, **38**) was developed in 1974–1976 by the Ciba-Geigy AG (Ciba-Geigy, 1976).

Of all the known related derivatives thiazafluron has the highest solubility in water: 2100 ppm at 20°C. It is adsorbed in the soil only to small extent, its leaching index being 16 (1 is very low, 20 very high). Owing to its high solubility in water, it is easily leached into the root-zone of deep-rooted weeds. It is recommended as a preemergence herbicide for total vegetation control at a rate of 3–12 kg active ingredient/ha. Used at a rate of 1.5–3 kg it kills annual weeds sprouting from seed, and at a rate of 3–12 kg it also kills perennial weeds and bushes. *Cyperrus rotundus* is difficult to control.

Thiazafluron is of medium toxicity, the formulation of 50 WP is of moderate toxicity to mammals. The acute oral LD_{50} for rats is 278 mg/kg, that of the formulation is 804 mg/kg. The acute dermal LD_{50} for rats is more than 2150 mg/kg. It does not irritate the skin or the eyes.

It is virtually nontoxic to birds and fish and is non-hazardous to bees.

Sulfadiazole (Bay 6579, **39**), thiadiazolyl urea derivative was developed in 1974 by the Bayer AG and has been further developed by the Chemagro Division of the Baychem Corp. in the USA (Thompson, 1975).

Sulfadiazole is an experimental herbicide for pre- and postemergence application. Used at a rate of 1.5–7 kg active ingredient/ha it is effective against most of the annual and perennial weeds. It is a herbicide for total weed control. When applied postemergence, combination with a contact herbicide is recommended to improve the burn-down effect. Its residual effect is longer than 6 months. The acute oral LD_{50} for rats is 5000 mg/kg.

The herbicide benzthiazuron (**43**) was developed in the research laboratories of the Bayer AG under the code number 60 618 and was introduced on the market in 1966 (Hack *et al.*, 1966).

The compound decomposes under sublimation at 287°C. Its solubility in water at 20°C is 12 ppm. It is slightly soluble in organic solvents.

In pre-emergence application it is used at rates of 3–6 kg active ingredient/ha in turnips. It is strongly adsorbed by the organic substances of the soil, so it is ineffective on peat or mulch soils or other soils with a high proportion of organic material. It is less effective against grass weeds than against broad-leaved weeds.

Combined with lenacil under the name Merpelan®, it is recommended by the Bayer AG, for weed control in turnips. Combination with other pesticides, such as PCNB and disyston, is not recommended.

Its persistence is not exactly known. In the year of treatment cereals, maize and potato can be sown as second crops.

The acute oral LD_{50} for rats is 1250 mg/kg, for mice and dogs 1000 mg/kg. It is not toxic to the skin: doses of 500 mg/kg produce no symptoms. A dose of 50 mg has a slightly irritating effect on the conjuntiva of rabbits.

Methabenzthiazuron (**44**) was developed in 1968, two years after the introduction of benzthiazuron, under the code number "Bayer 74 283" by the Bayer AG, (Hack, 1968, 1969; Bagnall and Jung, 1968).

It is effective for the control of seed-propagated grass and broad-leaved weeds in the seedling and early development stages, but is ineffective against deep-rooted weeds.

It is not recommended for use on light, sandy soils because of the hazard of phytotoxicity. In soils with a proportion of high organic matter it is strongly adsorbed and thus rendered ineffective. Weeds die 14–20 days after treatment. Combined with phenoxy herbicides it has a synergistic action.

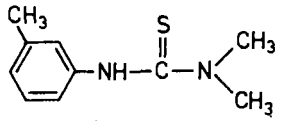
It is nonpersistent in the soil and has no after-effects on subsequent crops. It is incompatible with urea and with liquid fertilisers.

The acute oral LD_{50} of methabenzthiazuron for rats and guinea pigs is 2500 mg/kg, for rabbits, cats and dogs more than 1000 mg/kg. Its acute dermal LD_{50} for female rats is more than 500 mg/kg.

Its other toxic properties are the same as those of benzthiazuron. It is toxic to bees (Beran, 1970).

6.13.9 Thiourea derivatives

In addition to ureas, several thiourea derivatives are described in the patent literature; generally, however, they have weak effects. Of the experimental herbicides, 1,1-dimethyl-3-(3-methylphenyl)thiourea (methiuron, **45**) and 1-(4-chlorophenyl)-3-methyl-3-phenyl)thiourea (Ortho 11413, **46**) seem to be promising.



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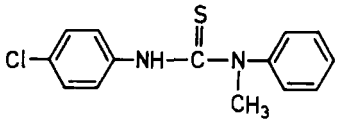

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6.13.10 Action and mode of action of urea herbicides

Urea herbicides are generally absorbed through the roots of plants and translocated *via* the transpiration system. After penetrating the cuticule, they are translocated by diffusion from the aqueous phase of the apoplast system into the interior of the leaves, but in general are not basipetally translocated from the leaves (Jones and Foy, 1972). Absorption and translocation of urea herbicides have been investigated by many research workers on different plant species, mostly by radiotracer methods. For reference, the following publications are cited: Bucha and Todd (1951), McGall (1952), Muzik *et al.* (1954), Fang *et al.* (1955), Crafts and Yamaguchi (1960), Crafts (1962, 1967). Urea derivatives are taken up by the plants at different rates and in different quantities, and the amounts accumulated also vary from compound to compound. Differences in uptake and translocation according to plant species contribute to the selective applicability of urea herbicides, though not decisively.

After treatment characteristic phytotoxic symptoms are developed by plants sensitive to urea herbicides. Acute symptoms are manifested by the withering of leaf tips and leaf edges, chlorosis and water-soaked blotches. Subsequently, chronic symptoms, such as increased chlorosis, wilting, plant-growth reduction, defoliation, and stem collapse are seen. The process ends in the complete decay of the plant (Bucha and Todd, 1951; Minshall, 1954, 1957).

A purely apoplastic movement of monuron is inconsistent with the fact that the site of phytotoxic action is within the chloroplast, and that to reach it the herbicide must penetrate the protoplasm and the plasmalemma surrounding the chloroplast (Ashton and Crafts, 1973).

The passive diffusion of monuron through the roots has been experimentally proved by Donaldson (1967) who demonstrated by histoautoradiography that almost all monuron taken up is located in the cell walls.

Monuron absorbed by the leaves is uniformly distributed in the leaf tissues, accumulating in the vascular tissues, but it is translocated only into the xylem (Pickering, 1965).

The absorption and translocation of linuron and monolinuron in sensitive and tolerant plants have been investigated by several research workers (Börner, 1964, 1965b; Knake and Wax, 1968; Taylor and Warren, 1968; Moody *et al.*, 1970). Experiments showed that the selective action is due to different degrees of absorption and translocation.

Investigations of the absorption and translocation of chloroxuron by Aebi and Ebner (1962) gave similar results.

In the case of fluometuron the herbicide was absorbed in the same measure by sensitive and tolerant plants. Thus, in the case of fluometuron a different translocation and metabolism may explain the selectivity.

Voss and Geissbühler (1966) compared the translocation of fluometuron, chloroxuron and metobromuron and found a considerable difference in the mobility of the three herbicides. Of the labelled compounds taken up from the nutrient solution through the roots of beans, chloroxuron was absorbed mainly in the roots, only a small quantity entering the stalk. Metobromuron and fluometuron were rapidly translocated into the leaves, but metobromuron accumulated in the leaf veins, while fluometuron accumulated in the spaces between the leaf veins.

The development of toxic symptoms caused by urea herbicides depends on the particular herbicide, on the species of the plant and the application rate. Generally, the action of urea herbicides is not rapid, though after the application of higher doses chlorotic symptoms develop within a few days in sensitive plants such as beans. The death of the plants usually occurs within weeks.

After treatment with monuron, the needles of red pine *(Pinus resinosus)* showed no changes for 30 days, chlorosis appearing only after 40 days (Sasaki and Koslowski, 1961).

Urea herbicides, in addition to causing the degradation of photosynthetic tissues, inhibit root growth. Muzik *et al.* (1954), and Voderberg (1961) describe this action of CMU and monuron.

Grant (1964) and Jordan and co-workers (1966) reported on other aberrative effects on nonphotosynthetic tissues, such as growth inhibition and abnormal meiotic cell formation.

Monuron and linuron cause chromosome aberration in the C_1 generation of barley (Wuu and Grant, 1966).

On the basis of a great number of research reports and several excellent reviews, a fairly clear if not unequivocal picture can be formed of the mode of action of urea herbicides. Of the reviews the following should be mentioned: van Overbeck (1964), Moreland (1967, 1969), Ashton and Crafts (1973), Corbett (1974).

Urea herbicides inhibit photosynthesis in plants. If the photolytic process, under normal conditions proceeding by the action of light in the chloroplasts, is permanently inhibited because of an inability to function or the decay of chlorophyll the plant starves.

During photosynthesis in green plants two photoreactions take place (Vernon and Avron, 1965). By the action of light chlorophyll absorbs electrons and attains an excited state. The energy of the excited chlorophyll electrons is expanded on the reduction of various coenzymes, quinones and cytochrome components. In the electron transport chain of the photosynthetic phosphorylation process part of the energy is used for ATP formation. Oxygen is formed as a by-product. This process is photoreaction II. It should be noted that the reaction mechanism according to which oxygen is generated, is still unknown.

In photosystem II electrons that lost part of their energy during photoreaction I take up energy again, the energy being used for the reduction of NADP (nicotinamide adenine dinucleotide diphosphate) in photoreaction II. $NADPH_2$ formed is a stable transport metabolite of hydrogen.

The electron transport chain process of photoreactions I and II is noncyclic photophosphorylation. Cyclic photophosphorylation, which may proceed in the case of oxygen deficiency and can be considered as a "shortcircuiting" of electron transport, presumably does not play a role in the normal photosynthesis energy storing of the cells.

The final steps of photosynthesis, the so-called "dark" reactions can also take place in complete darkness.

During photoreaction II, TPN (triphosphoridine nucleotide) is reduced by extracyclic electron transport to TPNH. With the energy of ATP, TPNH reduces CO_2 by combination with hydrogen, and carbohydrates are formed in several steps, with the intermediation of various enzymes.

Cooke (1955) reported first that the sugar content of plants treated with monuron greatly decreased, and attributed this finding to a correlation of the phytotoxic effect of monuron with photosynthesis.

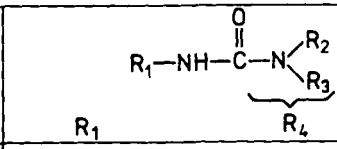
Photoreaction II, the photolysis of water accompanied by O_2 formation (Hill reaction), can be catalysed by isolated chloroplasts in the presence of synthetic electron acceptors, such as ferricyanides or reducible dyes. It can easily be seen if a compound has an inhibiting effect on this step of photosynthesis through measurement of the oxygen produced.

The Hill reaction inhibiting effect of herbicides is given numerically as the molar concentration (I_{50}) or the logarithm of the reciprocal of the molar concentration (pI_{50}) causing 50% inhibition of the reaction.

Moreland (1969) investigated the Hill reaction inhibiting effect of a few aryl and alicyclic dimethylurea herbicides (Table 6.8) and found a fairly good correlation of the pI_{50} values and the actual herbicidal activities.

Moreland concluded with respect to the relationship between the structure and the action of Hill reaction inhibiting herbicides that they establish multipoint attachment with the active centre of chloroplasts by means of hydrogen bonds, thus

Table 6.8
Inhibition of Hill reaction by aryl and alicyclic ureas (Moreland, 1969)

Designation		pI_{50}*
Fenuron		5.00
Monuron		
Diuron		6.75
Neburon		6.85
Chloroxuron		6.80
Cycluron		5.25
Noruron (Norea)		5.80
Linuron		6.70

*pI_{50} — log of the reciprocal of the molar concentration causing 50 inhibition

blocking their function. To exert this action, the amide or imino hydrogen must be free or sterically unhindered. A change in the molecular structure, for example, the substitution of hydrogen for an alkyl group, reduces the tendency towards hydrogen bond formation, and this results in reduced inhibitor activity. If the inhibiting effect can be easily reversed, for example, if the herbicide can be washed off with water, this indicates weak hydrogen bonds. Groups able to form hydrogen bonds are amide hydrogens, imino hydrogens, carbonyl oxygens, ester oxygens and azomethine nitrogens in triazines (see Section 6.14: *s*-triazines), benzimidazoles and

imidazoles. The functional structure of the proteins and nucleic acids of biological systems is also held together by such hydrogen bonds.

The conclusions of Moreland seem to be inconsistent with the results of Good and Izawa (1973), according to which thiourea derivatives, which easily form hydrogen bonds, have a weak inhibitory effect. Moreover, they found that triazines and chloroacetanilides do not form hydrogen bonds with carbonyl oxygens.

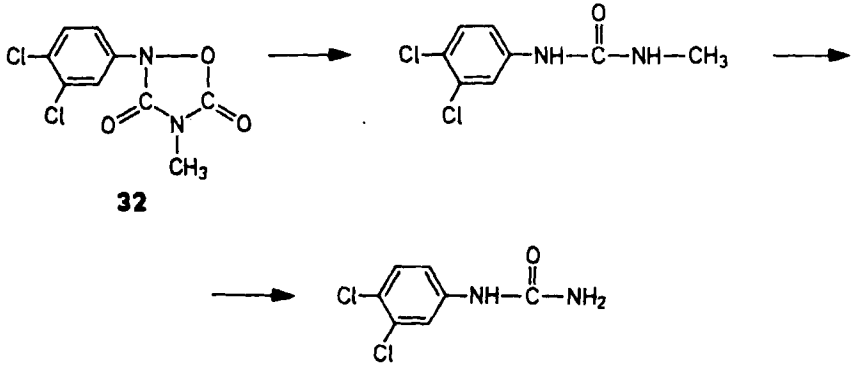
The picture is further complicated by the fact that several commercial herbicides do not inhibit the Hill reaction *in vitro*, and at the same time, there are compounds that strongly inhibit the Hill reaction, but have no phytotoxic activity.

The lethal mechanism of the plant-killing effect of urea herbicides is not yet known. Though death by "starving" through the inhibition of photosynthetic processes seems to be a convincing explanation, it does not explain several experimental observations.

A new so-called "damage" hypothesis has been developed on the basis of earlier experiments of Ashton (1965) and recent experiments of Stanger and Appleby (1972). According to this hypothesis, urea herbicides not only block the reduction of chlorophyll molecules activated by light but also inhibit the formation of $NADPH_2$. Owing to the inhibition of $NADPH_2$, carotenoid pigments are oxidised and rendered unable to reduce the oxidised chlorophyll molecules. Thus, the photosynthesis system of the plant becomes permanently damaged, and death is brought about by the combined effect of the inhibition of photosynthesis and the irreversible injury to the system.

It has been established that fluometuron at concentration of 50 μmole/dm^3 uncouples plant mitochondria (McDaniel and Frans, 1969); however, as it reduces the light-dependent growth of *Chlorella* at a concentration as low as 4 μmole/dm^3, it should be considered primarily as an inhibitor of photosynthesis (Kratky and Warren, 1971).

Jones and Foy (1972), investigating the mode of action and degradation of methazol, found that cotton metabolises the active substance in two steps. In the first step, 1-(3,4-dichlorphenyl)-3-methylurea, very similar to diuron, is formed, and this is demethylated in the second step to 1-(3,4-dichlorophenyl)urea:



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This degradation pathway makes it very likely that methazol is the precursor of the Hill reaction inhibiting 1-(3,4-dichlorophenyl)-3-methylurea, which is the carrier of the herbicidal action.

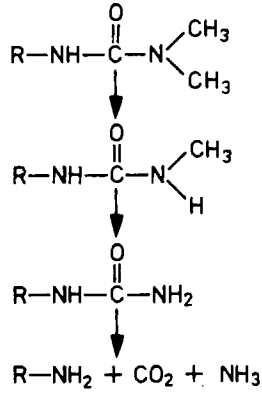
Similarly, meturin can also be considered as a precursor (Baskakov, 1973; Stonov *et al.*, 1974). Though the herbicide has a greater effect in light than in the dark, it has no effect on photoreactions I and II in isolated spinach and pea chloroplasts. It is assumed that meturin is metabolised within the plant to a compound or compounds inhibiting photosynthesis.

The Hill reaction inhibiting effect of herbicides of thiourea type is small compared to that of the C=O analogues. Moreland (1969) presumes that a C=S→C=O conversion takes place within the plant, or that thioureas have a completely different mode of action.

Urea herbicides reaching the natural environment are gradually decomposed over a shorter or longer period, the steps and the rate of decomposition depending on the stability of the molecule and on the medium. The active substance reaching the soil surface or into water is chemically decomposed by the action of the ultraviolet radiation of the sun or of the acid or alkaline components of the soil. Compounds absorbed by the plants are metabolically degraded, and compounds in the soil are similarly metabolised by the microflora and microfauna of the soil.

Urea compounds are predominantly soil-applied herbicides and are thus metabolised in the microflora of the soil (Hill *et al.*, 1955; Sheets and Crafts, 1957; Hance, 1967a, 1967b; Geissbühler, 1969). In soils with intensive microbial activity degradation is more rapid.

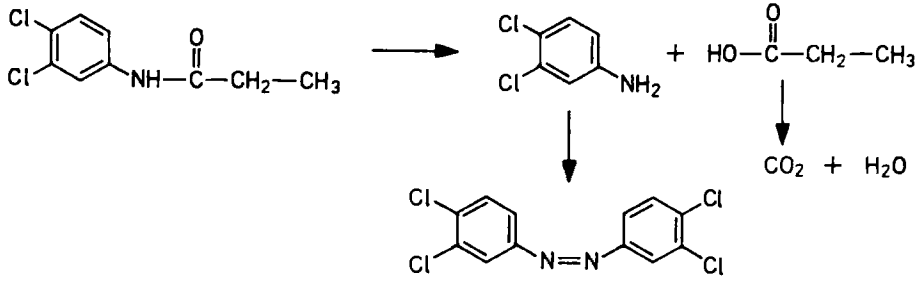
The microbial degradation of 3-aryl-1,1-dimethylurea herbicides proceeds by stepwise demethylation into 3-aryl ureas, which are then decomposed into aryl amines, carbon dioxide and ammonia according to the following scheme:



The microbial degradation of 3-aryl-1-methyl-1-methoxyureas, of monolinuron and linuron, for example, proceeds in a very similar way (Börner, 1965b, 1967).

The aniline derivatives formed are the end-products of microbial degradation. Bartha and Pramer (1967) found in experiments that the microbial degradation of

3,4-dichloropropionanilide (propanil) *in vitro* does not terminate with the formation of 3,4-dichloroaniline, but that the latter is oxidised in a way similar to the microbial route, to 3,3',4,4'tetrachloroazobenzene:



The same potentially carcinogenic compound can be formed during the microbial degradation of diuron, neburon, linuron, methazole and Proban.

Field tests with monuron, linuron and with diuron (Belasco and Pease, 1969; Maier–Bode, 1971) unequivocally showed that under natural conditions no azo compounds are formed in the soil in analytically detectable quantities; neither could they be detected by gas chromatography (detectability 0.01 ppm) in cultured crops grown on soils treated with urea herbicides.

Thus, the application of urea herbicides does not actually involve the danger of the formation of azo compounds in the environment or in food.

On the basis of the results obtained so far in the investigation of the action mechanism of urea herbicides, the fundamentals of their biochemical mode of action can be considered as elucidated, though their sites of action and the chemical reactions involved are obviously still to be resolved.

The causes and the mechanism of their selectivity cannot be uniformly and generally explained.

In all probability it can be accurately stated that by each bioactive compounds that exist or can be prepared entering the various living plant or animal organisms a different biological effect may be produced.

Some of the urea herbicides are compounds with total action. The precondition of their total herbicidal effect is their presence during the germination or active growth stages of the plants in absorbable form with adequate quantity in the absorption zone of the roots. In the exertion of total action, one factor is the irreversible injury caused to the plant, the other the plant's inability to metabolise these herbicides into harmless compounds at a sufficient rate.

Several factors play a role in the selectivity of urea herbicides with selective action.

The cause in some of the cases is of a physical character. Herbicidal compounds poorly soluble in water are located in the upper layer of the soil, and are thus absorbed by the shallow-rooted weeds, which are killed while they do not reach the roots of the deep-rooted crop plants, which can grow unhindered. Translocation proceeding at different rates in tolerant and sensitive plants and the detoxication of the translocating herbicide through deposition in parts of the plant, such as the cell

walls, where it does not interfere with metabolic processes have already been mentioned in the section dealing with the mode of action.

Ultimately, the biochemical activity of the plants plays a very important role in selective action.

The life-functions, development and detoxication processes of plants are regulated by their specific enzyme systems. The enzymes performing detoxication — conjugation, dealkylation, hydroxylation, hydrolysis, etc. — and the activity of the individual enzymes vary according to the plant species. Because of this, the metabolic activity of the plants and consequently their tolerance to various urea herbicides are qualitatively and quantitatively species-specific.

It is hoped that a better knowledge of the enzyme systems and enzymatic processes of weeds and crop plants will make possible the future planning and preparation of "tailored" herbicide molecules. Meanwhile, pesticide chemists must content themselves with analogy and trial and error methods in the preparation of new active molecules.

At the normal rates of application urea herbicides do not interfere with the life of microflora. High rates may cause a transitory thinning of the population; however, in evaluating this it must be taken into consideration that the absence of weeds may also contribute to the decrease in population (Kruglov *et al.*, 1973).

Plants of higher order metabolise urea herbicides in steps similar to those occurring in microorganisms, but the process is slower. The metabolic activity of each individual plant species is also different, the time required for the metabolic reactions as well as the metabolites will therefore be different. As mentioned, this is one of the very reasons for selectivity towards sensitive and tolerant plants.

For example, in the leaves of cotton, highly tolerant to diuron, 50% of the diuron taken up was present in the form of nontoxic 3-(3,4-dichlorophenyl)urea, while no unchanged diuron was found. On the other hand, in the leaves of soybean, sensitive to diuron, 48% of the diuron taken up was found under identical experimental conditions in the form of phytotoxic 3-(3,4-dichlorophenyl)-1-methylurea and 9% as unchanged diuron (Van Oorschot, 1965; Smith and Sheets, 1967; Swanson and Swanson 1968). Field experiments gave similar results. In cotton leaves the main metabolite was 3-(4-chlorophenyl)urea, in soybean leaves 3-(4-chlorophenyl)-1-methylurea. Metabolism proceeded in cotton leaves as far as 4-chloroaniline, while this final metabolite could not be detected in soybean.

A microsomal enzyme system able to demethylate monuron, diuron and fluometuron can be isolated from the leaves of cotton. The cofactors are NADP or NADPH and molecular oxygen (Frear, 1968; Frear and Swanson, 1969).

Of the 3-methyl-3-methoxyureas, it has been shown that linuron is decomposed scarcely or not at all in sensitive plants, while it is demethylated and demethoxylated in tolerant species (Börner, 1964, 1965; Nashed and Ilnicki, 1970). Metobromuron is metabolised in potatoes to 3-(4-bromophenyl)urea (Voss and Geissbühler, 1966).

The final decomposition products of dealkylated and/or dealkoxylated urea herbicides, the respective anilines are not stable but are further transformed by the enzyme systems of the plants by oxidation or conjugation (Onley *et al.*, 1968).

In recent experiments mass spectrography has been used to identify 3-(2-hydroxy-4-chlorophenyl)-1,1-dimethylurea and 3-(2-hydroxy-4-chlorophenyl)-1-methylurea in bean leaves as metabolites of monuron (Lee *et al.*, 1973). This is, in the case of urea herbicides, experimental proof of the hydroxylating (oxidative) detoxication process, performed together with N-dealkylation by the microsomal oxidase enzyme system.

In their radiolabelled monuron experiments, Fang *et al.* (1955) also found a conjugate in bean leaves. Unchanged monuron could be liberated from the conjugate by hydrochloric acid.

It was later shown that in this conjugate low molecular weight protein or peptide is linked to monuron (Freed *et al.*, 1961).

Linuron, chlorbromuron and metobromuron too form conjugates in plants of higher order. The original herbicide molecules could be partly liberated from these conjugates, but partly their composition has not been identified. It is assumed that some of these conjugates are not the derivatives of the original herbicide molecule but of its metabolite (Voss and Geissbühler, 1966; Katz, 1967; Nashed and Ilnicki, 1970; Nashed *et al.*, 1970).

Wallnöfer *et al.* (1974) investigated the microbial degradation of some urea herbicides by *Rhisopus japonicus* and showed that this microorganism only demethylates monuron, fluometuron and monolinuron, while from buturon it splits off the 1-methyl-2-propynyl group.

Methabenzthiazuron is metabolised in plants of higher order in a different way than are N-phenylureas. The herbicide absorbed through the roots is rapidly translocated to the leaves where, depending on the species, it is metabolised to a greater or latter extent. In the first step, relatively stable hydroxymethyl-MTB is formed, which is then gradually demethylated at the urea chain. Moreover, conjugated products are formed with glucose, from which the methabenzthiazuron metabolite can be liberated by metabolic reactions (Collet and Pomp, 1974). The following reaction scheme is suggested:

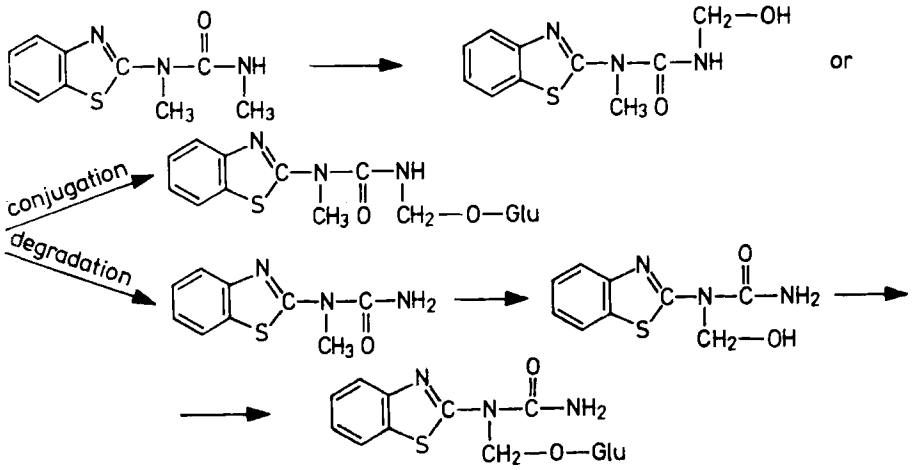


Table 6.9
Metabolic degradation of diuron in animals and humans on the basis of the results of Böhme and Ernst (1965), Hodge *et al.* (1967) and Geldmacher *et al.* (1970)

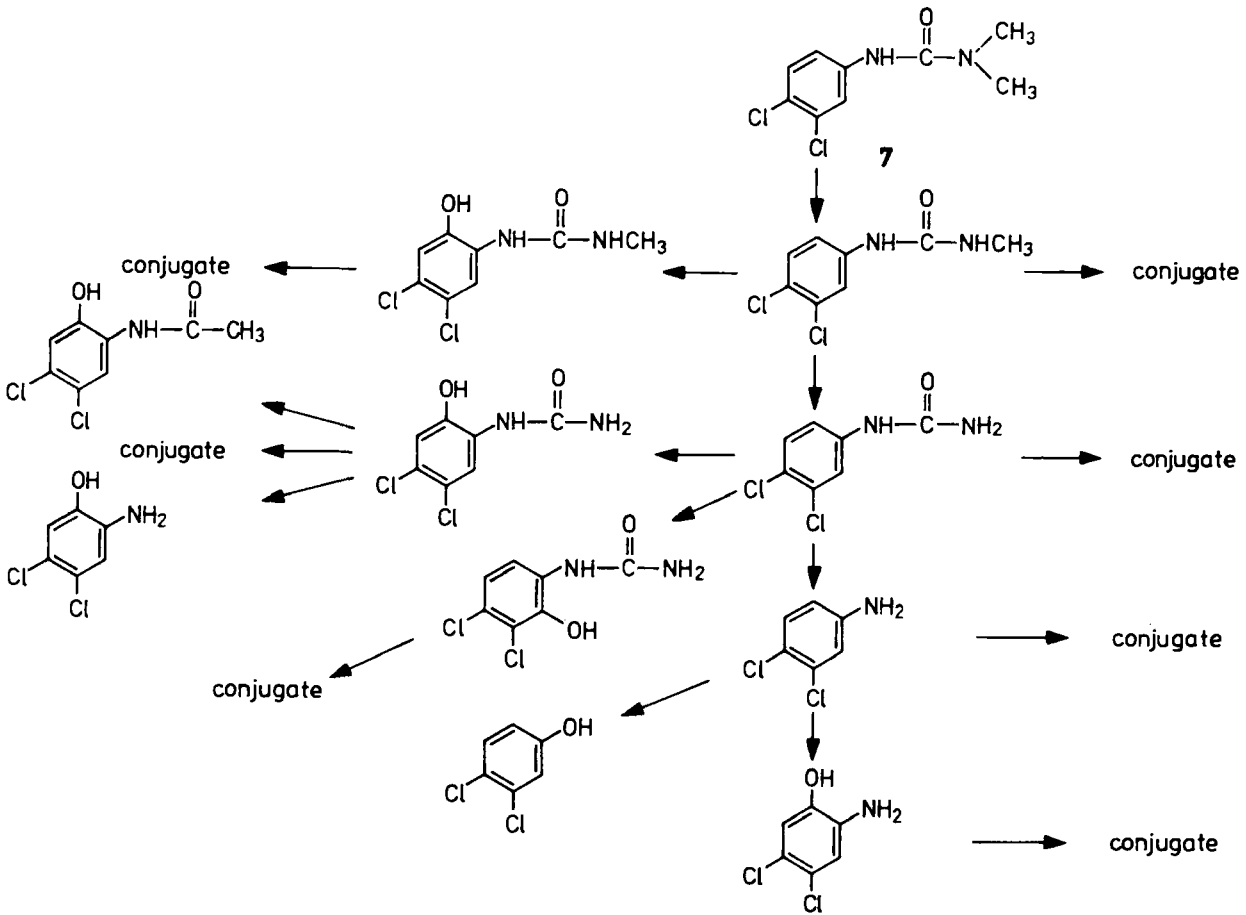


Table 6.10
Metabolic degradation of monolinuron in rats and dogs according to Böhme and Ernst (1965) and Ernst and Böhme (1965)

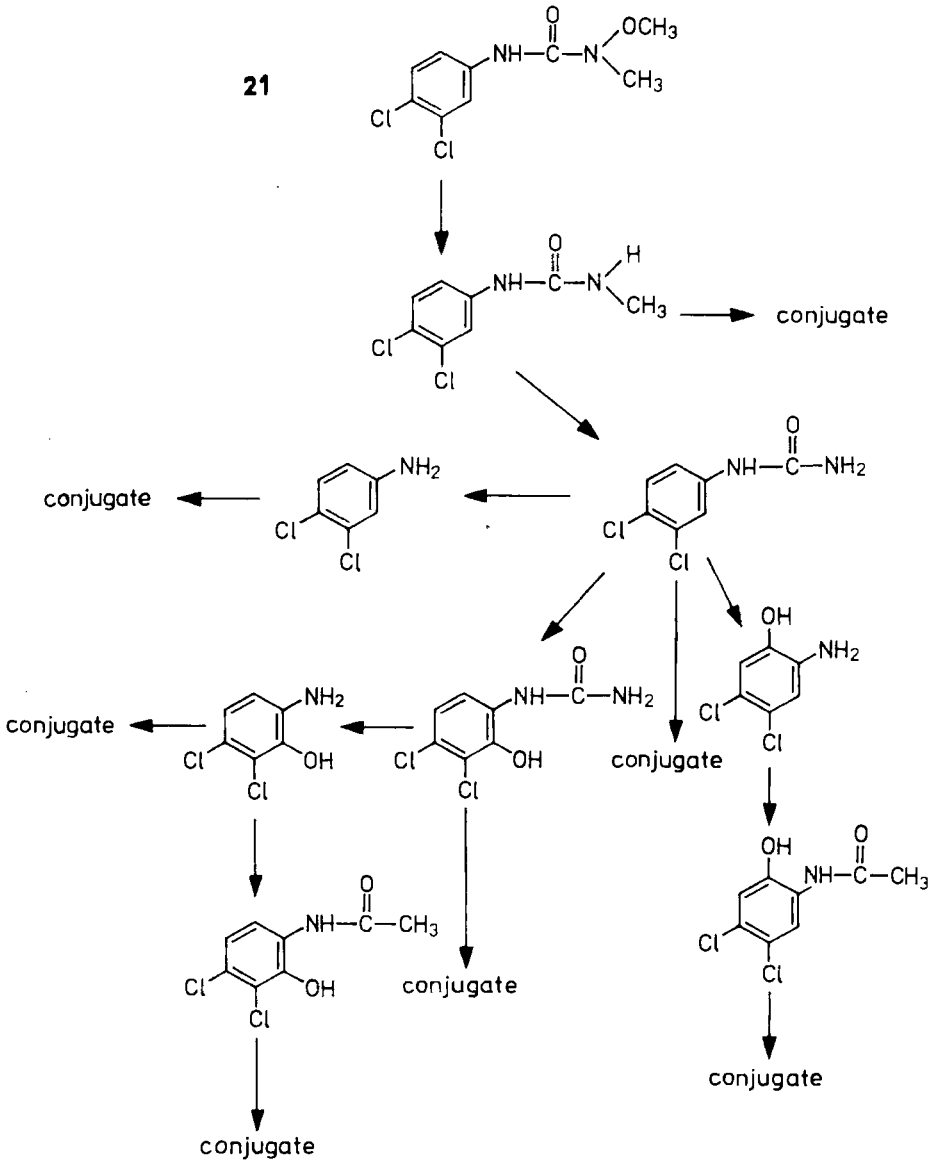
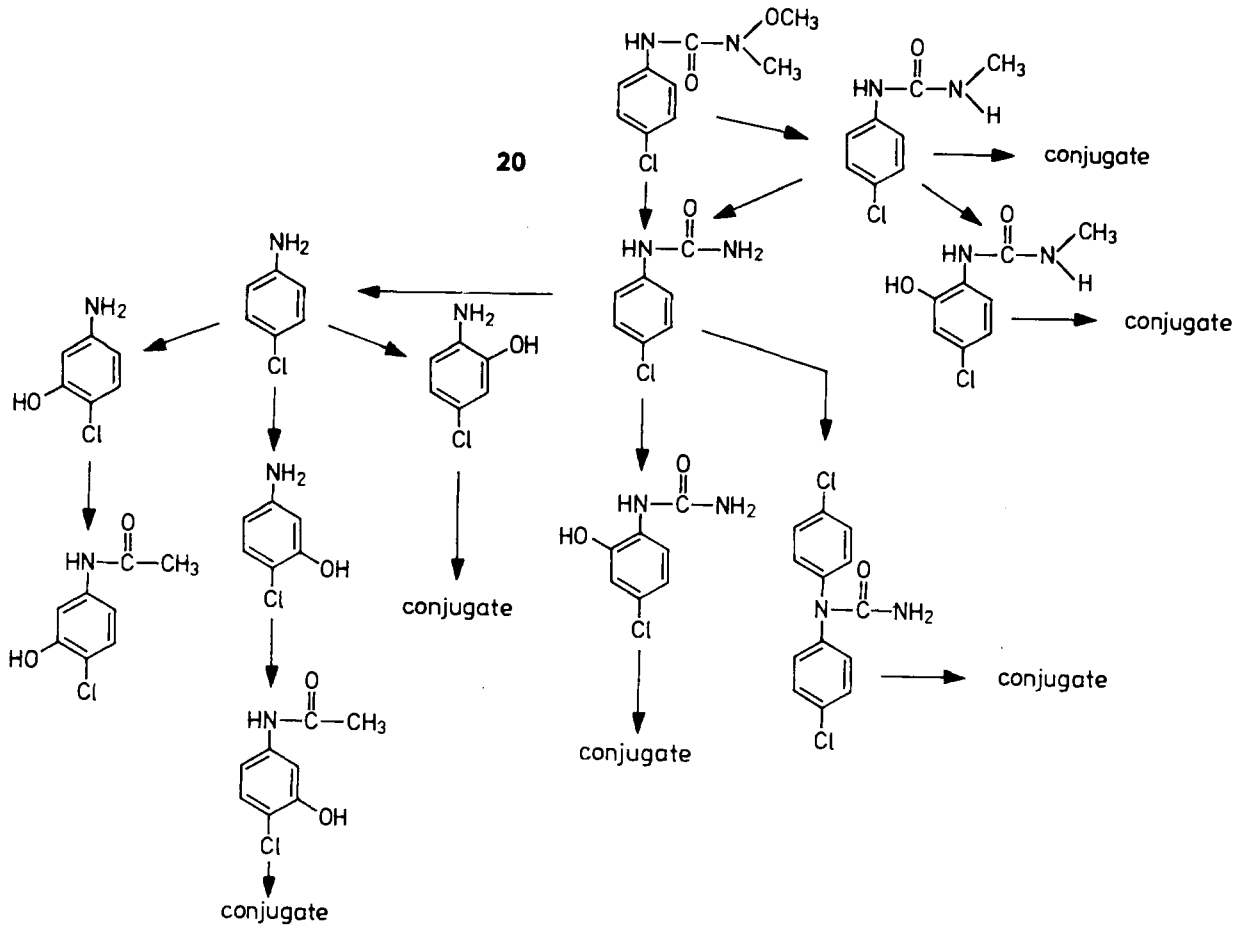


Table 6.11
Metabolic degradation of linuron in rats according to Böhme and Ernst (1965) and Ernst and Böhme (1965)



The photolytic degradation of urea herbicides also proceeds in several steps. In addition to hydrolysis reactions, degradation products hydroxylated in the ring are formed in photonucleophilic reactions. In the case of monuron and linuron, hydrolysis is even preceded by the exchange of the chlorine atoms of the ring for hydroxyl groups (Rosen *et al.*, 1969; Crosby and Tang, 1969).

The photodecomposition of methazol proceeds in several elaborate steps. The decomposition products comprise two isomeric benzimidazolinon derivatives, which are not phytotoxic but are very toxic to mammals (Ivie *et al.*, 1973).

Paulson (1975) gave a clear overall picture of the metabolic fates of urea herbicides in animal organisms.

Mammals do not accumulate urea herbicides introduced orally. The dose administered is excreted within a few days in the urine and the feces, partly in unchanged form, partly in the form of metabolites. As in plants the main pathways of metabolism are demethylation, demethoxylation, ring hydroxylation and conjugation, although animals metabolise the compounds more rapidly.

We do not yet have a quantitative picture of the metabolic processes, because experimental reports are either confined to the detection and identification of the decomposition products formed or, if they also give quantitative data for certain metabolites, these account for only 10–20% of the dose administered.

The metabolism of diuron in rats, dogs and humans was investigated by several workers. The metabolites of diuron, administered as a single dose or over a longer period, have generally been detected and determined in the urine. The main metabolites are 3-(3,4-dichlorophenyl)-1-methylurea and 3-(3,4-dichlorophenyl)-urea. In smaller quantities 3,4-dichloroaniline and several conjugated products have been detected (Böhme and Ernst, 1965; Hodge *et al.*, 1967; Geldmacher *et al.*, 1970).

The metabolic degradation of monolinuron and linuron in rats proceeds, on the basis of metabolites identified in urine, according to a pattern similar to that of diuron. Demethoxylation is followed by demethylation and several ring-hydroxylating and conjugation reactions. The main metabolites are free and conjugated 3-(2-hydroxy-4-chlorophenyl)urea (Böhme and Ernst, 1965).

On the basis of the results, of such experiments, the probable metabolic pathways are shown for diuron in Table 6.9 for monolinuron, in Table 6.10 and for linuron in Table 6.11 (see pp. 687—689).

Recently Tsu Hui *et al.* (1976) investigated the metabolism of chlortoluron, fluometuron and metobromuron in human embryonal lung cell culture. More than 9.5% of the original compounds could be recovered. Oxidative metabolism predominated over hydrolytic metabolism.

The oxidative metabolites of chlortoluron were 1-(3-chloro-4-methylphenyl)-3-formyl-3-methylurea, 1-(3-chloro-4-methylphenyl)-3-formylurea, 1-(3-chloro-4-methylphenyl)-3-methylurea and 1-(3-chloro-4-methylphenyl)urea; the metabolites of fluometuron 1-(3-trifluorophenyl)-3-methylurea and 1-(3-trifluoromethylphenyl)urea; and those of metobromuron 1-(4-bromophenyl)-3-methylurea, 1-(4-bromophenyl)urea and 1-(4-bromophenyl)-3-hydroxy-3-methylurea.

Merzer reports in his summary (1973) that rats metabolise chlortoluron to carboxylic acid derivatives.

According to the experiments of Boyd and Fogelman (1967), radiolabelled fluometuron is excreted by rats in the urine in the form of demethyl derivatives.

In long-term experiments with siduron in dogs, Belasco and Reiser (1969) detected in the urine conjugated metabolites hydroxylated in the ring.

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6.14 *s*-Triazine derivatives

Research on symmetrical triazine derivatives and the screening of these as herbicide compounds began in Bern in 1952 in the research laboratories of the Swiss company Geigy. This was the work that led to the development of one of the most important groups of herbicides known today, the triazine herbicides.

The first publication on this work, describing 2-chloro-4,6-bis(diethylamino)-*s*-triazine and its herbicidal effect, appeared in 1955 (Gast, *et al.* 1955). This compound (chlorazine), which is effective against mono- and dicotyledons, acts by absorption through the leaves. However, its selectivity is rather poor, and it was not put on the market.

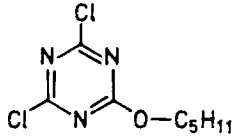
Gast, Knüsli and Gysin reported on 2-chloro-4,6-bis(ethylamino)-*s*-triazine (simazine), one of the most important triazine herbicides even today (Gast *et al.*, 1956).

Since the discovery of triazine herbicides a great number of triazine compounds have been synthesised, primarily by the Geigy Co. (now Ciba-Geigy AG) but more recently by other international concerns as well. As a result, about 20 different herbicidally active *s*-triazines are available today on the international market. It is estimated that in 1980 *s*-triazine derivatives accounted for 20–25% of the world production of herbicidally active substances.

Several thousand publications have dealt with the herbicidal activity, mode of action, metabolism, absorption mechanism, biological and nonbiological detoxication and persistence of *s*-triazine derivatives.

Two important reviews on triazine herbicides have appeared in the scientific literature. The first was written by Gysin and Knüsli (Gysin and Knüsli, 1960); the second was published in Residue Reviews (Günther, 1970).

Chlorazine [2-chloro-4,6-bis(diethylamino)-*s*-triazine], already mentioned as the first *s*-triazine described, is a total herbicide. Some triazine derivatives with a contact effect are also known. Typical contact herbicides are 2,4-dichloro-6-butoxy-*s*-triazine (**1**) and 2,4-dichloro-6-propylamino-*s*-triazine (**2**).



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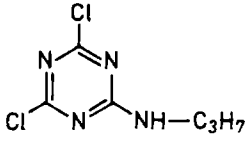


2

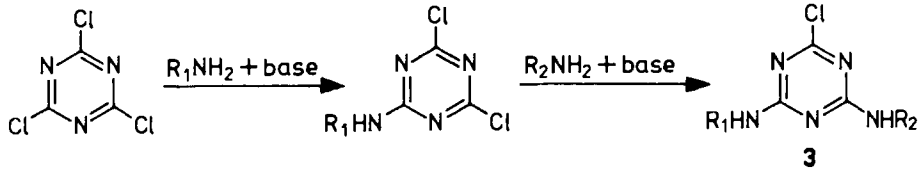
As neither of these two compounds nor 2,4-dichloro-6-alkylmercapto-*s*-triazines is sufficiently stable they have found no general use in practice. The two compounds given above have been described by Koopman *et al.* (1957).

The skeletal structure common to the herbicides based on triazine is the *s*-triazine ring. Two of the three carbon atoms of the ring are substituted with alkylamino groups, while the third is substituted with a chlorine atom, or alkoxy or alkylmercapto groups. *s*-Triazine herbicides with different substituents are also known, although they have not yet attained any great importance. These will be discussed at the end of the chapter.

In the synthesis of all symmetric triazines, the starting material is cyanuric chloride, which is obtained by the trimerisation of cyanogen chloride. Cyanogen chloride is synthesised from hydrogen cyanide and chlorine. Cyanuric chloride is used in large quantities by organic chemical industries as an intermediate in the preparation of dyes, optical bleaching agents, and resins, and to a lesser extent, drugs.

Cyanuric chloride can be considered as a trimeric imide chloride, the chlorine atoms of which can easily be substituted by nucleophilic reactants, such as e.g. alcohols, phenols, mercaptans, thiophenols and amines.

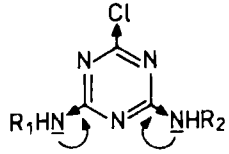
The preparation of 2-chloro-4,6-bis(alkylamino)-*s*-triazines (**3**) from cyanuric chloride and alkylamine is shown by the following reaction scheme:



3

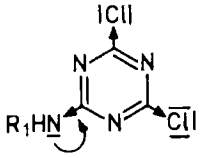
The reactivity of the chlorine atoms of cyanuric chloride decreases stepwise after the additional substitution of each single chlorine atom. It is because the first two chlorine atoms can be exchanged selectively for different amines by careful observation of the appropriate reaction conditions.

The stepwise reactivity of cyanuric chloride can be readily interpreted on the basis of the electron structure. The nitrogen atoms of the triazine ring possess a larger nuclear charge than the carbon atoms and thus deform the π-electron system of the ring and a distorted cycle, in a direction opposite to that of the carbon atoms, is formed:

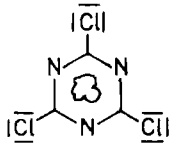


Naturally, this phenomenon weakens the C—Cl bonds and results in the high reactivity of the chlorine atoms of cyanuric chloride.

After the nucleophilic attack by the amine, however, the substituent + T effect of the amine overcompensates the − I effect, and the unshared electron pair of the nitrogen atom of the substituent penetrates the π-electron cloud of the ring. The higher electron density produced thereby decreases the reactivity of the remaining two chlorine atoms:



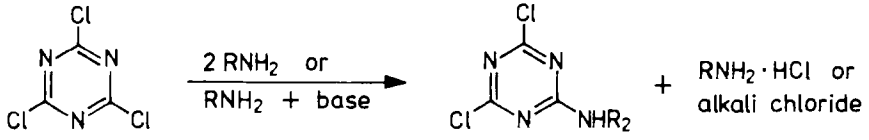
The exchange of a further chlorine atom for an amine enriches the π-electron cloud, with a further electron pair, the density of which already gives a very high stability to the remaining C—Cl bond:



The first chlorine atom of cyanuric chloride reacts instantaneously with the amine present in a homogeneous medium between −15 and 0°C. The substitution of the second chlorine atom requires a higher temperature and longer reaction time. For exchange of the third chlorine atom vigorous and long boiling is required.

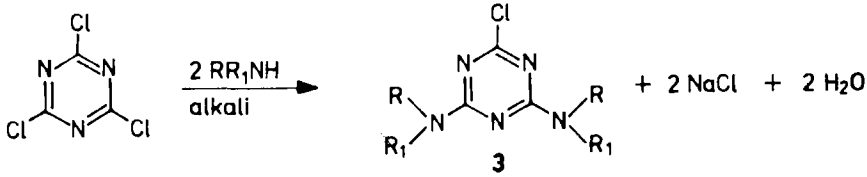
The preparation of 2,4-dichloro-6-alkylamino-*s*-triazines is an important intermediate step in the synthesis of bisalkylamino-*s*-triazines. The selective realisation of this substitution step determines whether the asymmetrically substituted bis(alkylamino)-*s*-triazines can be prepared in the required purity, that is, free of homologues. This is of decisive importance from the point of view of practical weed control.

2,4-Dichloro-6-alkylamino-*s*-triazines can be prepared in the temperature range −20−0°C from cyanuric chloride and the corresponding alkylamine in an absolute solvent (Diels, 1899) or in an aqueous solvent medium (Pearlman and Banks, 1948; Thurston *et al.*, 1951), according to the following reaction scheme:



2,4-Dichloro-6-alkylamino-*s*-triazines are unstable compounds with skin-irritating properties. They are quickly hydrolysed to the hydroxy compound, by the action of atmospheric moisture. Therefore, they are not isolated during the industrial manufacture of 2-chloro-4,6-bis(alkylamino)-*s*-triazines. It is interesting that 2,4-dichloro-6-dialkylamino-*s*-triazines, on the other hand, are resistant to hydrolysis (Thurston *et al.*, 1951). The only 2,4-dichloro-*s*-triazine in commercial use is 2,4-dichloro-6-(*o*-chloroanilino)-*s*-triazine (anilazine, Dyrene®), a leaf fungicide.

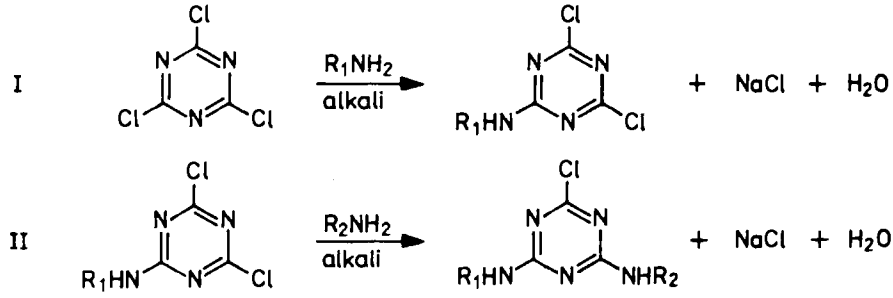
From the practical point of view, the most important group of *s*-triazine herbicides is the 2-chloro-4,6-bis(alkylamino)-*s*-triazines (**3**). These symmetrically and asymmetrically substituted derivatives are manufactured industrially from cyanuric chloride and the corresponding alkyl amines by a single-step synthesis according to the following reaction scheme:



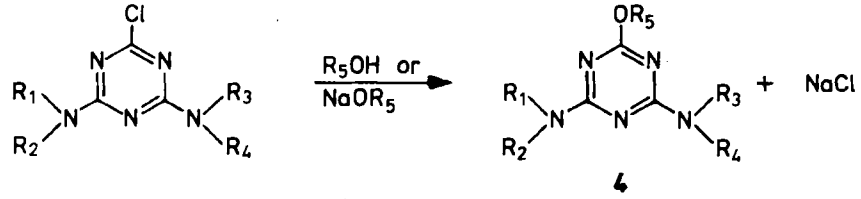
3

For the synthesis of the symmetrical derivatives two equivalents of the same alkylamine are used; for the asymmetric derivatives one equivalent of each of two different alkylamines is used.

For the preparation of the symmetrically substituted 2-chloro-4,6-bis(alkylamino)-*s*-triazines, cyanuric chloride, suspended in the solvent–water mixture, is reacted with the amine in two temperature steps (0–5°C and 40–45°C) in the presence of inorganic acid acceptor (Pearlman and Banks, 1948; Thurston *et al.*, 1951; Gysin and Knüsli, 1959). Asymmetric 2-chloro-4,6-bis(alkylamino)-*s*-triazines (ametryne, sebuthylazine, terbuthylazine) can be synthesised in two reaction steps without the formation of symmetrical analogues. In the first step, the 2,4-dichloro-6-alkylamino derivative is prepared, which is reacted in the second step with the corresponding amine (Gysin and Knüsli, 1959). Asymmetric



2-chloro-4,6-bis(alkylamino)-*s*-triazine containing a small percentage of symmetrically substituted analogues can be synthesised in a single reaction step in a chlorobenzene–water medium (Müller *et al.*, 1964) or in an aqueous surfactant solution as reaction medium (Andriska *et al.*, 1962a). 2-Methoxy-4,6-bis(alkylamino)-*s*-triazines **(4)** can be prepared from the respective 2-chloro-4,6-bis(alkylamino)-*s*-triazines in alcohols (Dubley *et al.*, 1951), acetone (ICI, 1952) or benzene, together with equivalent quantities of sodium hydrogen carbonate or sodium alcoholate:

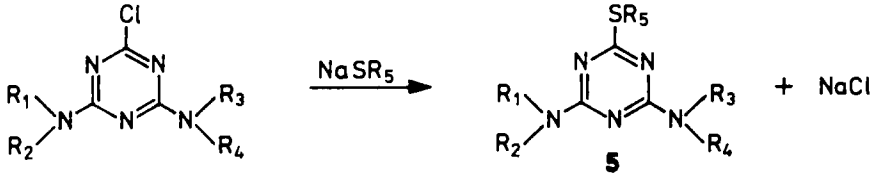


4

2-Methoxy-4,6-bis(3-methoxypropylamino)-*s*-triazine, for example, can be prepared, from the respective chlorotriazine by boiling with sodium methoxide in methanol with a yield of 88% (Hamm and Speciale, 1966).

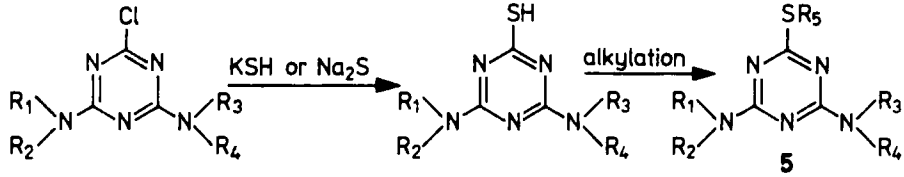
2-Alkylthio-4,6-bis(alkylamino)-*s*-triazines **(5)** can be readily prepared from 2-chloro-4,6-bis(alkylamino)-*s*-triazines by the following synthesis routes.

One method of preparation is from the respective 2-chloro-4,6-bis(alkylamino)-*s*-triazine and sodium mercaptide according to the following reaction scheme (Dubley, *et al.*, 1951; Hamm and Speciale, 1966; Speciale, *et al.*, 1967):

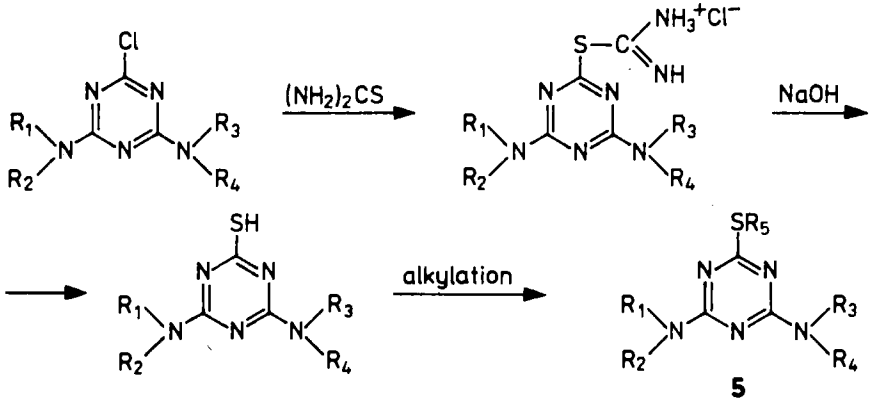


In other processes (Gysin, 1962; Knüsli and Gysin, 1967; Kipping, 1964) the chlorine atom is reacted with alkaline-metal hydrogen sulfide, or with sodium sulfide, to yield 2-mercapto-4,6-bis(alkylamino)-*s*-triazine, containing a free SH group in position 2; this mercapto group is then methylated with the usual alkylating agent.

The synthesis is represented by the following equation:

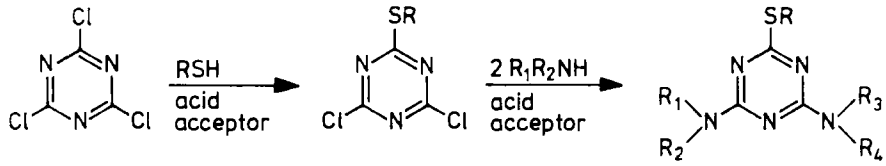


The mercapto group can also be formed *via* the isothiouronium salt (Andriska *et al.*, 1962b; Knüsli *et al.*, 1962). With thiourea 2-chloro-4,6-bis(alkylamino)-*s*-triazines give isothiouronium salt in a practically quantitative yield; this is then decomposed by alkali to the corresponding mercapto compound and dicyano diamide. From this, the 2-mercapto-4,6-bis(alkylamino)-*s*-triazine derivative is obtained with a methylating agent. The reaction scheme is as follows:



The alkylthio group can also be attached directly to cyanuric chloride by alkylmercaptan, in the presence of an acid acceptor (Koopman *et al.*, 1959). The alkylmercapto-dichloro-*s*-triazine obtained is then reacted with two equivalents of amine to give the end-product, according to the following reaction scheme: (see p. 700).

By changing the operational order of the synthesis starting from cyanuric chloride, an end-product of higher purity with improved yield can be obtained.

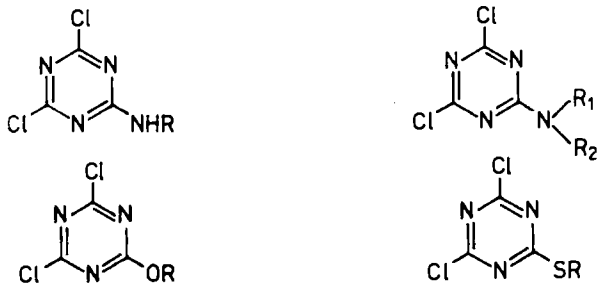


Cyanuric chloride is first reacted with an aliphatic amine in the presence of an acid acceptor, and 2,4-dichloro-6-alkylamino-*s*-triazine, obtained as an intermediate product, is then converted with alkylmercaptan (in the presence of an acid acceptor, or with the alkaline-metal salt of alkylmercaptan) to 2-alkylmercapto-4-chloro-6-alkylamino-*s*-triazine. The end-product is then obtained by the coupling of this intermediate with alkylamine.

The herbicidal effects of the alkyl, dialkylamino and alkoxy 2,4-dichloro-6-substituted *s*-triazines have been described by the research workers of Geigy Co. (French Patent 1 135 848, 1957) and by Koopman *et al.*, (1957).

The fungicidal activity of 2,4-dichloro-6-arylamino-*s*-triazines has been studied by both Geigy Co. and the Ethyl Corporation. In 1953 Grob (Geigy Co., unpublished) studied the effects of 2,4-dichloro-6-(*p*-chloroanilino)-*s*-triazine. In the course of greenhouse investigations no herbicidal action was found, but the compound showed a fungicidal effect on grapes. However, the fungicidal effect was unsatisfactory and, moreover, the compound had a leaf-scorching side-effect. Experiments were therefore discontinued. It is interesting that in spite of the scorching action no satisfactory preemergence herbicidal effect could be attained by increasing the dose used.

However, 2,4-dichloro-6-alkylamino-*s*-triazines, 2,4-dichloro-6-dialkylamino-*s*-triazines, 2,4-dichloro-6-alkoxy-*s*-triazines and 2,4-dichloro-6-alkylmercapto-*s*-triazines have a considerable contact herbicidal effect (Koopman *et al.*, 1957; Gysin and Knüsli, 1956).



All three groups contain compounds that have both some preemergence herbicidal effect and a hormonal effect.

Alkylamino derivatives were in general found to be considerably more active than the dialkylamino derivatives. Of the latter, only the dimethyl- and diethylamino compounds gave some contact effect.

Among the alkoxy derivatives, 2,4-dichloro-6-*sec*-butoxy-*s*-triazine and 2,4-dichloro-6-*sec*-amyloxy-*s*-triazine have a good contact herbicidal activity. Of the

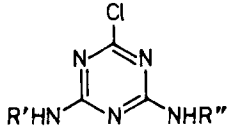
2,4-dichloro-6-alkylmercapto-*s*-triazines, 2,4-dichloro-6-butylmercapto-*s*-triazine was particularly active.

2,4-Dichloro-6-alkylaminoalkoxy- and 6-alkylmercapto-*s*-triazines have a poor chemical stability, and they are also strong skin-irritants. They have therefore not been produced commercially. The chemical stability of the 2,4-dichloro-6-dialkylamino-*s*-triazines is satisfactory, but their selectivity is poor.

6.14.1 2-Chloro-4,6-alkylated diamino-*s*-triazines

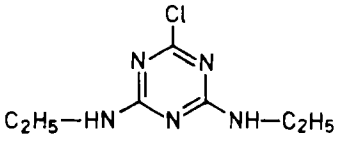
This group of triazine derivatives, the first to be developed, represent even today the triazine herbicides of greatest practical importance. This group has also been studied most extensively from the biological standpoint.

The most important members of the group are characterised by the following general formula:



R' and R" = alkyl

The best known representatives are 2-chloro-4,6-bis(ethylamino)-*s*-triazine (simazine, **6**), 2-chloro-4,6-bis(isopropylamino)-*s*-triazine (propazine, **7**), 2-chloro-4-ethylamino-6-isopropylamino-*s*-triazine (atrazine, **8**) 2-chloro-4-ethylamino-6-*sec*-butylamino-*s*-triazine (sebuthylazine, **9**) and 2-chloro-4-ethylamino-6-*t*-butylamino-*s*-triazine (terbuthylazine, **10**).



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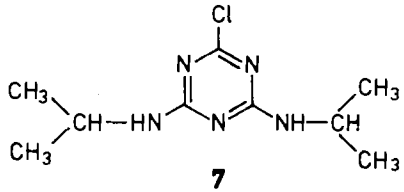

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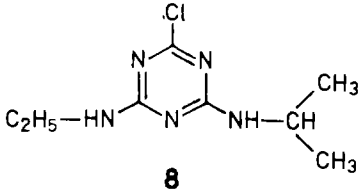

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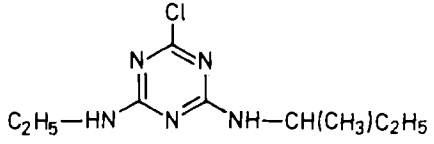

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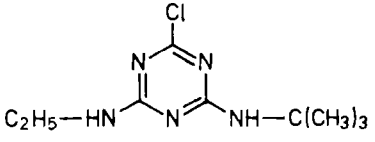

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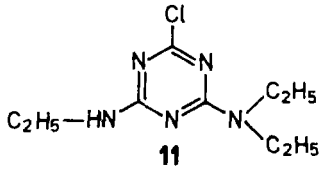
Among the 2-chloro-4-alkylamino-6-dialkylamino *s*-triazines, 2-chloro-4-ethylamino-6-diethylamino-*s*-triazine (trietazine, **11**) and 2-chloro-4-diethylamino-6-isopropylamino-*s*-triazine (ipazine, **12**) have gained practical importance, as have two of the 2-chloro-4,6-bis(dialkylamino)-*s*-triazines, 2-chloro-4,6-bis(diethylamino)-*s*-triazine (chlorazine, **13**) and 2-chloro-4,6-bis(diisopropylamino)-*s*-triazine (siprazine, **14**).



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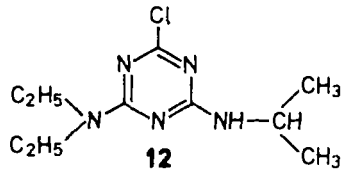

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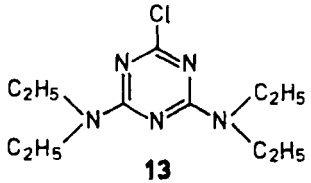

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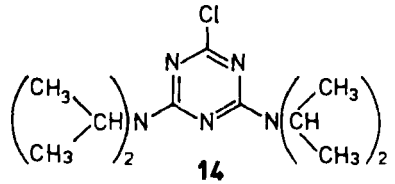

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The activity spectrum of the 2-chloro-4,6-bis(alkylamino)-*s*-triazines is about the same, although the quantitative effects of the individual compounds differ substantially. These relationships were studied most extensively by the Geigy research staff (Gysin and Knüsli, 1956).

Applied to beans *(Phaseolus vulgaris L.)* epicotyls the compounds do not affect the normal growth of the plant. In this they are similar to herbicides of the carbamate and urea types. They do not affect the germination of the seeds, their main effect being manifested on the growing young plants. After normal growth of 10–14 days, the plants begin to exhibit phytotoxic symptoms (chlorosis, leaf wilting, and are completely killed after about three weeks. The development of the action of the compounds is in close correlation with their solubility in water, insofar as the speed of action increases with increasing water-solubility.

Simazine has the lowest solubility in water of the group (5 ppm) and atrazine the highest (70 ppm).

In addition to solubility in water, the lipoid solubility and basicity of the compound play important roles in the development of action, the former influencing uptake through the leaves, the latter colloidal adsorption by the soil. These properties also determine the mode of application of each compound, that is, whether it is applied pre- or postemergence.

Derivatives with good water-solubility can also, in the case of lower soil moisture, reach the root zone of the plants and, being absorbed there, exert their action. However, several other factors contribute to the exertion of a selective action. Primarily responsible are the individual resistances of the plants, for which the factors determining uptake and translocation are still unknown today. The better-known biochemical factors of resistance also contribute.

The two 2-chloro-4,6-bis(alkylamino)-*s*-triazines with identical side-chains, 2-chloro-4,6-bis(ethylamino)-*s*-triazine (simazine, **6**) and 2-chloro-4,6-bis(isopropylamino)-*s*-triazine (propazine, **7**) are absorbed through the root by the plants and translocated to the xylem. Both compounds are taken up to a greater extent by the young plants than by the older ones; this, incidentally, is also characteristic of the other root herbicides. The spectrum of herbicidal action of these two triazine derivatives is almost identical, the differences is that among the cultured plants cereals show a relatively high resistance to simazine, umbelliferous crops to propazine.

Simazine and propazine are the two triazine herbicides with the longest duration of action: In a dose of 10–15 kg/ha the residual life is 2–3 years. Under dry climatic conditions their weed-control activity is unsatisfactory because with their poor water-solubility they are not leached by the low soil moisture to the roots of the weeds.

Among the 2-chloro-4,6-bis(alkylamino)-*s*-triazines with two different substituent side-chains, 2-chloro-4-ethylamino-6-isopropylamino-*s*-triazine (atrazine, **8**) is the most active, and followed, in decreasing order of activity, by 2-chloro-4-ethylamino-6-*sec*-butylamino-*s*-triazine (sebuthylazine, **9**) and 2-chloro-4-ethylamino-6-*t*-butylamino-*s*-triazine (terbuthylazine, **10**).

From the practical point of view, the most important representative of the triazine herbicides is atrazine which, owing to the biochemical resistance of maize, is the most widely used selective herbicide in maize culture. Its weed-control spectrum is the same as that of symmetric 2-chloro-4,6-bis(alkylamino)-*s*-triazines. Characteristic of atrazine, however, is its stronger action on dicotyledonous weeds and its higher efficiency against monocotyledonous perennial weeds resistant to propazine. It is also characteristic of the compounds of this group that they are also absorbed through the leaves and can therefore be used for postemergence application. The postemergence activity can be considerably increased by adjuvants such as mineral oils.

Millet and woody crop plants tolerate terbuthylazine and sebuthylazine. The methylmercapto and methoxy derivatives of terbuthylazine (terbuthyrene, or Caragard®, Geigy) and the methoxy derivative of sebuthylazine (Etazin®, Geigy) are special selective herbicides. From the standpoint of residual effect, these three triazine derivatives are highly persistent herbicides. After a dosage of 10 kg/ha, crop plants sensitive to triazines (particularly cereals) cannot be sown for several years.

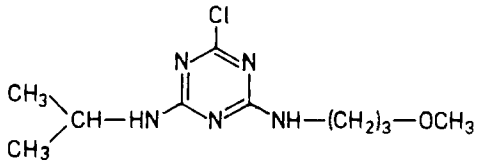
Among the other asymmetrically substituted 2-chloro-4,6-bis(alkylamino)-*s*-triazines, those carrying methyl–ethyl, methyl–allyl, methyl–propyl, ethyl–allyl, ethyl–propyl, isopropyl–propyl and isopropyl–butyl substituents show biological activity. However, they are less active than the derivatives discussed above.

Among the 2-chloro-4-alkylamino-6-dialkylamino-*s*-triazines, 2-chloro-4-ethylamino-6-diethylamino-*s*-triazine (trietazine, **11**) and 2-chloro-4-isopropylamino-6-diethylamino-*s*-triazine (ipazine, **12**) are the most active herbicides. Crop plants tolerant to both compounds are pea, potato, soybean, tobacco, tomato, millet and peanut, when the herbicides are applied in a dose of 2–4 kg/ha.

Their solubility in water is higher than that of simazine but lower than that of atrazine. Their activity and selectivity are lower than those of the compounds of the preceeding group. For these reasons they have not come into general use. As their persistence is lower than that of bis(alkylamino)-*s*-triazines, it is possible that they will be introduced in the future, their action lasting one growing season.

Of the 2-chloro-4,6-bis(dialkylamino)-*s*-triazines, 2-chloro-4,6-bis(diethylamino)-*s*-triazine (chlorazine, **13**) has been investigated most extensively by the Geigy Co. This compound has the best selectivity, though its herbicidal efficiency was found to be relatively low. In oily formulation, very good weed-control results have been attained in cotton by preemergent and, particularly, postemergent treatment without any phytotoxic side effects.

Among the other 2-chloro-4,6-bis(dialkylamino)-*s*-triazines, 4-dimethylamino-6-diethylamino-, 4-diethylamino-6-dipropylamino- and 4,6-bis(diallylamino)-*s*-triazines show considerable activity at a dose of 10 kg/ha. The activity of the compounds decreases with increasing length of the alkylamino side-chain. For example, 2-chloro-4,6-bis(di-*n*-butylamino)-*s*-triazine is already practically an inactive compound (Gysin and Knüsli, 1960).



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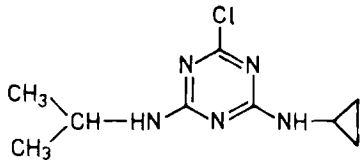

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Two new herbicides, 2-chloro-4-isopropylamino-6-methoxypropylamino-*s*-triazine (methoprotazine, **15**) and 2-chloro-4-isopropylamino-6-cyclopropylamino-*s*-triazine (cyprazine **16**), also belong to the group of 2-chloro-4,6-diamines (Burnside, 1969).

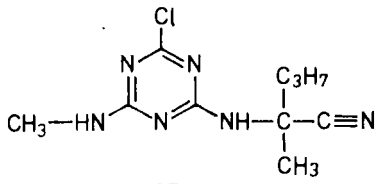
6.14.2 2-Chloro-4-alkylamino-6-cyanoalkylamino-*s*-triazines

Ubrizsy and Matolcsy (1961) were the first to describe 2-chloro-4,6-bis(alkylamino)-*s*-triazines, in which one of the alkyl side-chains carries a cyano substituent. They substituted a cyano group or another polar group in the side-chain in order to obtain herbicides with improved water-solubility which would thus be more suitable for use in areas of low precipitation.

Hughes *et al.* (1966), Chapman *et al.* (1968), Sandford *et al.* (1970) and Morris (1972 and 1974) reported on the derivatives that have attained practical importance.

Active members of the group known so far are 2-chloro-4-(1-cyano-1-methylethylamino)-6-methylamino-*s*-triazine (SD 15 417, **17**), 2-chloro-4-(1-cyano-1-methylethylamino)-6-ethylamino-*s*-triazine (cyanazine, **18**), 4-(1-cyano-1-methyl-

ethylamino)-6-ethylamino-2-methylthio-*s*-triazine (cyanatryn, **19**) and 2-chloro-4-(1-cyano-1-methylethylamino)-6-cyclopropylamino-*s*-triazine (CGA 18 762, **20**).



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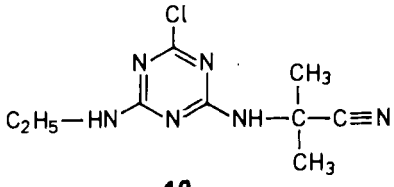

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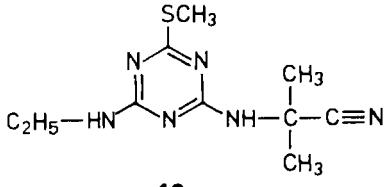

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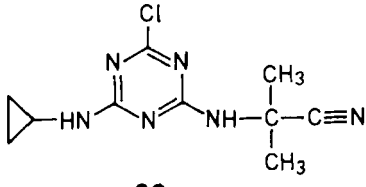

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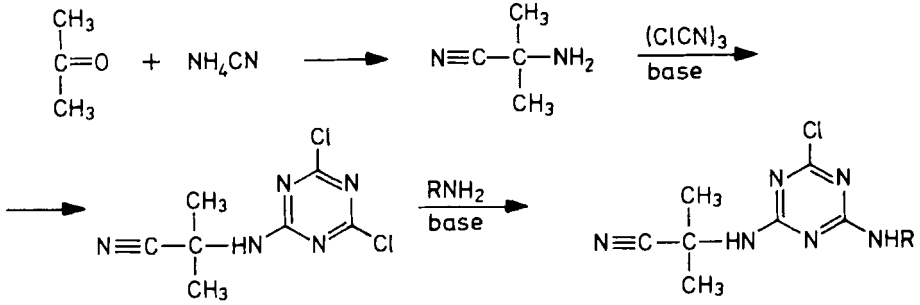
These compounds can be prepared by the processes described starting from cyanuric chloride; only one of the alkylamines is substituted for the respective cyanoalkylamine.

The process has been further developed by Matolcsy and co-workers (Bordás *et al.*, 1973) for the preparation of cyanazine and cyanatryn. In this process ammonium cyanide is added to a suspension of cyanuric chloride in acetone in the presence of an acid acceptor:



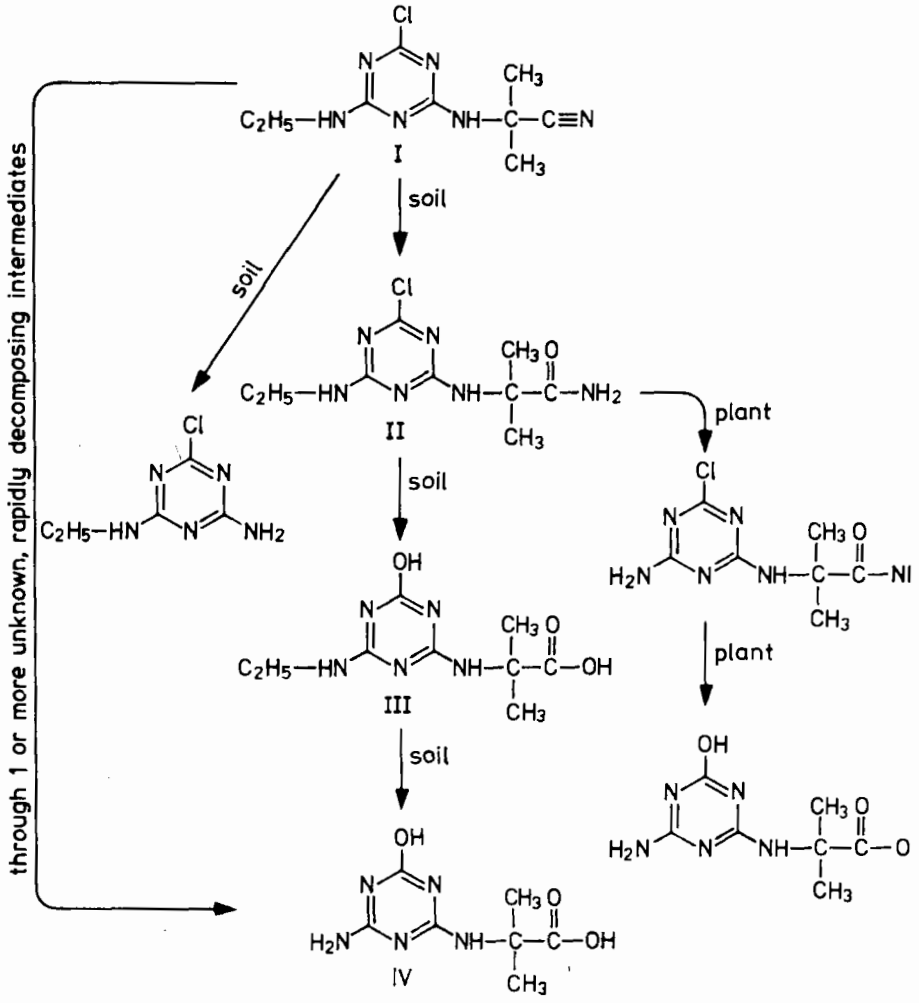
1-Cyanoisopropylamine formed *in situ* in the reaction mixture reacts at the rate of its formation with cyanuric chloride. Thus conversion is complete, although the formation of the amine is actually an equilibrium reaction.

Cyanoalkylamino-*s*-triazines, applied in dose of 0.25–4 kg active ingredient/ha, are herbicides of low persistence which can be used for pre- and postemergence treatment in maize, cereals, legumes and potato. They are not sensitive to heat or light and are hydrolytically stable in neutral solution. Their peroral acute toxicity in rats is 150–600 mg/kg.

Cyanatryn is efficient against aquatic weeds at a concentration of 0.05–0.5 ppm (Haddow and Stovell, 1974).

Cyanoalkylamino-*s*-triazines exert their action by inhibiting photosynthesis. The Hill reaction inhibition index of cyanazine is $I_{50} = 6.6$.

The metabolism of cyanazine in plants has been investigated in Wright's soils by Osgerby (Chapman *et al.*, 1968). The metabolism proceeds in maize and soil according to the following scheme (Beynon, 1972; Wright, 1970):

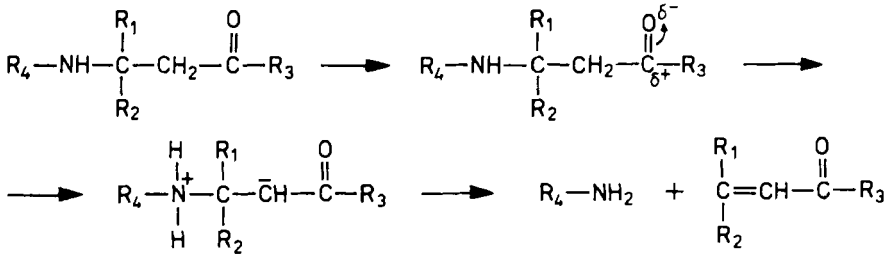


Remarkable in the metabolism shown in the scheme is that, while 2-chloro-4,6-bis(alkylamino)-*s*-triazines in plants and soil are converted first to the hydroxy derivative, the decomposition does not yield the hydroxy derivative until the third

step. The half-life of the decomposing compound in soil at 25°C is 12 days. The residual life of the compound after a treatment of 2 kg of active ingredient/ha is 9–10 weeks.

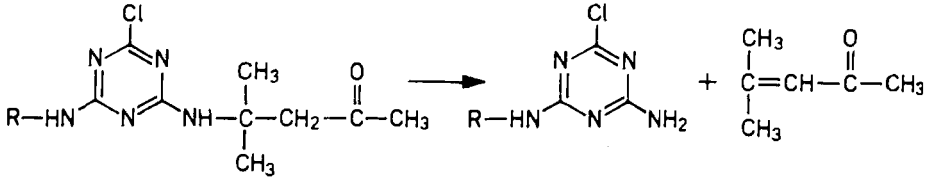
The selectivity can be partly explained by the fact that cyanazine is absorbed to a greater extent by the weeds than by maize (Kern *et al.*, 1975).

In the course of their research work on nonpersistent herbicides of the triazine type, Matolcsy and coworkers (Szatala *et al.*, 1972; Matolcsy, 1973) utilised the known elimination reaction of Mannich bases (3-oxoamines), which involves the formation of amine and unsaturated ketone. This specific reactivity of 3-oxoamines is caused by the $-I$ and $-M$ effects of the carbonyloxygen. Due to the partial positive charge of the carbonyl carbon atom, the adjacent carbon atom acquires an acid character, and with the participition of the nitrogen atom a zwitterion is formed, which furthers the amine elimination:



The reaction is further favoured if the carbon atom adjacent to the nitrogen atom carries substituents, the reaction rate increasing with increasing number and space requirement of the substituents.

On the basis of these findings and using diacetoneamine as amine, Matolcsy and coworkers prepared a series of 2-chloro-4-alkylamino-6-(2'-methyl-4'-oxoalkyl-amino)-*s*-triazines, assuming that in the course of the reaction 2-chloro-4-alkylamino-6-amino-*s*-triazine (known to be inactive) and mesityl oxide were formed in the soil from the active compounds by decomposition.



The derivatives prepared in these experiments have a strong herbicidal action that does not subside in the following year.

Kühle (Bayer Co., 1967) reported on the herbicidal efficiency of similar compounds alkylated only on the nitrogen atom.

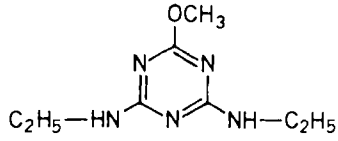
The weed-control properties of 2-chloro-4-alkyl-6-alkoxyamino-*s*-triazines and of their 2-alkoxy and 2-alkylmercapto derivatives have been described by Baskakov (Baskakov, 1973).

6.14.3 4,6-Bis(alkylamino)-2-alkoxy-*s*-triazines

The alkoxy triazines, of which only the methoxy derivatives have found practical use, are also compounds with high herbicidal activity. By the exchange of the chlorine atom for an alkoxy group, compounds with a water-solubility higher by 1–2 orders of magnitude are formed. They are thus readily absorbed through the leaves, and can therefore be used as foliage herbicides for postemergence treatment. Absorbed through the leaves the compounds are easily translocated in the plant.

The activity spectrum of these compounds is different from that of the chloroamine triazines. For example, maize does not tolerate higher doses, nor are they generally tolerated by either herbaceous crops or woody cultured plants. However, there are a few exceptions. They are generally used as total herbicides (Gast and Fankhauser, 1966). The various alkylamino substituents strongly influence their persistence in the soil, some having a persistence of a few weeks, others of several years (Holly and Roberts, 1963; Sheets and Shaw, 1963; Schwitzer and Hauser, 1960).

The most important members of the group are 4,6-bis(ethylamino)-2-methoxy-*s*-triazine (simeton, **21**), 4,6-bis(isopropylamino)-2-methoxy-*s*-triazine (prometon, **22**), 4-ethylamino-6-isopropylamino-2-methoxy-*s*-triazine (atraton, **23**), 4-ethylamino-2-methoxy-6-*sec*-butylamino-*s*-triazine (secbumeton, **24**) and 4-ethylamino-2-methoxy-6-*t*-butylamino-*s*-triazine (terbumeton, **25**).



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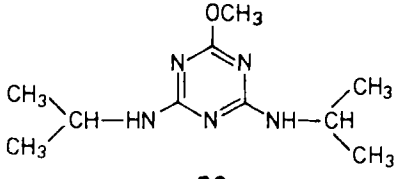

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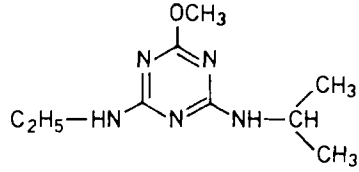

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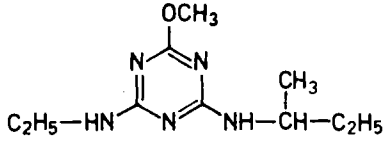

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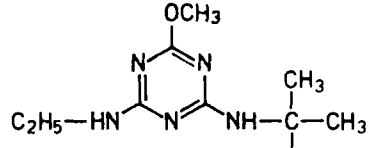

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Simeton, prometon and atraton are compounds used primarily as total herbicides, although atraton can be applied in flax, cotton and maize as a pre- and postemergent selective herbicide with good immediate effect and short duration of action. Simeton and prometon remain active in the soil for several months.

Secbumeton has a good, lasting action (several months) as a pre- and postemergence folian and soil-acting herbicide. It is efficient against *Artemisia* and *Cynodon dactylon* and is selective in alfalfa. Terbumeton is selective in citrus, and it controls efficiently *Setaria* and *Panicum* spp. in pre- and postemergence treatment. Its action lasts several months (Gast and Fankhauser, 1966; Mayshar, 1972).

6.14.4 4,6-Bis(alkylamino)-2-alkylthio-*s*-triazines

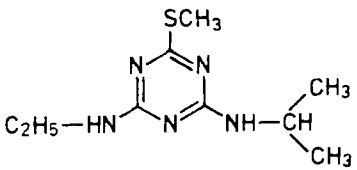
These compounds are broad-spectrum herbicides, more selective than the methoxy derivatives and with a shorter duration of action. They are absorbed through both roots and leaves. They are stronger bases than the chlorotriazine derivatives, and are thus more readily adsorbed in the soil.

Their most important application besides their use in maize culture is weed control in cereals, sugar cane, cotton, banana, pineapple, potato, sunflower and vegetable crops. Owing to their low persistence, which is favourable for crop rotation, their use is quickly becoming more widespread than the chloroamine triazines.

A vast number of publications deal with the practical application of alkylthio-*s*-triazines. Among these, we refer the reader to the Technical Bulletins of the Geigy Co., and the papers in the volumes of the 5th, 6th, 7th, 8th and 9th British Weed Control Conferences.

The most important members of the group are 4-ethylamino-6-isopropylamino-2-methylthio-*s*-triazine (ametryne, **26**), 4,6-bis(isopropylamino)-2-methylthio-*s*-triazine (prometryne, **27**), 4-isopropylamino-6-(3-methoxypropylamino)-2-methylthio-*s*-triazine (methoprotryne, **28**), 4-ethylamino-2-methylthio-6-*t*-butylamino-*s*-triazine (terbutryne, **29**), 4-isopropylamino-6-methylamino-2-methylthio-*s*-triazine (desmetryne, **30**), 4,6-bis(3-methoxypropylamino)-2-methylthio-*s*-triazine (MPMT, **31**), 4,6-bis(ethylamino)-2-methylthio-*s*-triazine (symetrine, **32**), 4-ethylamino-6-(1,2-dimethylpropylamino)-2-methylthio-*s*-triazine (C 18 898, **33**) and 2-ethylthio-4,6-bis(isopropylamino)-*s*-triazine (dipropetryne, **34**).

Ametryne can be used in orchards and for vine, citrus, forest, maize, sugar cane, banana and pineapple cultures. Prometryne is used in cotton, potato, sunflower, bean, pea and carrot crops; methoprotryne and terbutryne can be used in these crops and in cereals. Desmetryne and MPMT are used in soybean and cabbage crops for selective weed control.



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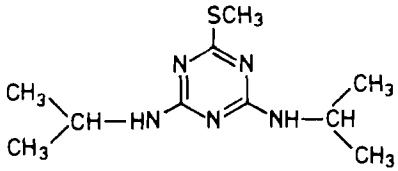

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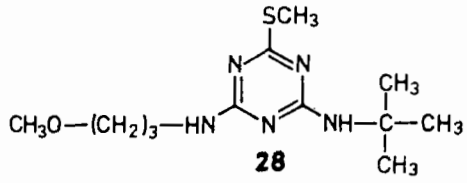

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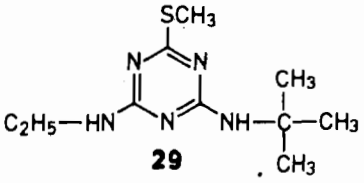

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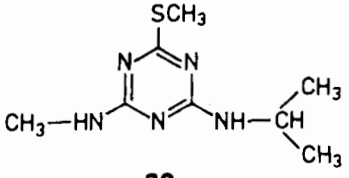

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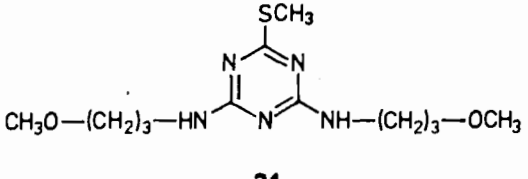

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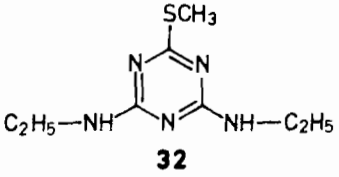

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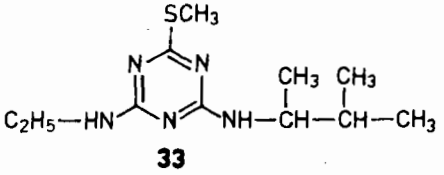

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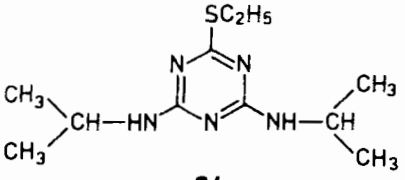

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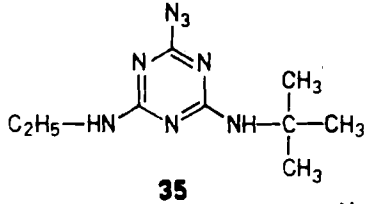
6.14.5 *s*-Triazines containing an azido group

Bis(alkylamino)-*s*-triazines containing and azido group have been developed by the Shell Co., and azido-alkylamino-alkylmercapto-*s*-triazines by the Ciba–Geigy AG (Gentner, 1967; Barnsley and Gabbot, 1966; Smith and Marks, 1968).

2-Azido-4-ethylamino-6-*t*-butylamino-*s*-triazine (WL 9385, **35**) is efficient for the selective control of dicotyledonous weeds in grain, maize and potato. 2-Azido-4-isopropylamino-6-methylthio-*s*-triazine (aziprotryne, **36**) is a selective herbicide efficient in the control of certain dicotyledonous weeds in cabbage, bean, sunflower, onion and maize, as is 2-azido-4-*sec*-butylamino-6-methylthio-*s*-triazine (C 8250, **37**) in soybean and cotton.

Azido-*s*-triazines break down quickly in the soil.



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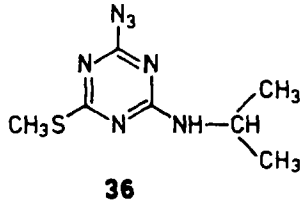

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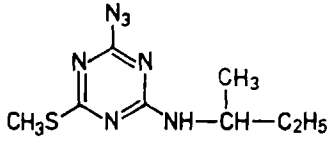

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6.14.6 Action of *s*-triazine herbicides

Relationships between the chemical structure and the effect of herbicides of the *s*-triazine type have been studied by several workers in addition to Gysin and Knüsli, whose work has already been cited (1960). McWhorter and Holstun (1961) established, from a comparative investigation of 2-chloro-, 2-alkoxy- and 2-methylthio-4,6-bis(alkylamino)-*s*-triazines, that the 2-chloro derivatives have the highest selectivity, that the alkylmercapto derivatives are less selective, and that the alkoxy derivatives have the lowest selectivity. In the last group selective compounds occur but rarely, and this selectivity holds only within narrow dose limits.

Selectivity improves with an asymmetric substitution and when one of the alkylamino substituents is exchanged for a 2-methoxypropylamino group. However, in this case the herbicidal efficiency decreases.

Selectivity can be expressed by a selectivity index. This index is the ratio of the concentration causing a 20% decrease in the growth of maize to the concentration causing an 80% decrease in the growth of the weeds.

Herbicidal efficiency can be expressed as an LD_{50} value, which is the concentration of herbicide in ppm which decreases the growth of weeds by 50%.

Relationships between the structure, efficiency and selectivity of some *s*-triazine derivatives are shown in Table 6.12.

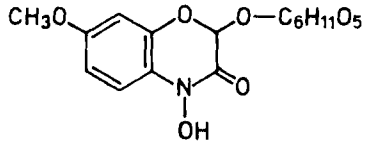
Table 6.12

Relationship between the structure, efficiency and selectivity of some *s*-triazine derivatives

Substituents on the *s*-triazines in positions			Efficiency LD_{50} ppm	Selectivity index
2-	4-	6-		
CH_3S—	*i*-C_3H_7NH—	*i*-C_3H_7NH—	0.05	0.73
CH_3O—	*i*-C_3H_7NH—	*i*-C_3H_7NH—	0.17	0.40
Cl—	C_2H_5NH—	C_2H_5NH—	0.18	4.00
Cl—	*i*-C_3H_7NH—	$CH_3OC_3H_6$—NH—	0.58	7.19
Cl—	*i*-C_3H_7NH—	*i*-C_3H_7NH—	0.92	3.51

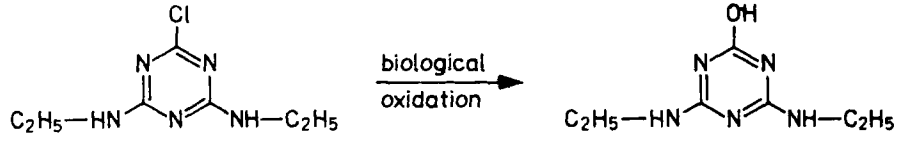
Several authors have investigated the relationships between the physical properties (e.g. water-solubility, distribution coefficient) of this group of compounds and their herbicidal action, (Koopman *et al.*, 1959; Nestler and Fürst, 1960; Matolcsy *et al.*, 1959; 1961).

The cause of the selectivity of herbicides of the triazine type has also been investigated by many authors. Roth (1957) investigated the resistance of maize to simazine, and established that the freshly pressed sap of the maize plant decomposes simazine during 100 hours of incubation, while simazine is not decomposed in the pressed-out sap of wheat, which is sensitive to simazine. However, this detoxifying effect does not occur after heat treatment of the pressed-out sap of the maize plant, indicating that a heat-sensitive substance is responsible for the effect (Roth and Knüsli, 1961). The substance that detoxifies simazine has been isolated by Castelfranco *et al.* (1961). This product, which is sensitive to heat in the raw state but thermostable after purification, proved to be identical with the 3-one-glucoside of 2,4-dihydroxy-7-methoxy-1,4-benzoxazine, isolated from maize by Wahlroos and Virtanan (1969):

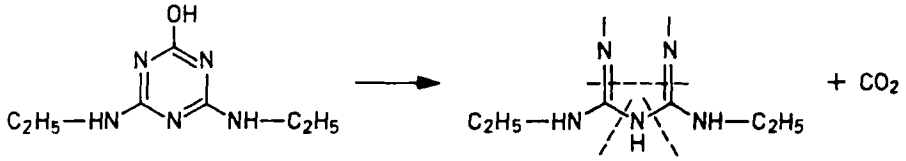


The hydrolysis product of the glucoside is also able to degrade simazine oxidatively *in vitro* and *in vivo*.

Hamilton and Moreland (1962) isolated from maize plant treated with simazine, 2-hydroxy-4,6-bis(ethylamino)-*s*-triazine (hydroxysimazine) formed by the oxidative route. Thus, in maize biological oxidation proceeds in the following way:



In the maize plant, degradation of simazine continues. Davis *et al.* (1959) found, in experiments with radiolabelled simazine, that radioactivity arising from $^{14}CO_2$ formed in the course of decomposition is distributed uniformly in the leaves:

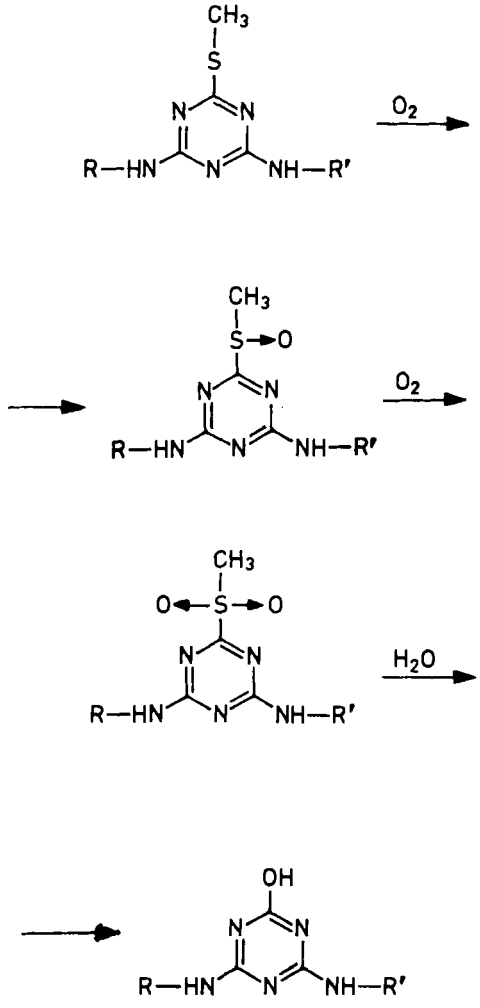


The skeleton of biguanidine type formed in the decomposition is readily decomposed further into amines, guanidines and similar simple metabolites.

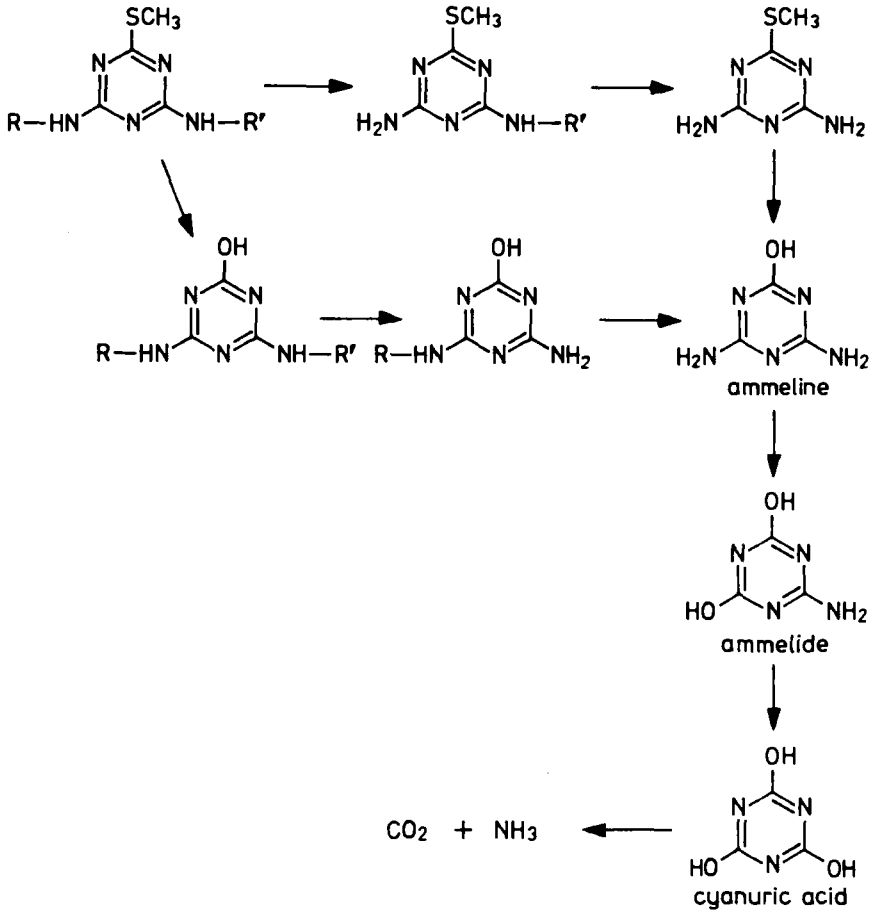
A similar degradation of the other chlorotriazines also occurs. This was detected by Davis in sensitive plants; here however, the degradation was a considerably slower process.

The degradation of 2-alkoxy- and 2-alkylthiosimazines in plants proceeds according to a similar mechanism. The lower selectivity of these two groups may be caused partly by the larger dose of the compound which is taken up due to higher solubility and the slower detoxification process.

Müller and Payot (1965) established by the radioactive-isotope method that the methylthio group of bis(alkylamino)-2-methylthio-*s*-triazines is oxidised in plants first to the sulfoxy then to the sulfon group, which is then quickly hydrolysed to the inactive hydroxy derivative:

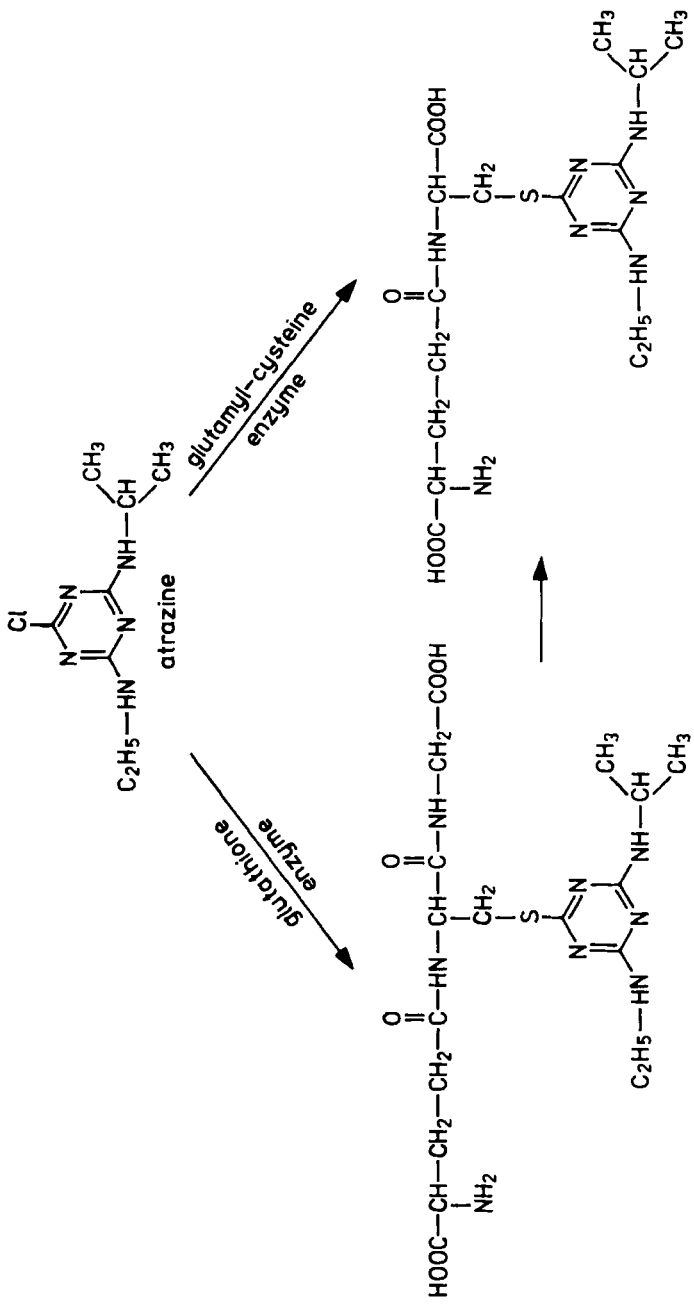


In addition to the above decomposition mechanism, dealkylation also takes place, partly preceding the oxidative cycle, partly after it (Geigy Co., 1967):

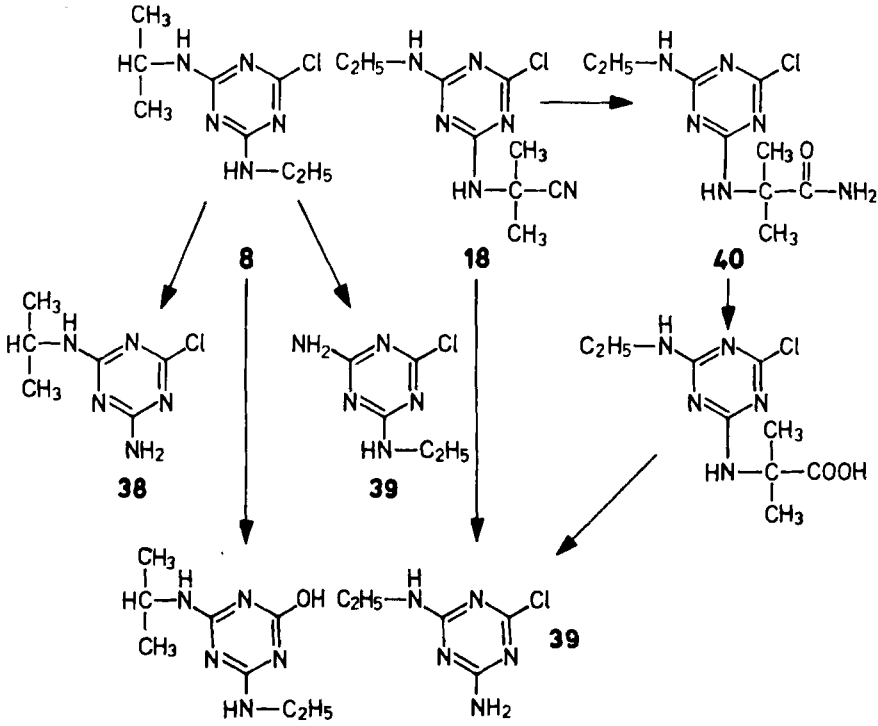


In addition to the detoxification processes described, other factors play important parts in determining the physiological selectivity. For example, the translocation rate of the *s*-triazine taken up by a plant varies considerably, depending on the plant species. When translocation is rapid, the quantity of triazine needed to cause wilting more easily reaches the chloroplasts.

Shimabukuro *et al.* (1971), investigating the metabolism of atrazine in maize, found that the tolerance of maize is not brought about by the above nonenzymatic inactivation alone, but that the primary factor is an enzyme, which conjugates triazine with glutathione, which is then converted to the glutamyl-S-cysteine derivative:


atrazine
glutamyl-cysteine
enzyme
glutathione
enzyme

Recently, Sirons *et al.* (1973) investigated the degradation of atrazine (**8**) and cyanazine (**18**) in soil. Both compounds yield three phytotoxic metabolites: 2-chloro-4-amino-6-isopropylamino-*s*-triazine (deethylated atrazine, **38**), 2-chloro-4-amino-6-ethylamino-*s*-triazine (**39**) (deisopropylated atrazine), and 2-chloro-4-(1-carbamoyl-1-methyl)ethylamino-6-ethylamino-*s*-triazine (cyanazine amide, **40**). Cyanazide amide is then quickly hydrolysed and decomposed into microbiologically deisopropylated atrazine. The proposed metabolism of atrazine and cyanazine in soil thus yields products according to the following scheme:



Prometryne is deposited in the lysigenic glands in the stalks of triazine-resistant plants and is thus prevented from reaching the chloroplasts (Dubach, 1971).

A deeper knowledge of the biochemical processes of plants would be needed for a complete explanation of physiological selectivity in herbicides.

Essentially, the basic biochemical processes of plant and animal organisms are identical. The most important difference is that plants synthesise energy-rich carbohydrates from atmospheric carbon dioxide with the aid of sunlight. The plant builds up its other organic constituents with the energy liberated from the carbohydrates during respiration.

This process, photosynthesis, proceeds with the aid of chlorophyll contained in the chloroplasts of the plant.

Of the herbicides, triazines, carbamates, acid amides and phenylureas inhibit photosynthesis. Due to this specific activity, these herbicides are more toxic to plants than to animals.

In the course of photosynthesis, the chlorophyll molecules absorb quanta of light and convert the light energy into chemical energy. Part of the insolation energy, however, is reflected unused in the form of heat or fluorescence.

In the course of its conversion to chemical energy, light reduces the plant acceptor by electron transfer. This process results at the same time in an oxidised chlorophyll molecule, which must be reduced before it can function again (Fig. 6.1) (Corbett, 1974).

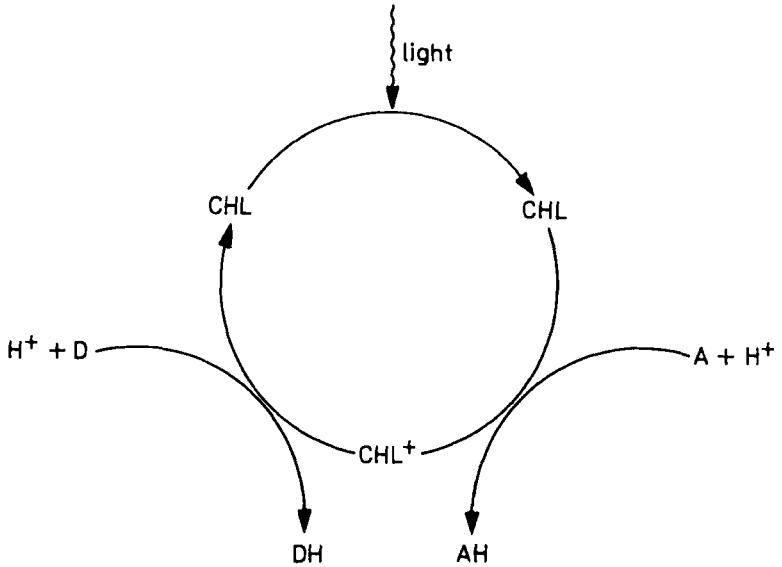


Figure 6.1 Excitation of chlorophyll (CHL) and reduction of acceptor (A) by the donor (DH) (DH = water, A = unknown)

Eventually, the acceptor A is reduced by the donor DH, and if AH is a stronger reducing substance (i.e. its redox potential is more negative) than DH, the light energy is converted into chemical energy in the course of the cyclic oxidation–reduction process.

In the chloroplasts, photosynthesis proceeds with the aid of the light energy received. Carbohydrates (sugar, starch) are formed from carbon dioxide and water and oxygen are liberated. In an aqueous algal suspension the oxygen liberated can easily be observed in the form of bubbles.

On the basis of the investigations of Vernon and Avron (1965) and of Elbert and Müller (1968), we can form a fairly detailed but not yet complete picture of the biochemical steps proceeding during photosynthesis. Two light reactions (I and II) take place. As in the mitochondrial electron transport chain, the two reactions are

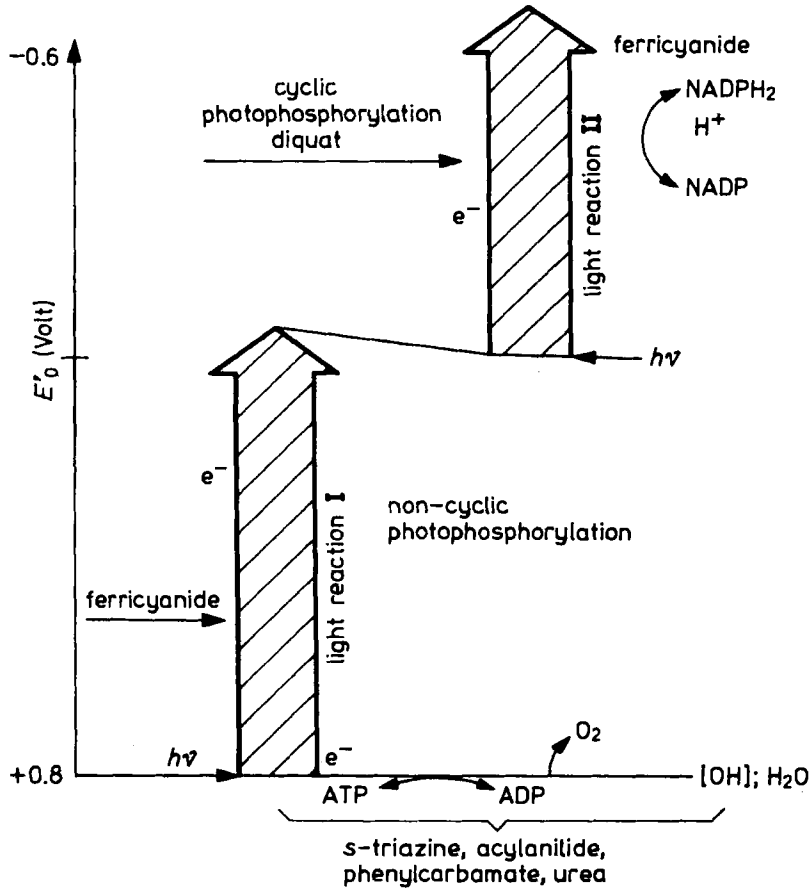


Figure 6.2 Scheme of the two light reactions (I and II) of photosynthesis and mode of action of the herbicides blocking these reactions

coupled in series (Fig. 6.2). Some of the electrons formed are taken up by the chinones and by the cytochrome components which are electron acceptors, transferring part of their energy to meet the energy required in the conversion of ADP to ATP. This light-catalysed conversion of ADP (adenosine diphosphate) to ATP is called photophosphorylation to distinguish it from the analogous respiratory oxidative phosphorylation. In the last part of the process, the cytochromes return the electrons taken up to the functional units of the chlorophyll.

The other electrons formed by the photons impacting on the chlorophyll units are absorbed by NADP (nicotinamide adenine dinucleotide 2'-phosphate) which thereby acquires a negative charge. This negatively-charged NADP attracts protons (H^+) from water and is converted to $NADPH_2$.

The $NADPH_2$ formed is very rich in energy and is able to realise the first steps of carbon dioxide assimilation. The electron transport mechanism of light reactions I and II is a noncyclic electron transfer process. Its by-product is oxygen, the formation mechanism of which is unknown.

Triazines, ureas, carbamates and acylanilides block light reaction II, stopping transport of the electrons to the chlorophyll functional units. Therefore, after a certain time the chlorophyll is oxidised and decolourises. The visible effect of this herbicidal action is chlorosis of the leaves.

The other point of action by herbicides is light reaction II, in which the formation of $NADPH_2$ is blocked. This is the mode of action, for example, of paraquat. In this case, the formation of oxygen bubbles in illuminated algal cultures is unchanged (proof of the normal light reaction I).

Gast (1958), in his investigation of triazine herbicides, found that simazine, like urea herbicides, decreases the accumulation of starch in *Coleus blumei*. On the other hand, when plants kept in sugar solution were treated with simazine, starch formation was normal, which proved that simazine inhibits sugar synthesis. This result was supported by Moreland *et al.* (1958), who found that the phytotoxic effect of simazine can be prevented by the addition of carbohydrates.

The Hill reaction inhibiting effect of triazine herbicides has been investigated by Exer (1958), while Gysin and Knüsli (1960) investigated this effect for a few triazine metabolites (Tables 13 and 14). The Hill reaction inhibiting values of several important triazines have been summarised by Moreland (1969) and Gabbot (1969).

Hill recognised in 1937 that the isolated chloroplasts of green plants are able to catalyse the photolysis of water in the presence of electron-accepting ferric salts. The overall Hill reaction can be represented by the following scheme:

$$2\,H_2O + 2A \xrightarrow[\text{chloroplasts}]{h\nu} 2\,AH_2 + O_2$$

where A is the Hill reagent or Hill acceptor.

The Hill reaction can be monitored by measuring the oxygen produced with an oxygen electrode or a Warburg manometer, or by spectrophotometry. The ferricyanide → ferrocyanide reduction can readily be measured by the last method; ferrocyanide acceptor and spectrophotometry are therefore used to measure the Hill reaction inhibiting effect of herbicides (Hill, 1937, 1940, 1965).

There is an approximate but not direct correlation between the Hill reaction inhibiting effect and the actual herbicidal effect of herbicides inhibiting photosynthesis.

Relevant investigations by Shimabukuro and Swanson (1969), Hansch (1969), Moreland (1969) and Buechel (1972), show that the mechanism of the Hill reaction inhibiting effect is still insufficiently known at the molecular level. This is due partly to the experimental techniques used, and partly to the varying sensitivities, which cannot be standardised, of the chloroplasts of the various plant species. The results obtained are highly dependent on the site of attachment of the inhibiting substance,

on the strength of the bond (K-value) and on the site of action (Izawa and Good, 1965).

Moreover, it is probable that compounds of different structure are attached to different points of the chlorophyll molecule (Moreland, 1969).

As a result of the different experimental conditions and techniques used, there is often a wide divergence between the results of the various authors. For example for the *in vitro* activity (concentration in μM giving a 50% inhibition of the Hill reaction) of simazine, the following values were reported by different authors: Gysin and Knüsli (1960) 0.7; Good (1961) 0.40; Moreland and Hill (1962) 5.9–8.4; Moreland (1969) 2.2.

Table 6.13

The Hill reaction inhibiting effect of 2-halo-4,6-bis(alkylamino)-*s*-triazines and some known herbicides (Exer, 1958; Gysin and Knüsli, 1960)

Z	X	Y	V_a
Cl	H_2N	H_2N	10^{-4} mole/dm^3→0–10% inhibition
Cl	CH_3NH	CH_3NH	0.002–0.01
Cl	C_2H_5NH	C_2H_5NH	1
Br	C_2H_5NH	C_2H_5NH	2–2.4
Cl	i-C_3H_7NH	i-C_3H_7NH	1.03–3
Br	i-C_3H_7NH	i-C_3H_7NH	1.8
Cl	n-C_3H_7NH	n-C_3H_7NH	0.4–0.67
Br	n-C_3H_7NH	n-C_3H_7NH	1.7–2
Cl	n-C_4H_9NH	n-C_4H_9NH	10^{-4} mole/dm^3→0% inhibition
Cl	H_2N	C_2H_5NH	0.2
Cl	CH_3NH	i-C_3H_7NH	0.27–0.44
Cl	C_2H_5NH	i-C_3H_7NH	1.8–2.1
Cl	C_2H_5NH	n-C_4H_9NH	3.6–3.8
Cl	C_2H_5NH	$(C_2H_5)_2N$	0.0025–0.008
Cl	i-C_3H_7NH	$(C_2H_5)_2N$	0.013–0.048
Cl	$(C_2H_5)_2N$	$(C_2H_5)_2N$	0.021–0.04
Cl	HNCl	HNCl	0.001

3-(4-chlorophenyl)-1,1-dimethylurea (monuron)	0.7–1
3-(3,4-dichlorophenyl)-1,1-dimethylurea (diuron)	4.1–6
2,4-dichlorophenoxyacetic (2,4-D)	10^{-4} mole/dm^3→0% inhibition
isopropyl-N-(3-chlorophenyl)carbamate (CIPC, chlorpropham)	0.0067–0.0075
Maleic hydrazide (MH)	10^{-4} mole/dm^3→10% inhibition
Aminotriazole (AT)	10^{-4}→0% inhibition

V_a = concentration of simazine giving 50% inhibition, divided by the concentration of test substance giving 50% inhibition. Concentration of simazine giving 50% inhibition = $7 \cdot 10^{-7}$ mole/dm^3

The concentrations of the active herbicides of the triazine group giving 50% Hill reaction inhibition varied from 10^{-4} to 10^{-7} mole/dm^3. The discrepancy between the actual herbicidal effect and the Hill reaction inhibiting effect can be ascribed to the solubility, translocation ability and soil adsorption of the herbicide.

Table 6.14
The effect of some triazines and their possible metabolites on inhibition of the Hill reaction (Gysin and Knüsli, 1960)

Z	X	Y	V_a
OCH_3	C_2H_5NH	C_2H_5NH	1.3–1.5
SCH_3	C_2H_5NH	C_2H_5NH	1.5–5
OCH_3	i-C_3H_7NH	i-C_3H_7NH	0.44–0.62
SCH_3	i-C_3H_7NH	i-C_3H_7NH	6.1–9.1
OCH_3	CH_3NH	i-C_3H_7NH	0.18–0.21
SCH_3	CH_3NH	i-C_3H_7NH	3.9–4.4
OCH_3	C_2H_5NH	i-C_3H_7NH	1.3–1.5
SCH_3	C_2H_5NH	i-C_3H_7NH	6.1
H	C_2H_5NH	C_2H_5NH	10^{-4} mole/dm^3→0% inhibition
CH_3	C_2H_5NH	C_2H_5NH	0.93
C_2H_5	C_2H_5NH	C_2H_5NH	0.18–0.22
i-C_3H_7	C_2H_5NH	C_2H_5NH	0.23
n-C_3H_7	C_2H_5NH	C_2H_5NH	0.15
n-C_4H_9	C_2H_5NH	C_2H_5NH	0.0043
C_2H_5	i-C_3H_7NH	i-C_3H_7NH	0.20–0.29
C_2H_5	C_2H_5NH	C_2H_5NH	0.056–0.13
$N(C_2H_5)_2$	$N(C_2H_5)_2$	$N(C_2H_5)_2$	0.019–0.025
OH	C_2H_5NH	C_2H_5NH	10^{-4} mole/dm^3→0% inhibition
OH	C_2H_5NH	i-C_3H_7NH	0.0033–0.0077

V_a = concentration of simazine giving 50% inhibition divided by the concentration of test substance giving 50% inhibition. Concentration of simazine giving 50% inhibition = $7 \cdot 10^{-7}$ mole/dm^3

Consideration of the Hill reaction inhibiting concentrations of urea, carbamate, acylanilide and triazine herbicides, the dependence of their efficiency on light intensity, and so on, lead to the conclusion that these herbicides exert their effect according to a similar mechanism of the molecular level.

s-Triazine herbicides inhibit the growth of plants by inhibiting photosynthesis, and the plants arrested in growth show characteristic chlorotic (chlorophyll insufficiency) symptoms, and subsequent necrosis and death.

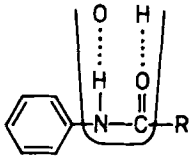
In the case of maize, cotton, citrus and other resistant plants, stimulation of growth and an increase in the chlorophyll content of the foliage could also be observed (Lorenzoni, 1962; Freney, 1965).

Overbeek (1964) pointed out that each of these herbicide types contains an —NH— group capable of forming a hydrogen bond. In the case of compounds of the amide, urea and uracyl type, there is a =C=O group adjacent to the —NH— group that is suitable for the formation of a further hydrogen bond, and in the case of the triazines, there is a =C=N— group.

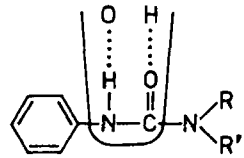
The similar mode of action and biological activity of herbicides of different chemical type can therefore be ascribed to their ability to form a hydrogen bond

with the protein part of the enzyme taking part in the photolysis of water, thereby inhibiting enzyme function (Goren and Monselise, 1966; Freeman *et al.*, 1966).

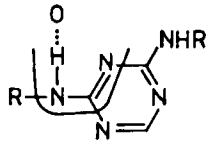
Good (1961) and Shimabukuro and Swanson (1969) investigated the photophosphorylation (ATP) inhibiting effect of triazine herbicides on isolated chloroplasts.



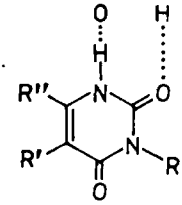
amide type



urea type



triazine type



uracyl type

Using flavine mononucleotide (FMN) as electron acceptor, the herbicides caused a decrease in ATP formation, while it did not decrease when N-methylphenazonium (PMS) was used for the same purpose.

The different results of the photophosphorylation-inhibiting experiments performed by Bishop (1962) indicate a difference in the action mechanism of triazine herbicides and urea herbicides (Ashton and Crafts, 1973). According to Avron, diuron inhibits photophosphorylation catalysed both by FMN and by vitamin K_3, whereas Bishop demonstrated that simazine inhibits only photophosphorylation catalised by FMN.

Ashton *et al.* (1960), Zweig and Ashton (1962) and Sikka and Davis (1968) investigated the fixation of CO_2 in various plants under the action of triazines. The triazines reduced drastically the quantity of CO_2 fixed by plants in light, but did not affect nonphotosynthetic CO_2 fixation. In sensitive plants this decrease was greater than in tolerant plants.

Concerning the effect of the triazines on the respiration of plants, several contradictory results have been published. In certain plants stimulation of respiration ocurred, but it was inhibited in others. In other experiments either no effect was detected or respiration was inhibited (Funderburk and Davis, 1963; Foy and Penner, 1965; Thomson *et al.*, 1969).

Under laboratory conditions micromolar concentrations of *s*-triazines increase the growth and protein content of several plants (Ries *et al.*, 1967; Wray *et al.*, 1970; Singh and Salunkhe, 1970; Ries and Wert, 1972; Hiranpradit *et al.*, 1972). With subtoxic doses of simazine and atrazine a substantial increase in the protein content of various cultivated plants was attained under field conditions (Fink and Fletchall, 1967; Ries *et al.*, 1968; Kay, 1971).

Ries and Gast (1965) observed a 90% increase in the nitrogen content of maize leaves with a low level of nitrogen-supply after two simazine treatments of 10^{-6} mole/dm^3. Similar results have been reported by Tweedy and Ries (1967) for maize grown at suboptimal temperature and low nitrogen supply. On the other hand, simazine did not enhance the growth of maize plants if the nitrogen was supplied in the form of ammonium. In maize plants treated with simazine, the nitrate reductase activity is increased by one order of magnitude under suboptimal conditions.

According to experiments carried out on rye (Ries *et al.*, 1967) the water-soluble protein content increased by 27% with a light supply of 21 000 Lux, but the protein content did not change in rye grown at 1600 Lux.

The initial action of simazine and atrazine is the increase of nucleic acid synthesis. This increases protein synthesis and, thereby, the absorption of nitrate. However, nitrate reduction can occur only if sufficient carbohydrate is present for the formation of NADH. An increase in glucose catabolism increases the quantity of α-ketoglutaric acid. As a result of this assumed mechanism, nitrogen assimilation is increased at the expense of carbohydrates if there is not sufficient carbohydrate present, because the temperature is high and the light poor, or the nitrogen supply is good and, in this case, the *s*-triazine effect is absent.

s-Triazines also stimulate or inhibit other enzymatic processes in plants (Singh and Salunkhe, 1970; Penner and Early, 1972).

By the action of atrazine, substantially more nitrogen compounds are synthesised in rye seedlings, but CO_2 fixation decreases, and, hence, the photosynthetic processes are inhibited. In atrazine-treated plants the quantity of insoluble photosynthesis remaining in the stem increases (Dill and Carter, 1972).

Ries *et al.* (1974) observed an increase in nitrate and water uptake by a barley culture grown in nutrient solution with 10^{-9} mole/dm^3 simazine. After 12 days the barley contained 22% more protein than the controls. When treated with 10^{-7} mole/dm^3 simazine, barley was of the same height as the control plant after 12 days, but contained 26% more protein. Atrazine increased the growth of the embrional axis of bean and enhanced its protein synthesis. These investigations indicate that sublethal doses of simazine and atrazine stimulate protein synthesis in plants.

According to Ladonin and Spesivtsev (1974), maize tolerant to chloro-*s*-triazines stores the triazine taken up in the cytoplasm and in the sensitive pea it is stored in the nucleus, chloroplasts and mitochondria. They assume that the triazines are thus incorporated into proteins and nucleic acids as antimetabolites during the biosynthesis of internuclear nucleic acids. This may also be one of the explanations of the different sensitivity of plants to triazines. Black currant is also tolerant to 4 ppm simazine. According to Shone and Wood (1972) triazine translocated into the leaves of black currant cannot get from the tissue system into the mesophyll. The simazine taken up remains in the leaf veins and does not enter the chloroplasts.

Recent investigations have shown that the prolonged use of triazines increased the tolerance of some weed species in certain places, and even resistance developed. Ryan (1970) found a simazine- and atrazine-resistant population of common groundsel *(Senecio vulgaris)* in a forest nursery, where these herbicides had been

used for 12 years. Peabody (1973) found in maize an *Amaranthus retroflexus* strain that was resistant to atrazine. Holliday and Putwain (1974) investigated *Senecio vulgaris, Chenopodium album* and *Capsella bursa pastoris* populations for simazine tolerance and found that tolerance changes with the number of years of application, but they did not find a *Senecio vulgaris* population resistant to simazine.

According to Kern *et al.* (1975) the selectivity of cynazine is due to the fact that sensitive plants *(Panicum dichotoniflorum, Setaria viridis)* and tolerant plants *(Zea mays)* absorb the herbicide through their leaves to different extents.

The compounds of the triazine group have been studied very thoroughly both with respect to warm-blooded animals and to humans. Maier-Bode's book (1971) and the toxicological bulletins of the Geigy Co. constitute a very good toxicological literature.

Herbicides of the triazine type and their metabolites have a very low toxicity for warm-blooded animals. Acute oral toxicities (LD_{50}) measured in rats are: simazine 5000 mg/kg, atrazine 3080 mg/kg, propazine 5000 mg/kg, prometone 2980 mg/kg, desmetryne 1390 mg/kg, ametryne 1405 mg/kg, prometryne 3150–3750 mg/kg, terbutryne 2400–2980 mg/kg, methoprotryne 5000 mg/kg, and aziprotryne 5833 mg/kg.

The dermal toxicity of these compounds is also low, and they do not irritate the mucous membranes or the eye. Their toxicity on inhalation is below the measurable limit.

s-Triazines do not accumulate in the organism and are excreted partly in dealkylated form and partly unchanged within a few days.

s-Triazine herbicides do not affect the microflora or the microfauna of the soil even at an overdosage. Simazine, for example, furthers the development of certain *Actinomycetae,* pectinolytic bacteria and mould fungi (Steinbrenner, 1960).

s-Triazines are innocuous to bees (Beran, 1970). They are moderately toxic to fish (Gast, 1964). However, their LD_{50} value is by 3–4 orders of magnitude higher than that of DDT.

The value of the *s*-triazine residues allowed varies from country to country (Maier-Bode, 1971, p. 390). Permissible residue values vary from 0.05 to 10 ppm.

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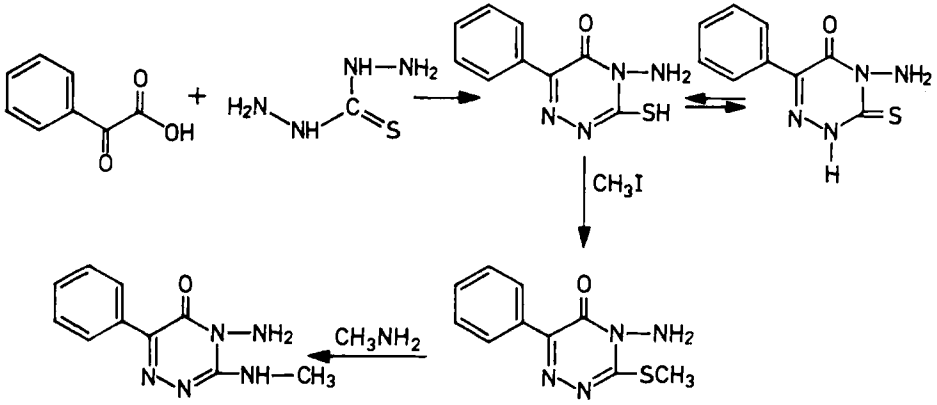
6.15 1,2,4-Triazinones

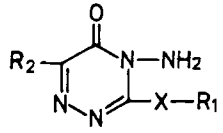
Theoretical investigations of Dornow *et al.* (1964) supplied the background for the discovery of this new herbicide group with asymmetric triazine skeleton. A reaction was elaborated which permitted the synthesis of 1,2,4-triazin-5-ones, substituted by SR and NH_2 in position 3 and by NH_2 in position 4.

The new reaction is shown by the following scheme:



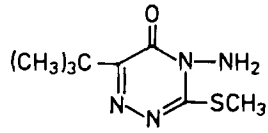
In the research laboratories of the Bayer AG the attention of Westphal and his coworkers was turned to this new group of compounds. Owing to their similarity to nucleic acids a series of 1,2,4-triazinone compounds were synthesised and tested for biological activity. This led to the recognition of the herbicidal activity of the group (Westphal *et al.*, 1966).

The general formula of the new group of compounds is:



where R_1 = alkyl; R_2 = alkyl, aryl, subst. aryl; X = O, S.

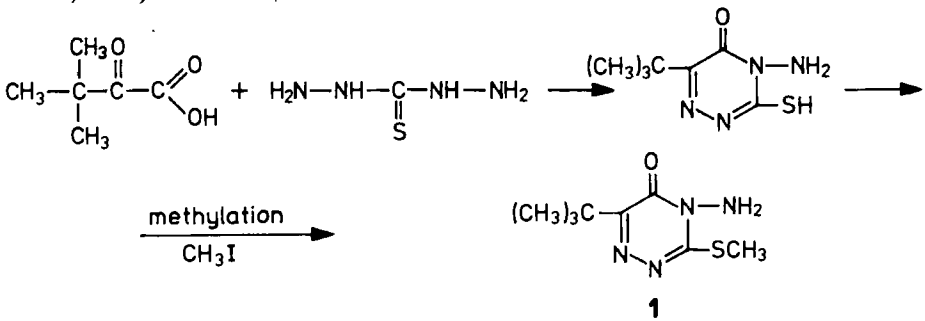
Of this group the compound of highest activity and at the same time highest selectivity is metribuzin, 4-amino-6-*t*-butyl-3-methylthio-1,2,4-triazin-5-one (**1**) (Draber *et al.*, 1968).



1

Metribuzin is a crystalline compound, very slightly soluble in water. Of the organic solvents it is relatively soluble in methanol.

The industrial synthesis of metribuzin proceeds by the reaction of thiocarbohydrazide with 2-oxo-3,3-dimethylbutyric acid, yielding 4-amino-6-*t*-butyl-3-thio-1,2,4-triazin-5-one, which is methylated to the endproduct (Jautelat *et al.*, 1973; Fawsi, 1975):



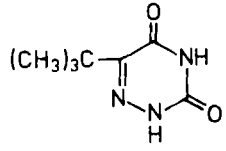
1

Metribuzin is a herbicide of pre- and postemergence. It is effective against annual grasses and many broad-leaved weeds including hard-to-control weeds, e.g. *Chenopodium album, Galinsoga* sp., *Stellaria media, Poa annua* and *Agropyron repens*, but some weed species are tolerant, such as *Tussilago farfara, Convolvulus arvensis* and, in a smaller degree, *Cyperus* spp. (Richardson and Dean, 1973; Kolbe and Zimmer, 1972).

Metribuzin is selective in soybean, potatoes, tomatoes, alfalfa, carrots, asparagus, maize and in cereals (Eue, 1972; Kolbe and Zimmer, 1972; Mulder, 1972; Kampe, 1972; Fortino and Plittstoesser, 1974) at doses 500–700 g active ingredient/ha. It is absorbed by plants through the leaves and roots, the latter is translocated in the xylem. Downward movement does not occur from the leaves. The herbicide translocated to the leaves effects by inhibiting the electron transport of the photosynthesis (Hill reaction) (Draber *et al.*, 1974b; Schmidt *et al.*, 1975b; Ladlie *et al.*, 1976a,b,c).

The reason of the selectivity of metribuzin is that the mechanism of the absorption, translocation and detoxification are different in the sensitive and tolerant plants. Hargroder and Rogers (1974) showed in tracer experiments, in

soybean (tolerant) and *Sesbania exaltata* (sensitive) that though the herbicide is absorbed and translocated nearly in the same degree in both plants, the metabolism is faster in soybean, and the main metabolite is the relatively nonphytotoxic deaminated diketo derivative 6-*t*-butyl-1,2,4-triazine-3,5-dione (**2**).



2

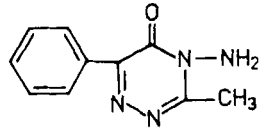
According to Smith and Wilkinson (1974) the sensitivity to metribuzin among soybean cultivates is because of the different capacities of conjugative detoxification.

Metribuzin is adsorbed strongly in the soil, mainly by the humic acids (Schmidt and Hoyer, 1975). It decomposes in the soil mainly *via* microbial degradation. The primer metabolite is deaminated diketo derivative (**2**), the final product is carbon-dioxide (Schumacher, 1974). Metribuzin is nonpersistent. Its half-life depends much on the climatic condition, optimally it is 14–28 days (Hyzak and Zimdahl, 1974).

Metribuzin is moderately poisonous. The oral LD_{50} of the technical product for rats is 1090–1206 mg/kg, it is less toxic to fish and avian species (Löser and Kimmerle, 1972; Schmidt, 1973).

Herbicides containing the asymmetric 1,2,4-triazinone ring were developed in the research laboratories of the Bayer AG (Schmidt *et al.*, 1975a; Schmidt *et al.*, 1975b).

The most active member of the group is 4-amino-3-methyl-6-phenyl-1,2,4-triazin-5-one, introduced under the common name metamitron (**3**).



3

Metamitron is absorbed by the plants through the foliage or, more readily, the roots. The herbicide taken up is rapidly translocated to the chloroplasts.

Metamitron inhibits photosynthesis. According to Draber *et al.* (1974a,b) it blocks light reaction II in the electron transport chain of photosynthesis.

Metamitron is a selective pre- and postemergence herbicide particularly suitable for selective weed control in sugar beet and red beet. The herbicide can be used very safely at a rate of 2.8–7.0 kg active ingredient/ha in all stages of development. It is

effective for the control of several grass and broad-leaved weeds. The best results are obtained at a rate of 3.5 kg active ingredient/ha by split application (preemergence and early postemergence) (Morris *et al.*, 1976; Hilton and Bray, 1980).

According to the investigations of Morris *et al.* (1978), the effect of metamitron, applied at a rate of 3.5 kg active ingredient/ha can be substantially increased by the simultaneous spraying of an adjuvant oil (e.g. Actipron). In this way also weeds in more advanced stages and more resistant weeds such as *Polygonum* spp. can be efficiently controlled. Metamitron has been used efficiently in tank mixtures in combination with propham, chloropropham, fenuron and phenmedipham for weed control in sugar beet (Elliott and Young, 1980).

Bray and Hilton (1980) report on extensive, combinative field tests for the pre- and postemergence control of weeds in sugar beet.

The probable cause of the very high tolerance of sugar beet is its ability to detoxicate metamitron (Schmidt, 1975a,b).

Metamitron is strongly adsorbed by the soil, hence its leachability is low. It is degraded in both the plant and in the soil to deamino-metamitron. $^{14}CO_2$ liberated from the radiolabelled 3-^{14}C-compound indicates that it is further broken down in the soil by micro-organisms (Jarczyk, 1976).

The toxicity of metamitron to humans, mammals and fish is low. Its acute oral LD_{50} for male rats is 3343 mg/kg, for female rats 1832 mg/kg, and for mice 1450–1463 mg/kg. The acute dermal LD_{50} for rats is more than 1000 mg/kg. In ninety-day feeding tests the no-effect level for rats was 460 mg/kg diet; for dogs 500 mg/kg diet. The LC_{50} (96 hours) for goldfish is more than 100 mg/l, for canaries more than 1000 mg/kg daily. Metamitron is not toxic to bees (Worthing, 1979).

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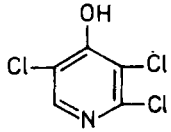
6.16 Pyridines

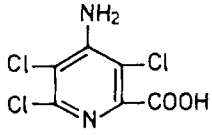
The quaternised derivatives of this group of compounds (diquat, etc) are discussed in Section 6.19.

The substituted pyridine derivatives are biologically active compounds. Nicotine, nornicotine and anabasine are natural insecticides known for a long time. Pyridine-2-thiol-1-oxide and pyridine-nitrile (2,6-dichloro-4-phenylpyridine-3,5-dicarbonitrile) are fungicides with wide range of action.

Pyridine derivatives with several halogen atom substituents show herbicidal activity. The herbicidal action of 2,3,4-trichloro-4-pyridinol (pyrichlor, **1**) and of 4-amino-3,5,6-trichloropicolinic acid (picloram, **2**) were described by Huraux and Lawson (1965).



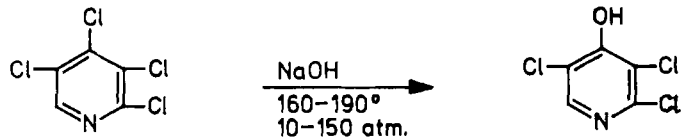
1



2

Pyrichlor (**1**) was introduced in 1965 by the Dow Chemical Co. as a potential grass killer.

Pyrichlor is prepared from 2,3,4,5-tetrachloropyridine by alkaline saponification according to the following reaction scheme:



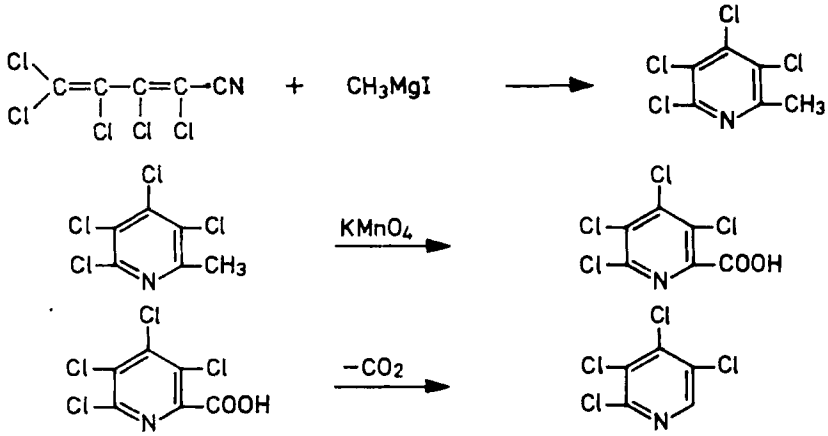
Pyrichlor is rapidly absorbed by the plants through both the leaves and the roots. The absorbed herbicide is rapidly translocated in the plant. Used for preemergence treatment at a rate of 100–300 g active ingredient/ha, it is effective against annual grass weeds and broad-leaved weeds. Applied at a rate of 1–4 kg active ingredient/ha it efficiently kills *Agropyron*. It was used for selective weed-control in sugar cane, banana and rubber plantations.

Pyrichlor inhibits photosynthesis. An excellent summary is to be found in the book of Ashton and Crafts (1973) on the investigations of its biological action carried out between 1968 and 1971.

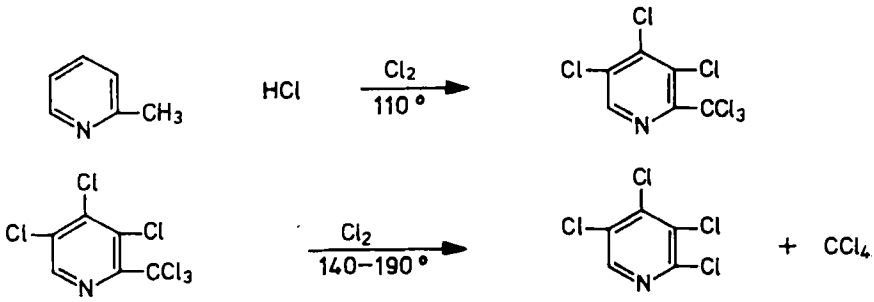
Picloram (**2**) may be prepared by several synthesis routes. The key intermediate in the case of both picloram and pyrichlor is 2,3,4,5-tetrachloropyridine, which can be prepared from pyridine, 2-picoline or pentachloropentadiene nitrile.

The chlorination of pyridine hydrochloride is circumstantial and, due to many by-products, of poor yield (Sell and Dootson, 1899).

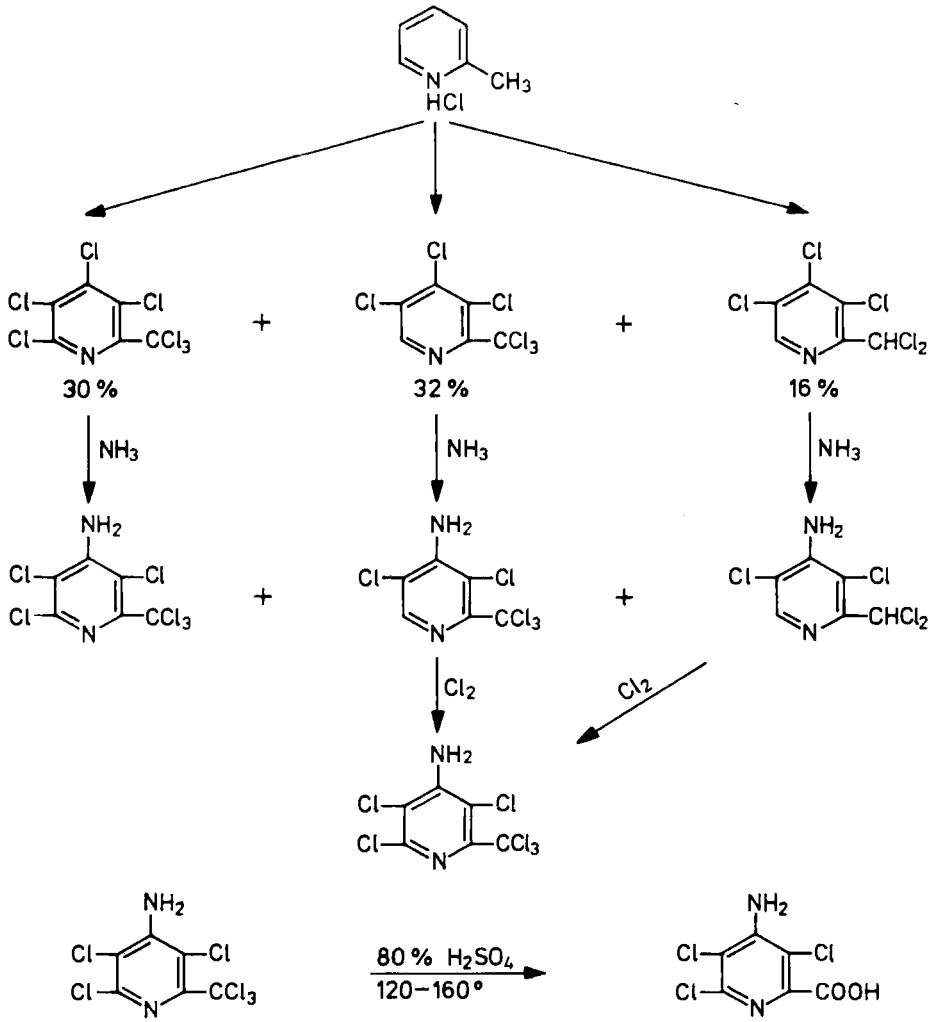
2,3,4,5-Tetrachloropyridine may be prepared from pentachloropentadiene nitrile by Grignard reaction, followed by oxidation with $KMnO_4$ and decarboxylation according to the following reaction scheme:



2,3,4,5-Tetrachloropyridine may also be prepared by the chlorination of the hydrochloride of 2-picoline (Sell, 1905; Johnston and Tomita, 1966):



The first step of this reaction does not yield 3,4,5-trichloro-2-(trichloromethyl)pyridine as a uniform product. 32% of the reaction mixture is 3,4,5-trichloro-2-(trichloromethyl)pyridine, 30% 3,4,5,6-tetrachloro-2-(trichloromethyl)-pyridine, and 16% 3,4,5-trichloro-2-(dichloromethyl)pyridine. The mixture is treated under pressure with NH_3, then further chlorinated to give on hydrolysis picloram (Melnikov, 1971):



The potassium salt of picloram, readily soluble in water, is absorbed by leaves and roots and is rapidly translocated in the xylem. It has a broad range of action and is used for the control of deep-rooted broad-leaved weeds and the killing of woody plants. For weed-control in turf, as total herbicide on non-crop areas and for brush

control it is recommended at rates of 0.2–8 kg active ingredient/ha. Formulations include combinations with sodium tetraborate, 2,4-D and 2,4,5-T (Tordon 101: picloram + 2,4 D; Tordon 225 E: picloram + 2,4,5-T; Tordon Beads: picloram + disodium tetraborate) (Anonym, 1985).

Picloram is very persistent in the soil. Even the smallest recommended dose persists more than 1 year. Applied at higher rates it is gradually degraded over several years.

Picloram is of low toxicity to mammals, its acute oral LD_{50} for rats is 8200 mg/kg. It has no teratogenic effect.

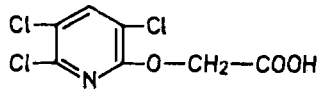
Picloram is, with respect to its action, a characteristic growth-regulating herbicide. Like the other growth-regulators of auxin type, picloram inhibits root growth in sensitive plants, enhances stem elongation, induces cell wall loosening and causes stem curvature and other formative effects (Martin *et al.*, 1970; Lee, 1970; Chang and Foy, 1971).

Picloram absorbed by the plants swells the cell membranes and disintegrates the chloroplasts in the new shoots (Ayling, 1976; Gaudiel and van den Born, 1979).

Picloram has multiple biochemical effects in the plants. In spite of the many investigations carried out so far, the exact mode of action is unknown. The main action is undoubtedly the effect exerted on nucleic acid synthesis and metabolism and, thus, on cell protein synthesis. Moreover, picloram probably affects to a different extent several enzymes and enzyme systems.

Chang and Foy (1978) investigated the relationships between the growth-modifying action of various α-substituted pyridines and their metal binding activity, but found no correlation.

In 1970, the Dow Chemical Co. developed the herbicide 3,5,6-trichloro-2-pyridyloxyacetic acid under the code number Dowco 233. Its common name is triclopyr (**3**) (Delabraze *et al.*, 1977).



3

Triclopyr is prepared by the coupling of 3,4,5-trichloropyridin-2-ol with chloroacetic acid. The compound is stable at room temperature but is rapidly decomposed by photolysis.

Triclopyr is available in the form of its 2-butoxyethyl ester as an emulsifiable concentrate formulation of 480 g active ingredient/l concentration (Garlon®). Its recommended dose is 1–3 gallons/acre. Its action can be enhanced by the addition of adjuvant oils (Delabraze *et al.*, 1977).

Triclopyr is absorbed by leaves and roots and is rapidly translocated in the whole plant. Important weeds controlled by triclopyr are pines, sassafras, hemlock, poison oak, maples, ash, blackberries, willows, rose, and many other perennial weed and brush species (Ryder, 1975).

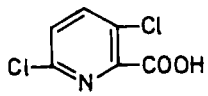
It has been tested with good results for vegetation management on right-of-ways, industrial and forestry sites and rangeland brush control. It is more potent for the control of ash and oak than 2,4,5-T, (Byrd *et al.*, 1974: Warren, 1975; Lichy, 1978; Morel, 1977). It acts most potently when used in the active growth period of the weeds. It may be used as injection for the killing of trees, or for the prevention of resprouting on freshly cut stumps.

Triclopyr is more efficient for the control of *Cruciferae* and *Graminaceae* than 3,6-dichloropicolinic acid, while the latter is more potent against *Compositae, Polygonaceae* and *Polypodaceae. Cirsium arvensae* is resistant to triclopyr after the blooming period (Geronimo, 1978).

Triclopyr is a nonpersistent herbicide with auxin effect (Chang and Foy, 1978) rapidly broken down in the soil by microorganisms.

Triclopyr is moderately toxic. Its oral LD_{50} for rats is 713 mg/kg. It irritates the eye and the skin. It is not toxic to fish and birds.

3,6-Dichloropicolinic acid (DPA, **4**) was introduced in 1975 under the code number Dowco 290 (Haagsma, 1975).



4

It is prepared by the reduction of 3,4,5,6-tetrachloropyridine-2-carboxylic acid (US Pat. 3 317 549, Dow Chem. Co.)

The amine salt of DPA has excellent water-solubility. It is therefore formulated as the 300 g acid equivalent, as monoethanolamine salt for agricultural use.

3,6-Dichloropicolinic acid is a herbicide with auxin action. Its characteristic effect is revealed by the grave epinasty of dicotyledons and by the fasciation of the crowns and leaf petiols. It is readily absorbed by both the roots and the leaves and is translocated; thus it is recommended at a rate of 50–400 g active ingredient/ha for preemergence and early postemergence selective weed control in cereals, maize, millet, flax, pature and *Brassica* cultures against *Compositae* and *Polygonaceae* (Engstrom, 1976; Gummeson, 1976). *Gramineae* and *Cruciferae* are resistant to DPA.

In combination with phenoxy herbicides (2,4-D, mecoprop, MCPA) it has a synergistic action, and its range of herbicidal action is also widened (Gilchrist and Page, 1976; Mayes *et al.*, 1976).

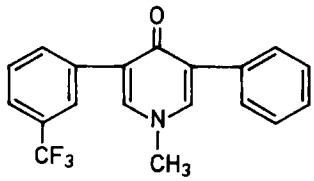
Gilchrist and Lake (1978) reported that postemergence treatment with 3,6-dichloropicolic acid at a rate of 150–200 g acid equivalent/ha efficiently killed *Cirsium avense* in sugar beet. The treatment is safe in the 1–8 leaf stage of the cultured plant. Total weed-killing could be enhanced by the addition of phenmedipham, lenacil or metamitron.

3,6-Dichloropicolinic acid is not metabolised by the plants. It is broken down relatively rapidly by soil microorganisms. On the basis of laboratory and field tests its average half-life is 49 days (Regan and Andriessen, 1973).

Farrow and Cheng (1978) found in their investigations that 0.016 μg/g is broken down in the soil weekly, so that at a concentration of 1 μg/g degradation time would be 1 year. Dichloropicolinic acid remains in the upper 20 cm layer of the soil.

It is only slightly toxic to mammals, birds and fish. The acute oral LD_{50} for male rats is more than 5000 mg/kg, for female rats 4300 mg/kg; the acute dermal LD_{50} is more than 2000 mg/kg for rabbits. It is mildly irritating to the skin and strongly irritating to the eyes if it is not washed out immediately after contact. Eight-day dietary LC_{50} values: mallard duck 4640 ppmw, bobwhite quail 4640 ppmw. Toxicity to fish: the LC_{50} (96h) value for bluegill is 125.4 mg/l water, for rainbow trout 103 mg/l water (Brown and Uprichard, 1976).

Fluridone, 1-methyl-3-phenyl-5-[3-trifluoromethyl(phenyl)]-4[1H]-pyridinone, **(5)** has been developed under the code number EL 171 in the Lilly Research Laboratories (Waldrep and Taylor, 1976).



5

It is manufactured by the condensation of (α, α, α-trifluoro-*m*-tolyl)-acetonitrile with ethyl phenylacetate and, after acidification of the intermediate, by cyclisation with methylamine and methyl formate (DOS 2 537 753, 1975).

Fluridone is a selective herbicide with translocation properties, used mainly preemergence but also postemergence for the control of broad-leaved and grass weeds at a rate of 0.3–2.4 g active ingredient/ha. Of the crops cotton is tolerant.

Used preemergence at higher rates it also kills *Agropyron* spp., *Convolvulus* spp., *Cynodon dactylon, Sorghum halepense, Cyperus rotundus* and *C. esculentus.*

Its action manifests itself slowly, in 2–3 weeks, by chlorosis, which is followed by necrosis, and the killing of the weeds.

The biochemical mode of action of fluridone, similar to that of norflurazon, is the inhibition of carotenoid synthesis (Waldrep and Taylor, 1976; Buenida *et al.*, 1978; Devlin *et al.*,1978).

Raffii *et al.* (1979) found that fluridone also blocks the RNA synthesis and the protein synthesis of plants, but that the main action is the inhibition of photosynthesis.

Selectivity between tolerant cotton and sensitive crops is caused by the accumulation of fluridone in the roots of tolerant cotton, while in sensitive plants it is translocated to the leaves, and inhibits photosynthesis there (Berard *et al.*, 1978).

The herbicidal action of fluoridone is strongly influenced by adsorption in the soil. According to Loh *et al.* (1979) a linear correlation exists between the adsorption coefficient (K_a) of the soil, its organic substance content and the

herbicidal action of fluridone. The appropriate application rate can be predicted if the correlation is known.

Fluridone shows promise for the control of aquatic weeds because of its general herbicidal action, good stability to hydrolysis, poor solubility (12 mg/l) in water and low toxicity to fish.

Fluridone is of low toxicity to mammals. Its oral LD_{50} for rats and mice is more than 10 000 mg/kg, for dogs more than 500 mg/kg, for cats more than 250 mg/kg. In 90-day feeding trials the no-effect level for rats was 1400 mg/kg diet. LC_{50} (96 hrs) for bluegill is 7 ppm (Berard *et al.*, 1978).

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Raffii, Z. Z., Ashton, F. M. and Glenn, R. K. (1979): *Weed Sci.*, **27**, 422.

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Sell, W. J. (1905): *J. Chem. Soc.*, **87**, 799.
Sell, W. J. and Dootson, F. W. (1899): *J. Chem. Soc.*, **75**, 979.
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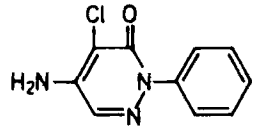
6.17 Pyridazines

The herbicidal properties of the pyridazine group were described by Fischer in 1962, and the first of them, pyrazon, 5-amino-4-chloro-2-phenyl-3-pyridazone (**1**), was introduced in 1962 by the BASF AG under the trade name Pyramin®.

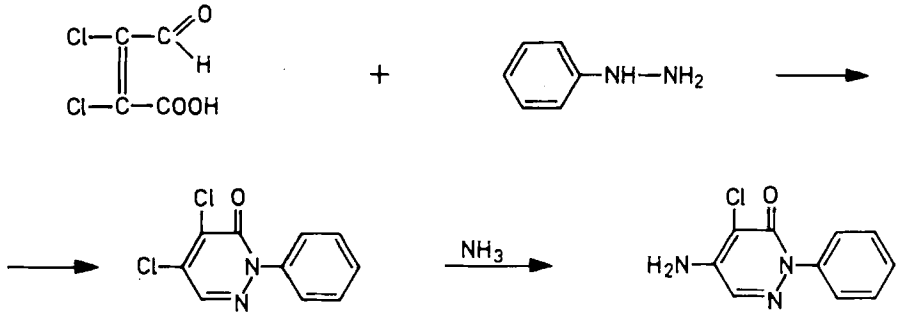


1

Technical pyrazon contains, besides the above compound, as impurity the isomer 4-amino-5-chloro-2-phenyl-3-pyridazone (isopyrazon).

Pyrazon is a crystalline compound virtually insoluble in water, soluble in dimethylsulfoxide and in dimethylformamide.

Several methods are described in the literature for the synthesis of pyrazon (Dury, 1965). Industrial processes generally follow the synthesis route described by Mowry (1953) and Reichenader *et al.* (1965), which starts from mucochloric acid and proceeds according to the following reaction scheme:



Mucochloric acid can be prepared by the oxidative chlorination of furfuraldehyde (furfural), or from furan carboxylic acid and butynediol.

The workers of the BASF research laboratories applied many patents for pyrazon analogues. Of these, several experimental products showed remarkable activity, but none of them have yet been introduced. Nevertheless, from the aspect of structure–activity relationships these endeavours in development are instructive (Fischer, 1962; 1965; 1967; 1968; Dury and Fischer, 1965).

Pyrazon is a preemergence herbicide effective against broad-leaved weeds. At a rate of 1.6–3.3 kg active ingredient/ha it is used for selective weed-control on sugar beet and other beet crops. It is less effective against grassy weeds, and is therefore used in combination with other herbicides that kill grassy weeds.

Pyrazon is absorbed by both roots and leaves of the plants and is translocated in the xylem. Owing to its poor water solubility, it is ineffective in dry weather.

The herbicidal action is manifested after a few days by the decolouration and slight curling of the leaves. The killing of the weed is complete in a few days.

Pyrazon is broken down in the soil by microorganisms. At normal temperature it persists for about 5 months. During degradation the benzene ring is split off, and pyrazon is decomposed to inactive 5-amino-4-chloropyridazin-3-one (Drescher and Otto, 1969).

The herbicidal mode of action of pyrazon is not yet completely known. In addition to inhibiting photosynthesis, pyrazon reduces CO_2-assimilation, O_2-uptake and the catalase activity in the leaves. All of these phenomena are manifested more strongly in the sensitive plants than in tolerant beet.

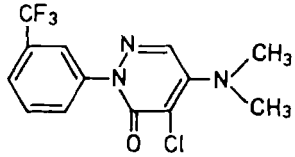
Tolerant sugar beet rapidly metabolises pyrazon absorbed through the roots or the leaves to N-glucoside, this is evidently the reason for selectivity (Ries *et al.*, 1968).

Pyrazon is moderately toxic to mammals. Administered per os, pyrazon is evacuated in 2 days in the urine, partly in the unchanged form, and partly coupled to glucuronic acid or as its hydroxylated derivative.

The acute oral LD_{50} is 3050 mg/kg for rats. The active substance has a mild skin irritating effect. It is not toxic to bees.

After the discovery of pyrazon the workers of the BASF prepared many substituted derivatives. Several patents and publications describe these new 1,2-pyridazones, but despite the indubitably interesting observations on the structure–herbicidal action relationships, this research had no practical results so far.

After almost 10 years two new pyridazinone derivatives have been developed in the Sandoz laboratories, differing from one another only with respect to one methyl group. The first of these is metflurazon, 4-chloro-5-dimethylamino-2-(α,α,α-trifluoro-*m*-tolyl)pyridazin-3-one (SAN 67064, **2**).



2

It is produced by the reaction of (α,α,α-trifluoro-*m*-tolyl)hydrazine with (*Z*)-2,3-dichloro-3-formylacrylic acid and the coupling of the product with dimethylamine.

Metflurazon is a selective preemergence soil herbicide effective for the control of several grasses and broad-leaved weeds on cotton, beet and flax at a rate of 4–8 kg active ingredient/ha. It efficiently kills several perennial grassy weeds, such as *Cyperus rotundus, C. esculentus, Cynodon dactylon, Sorghum halepense* and *Agropyron repens*. Because of its low water-solubility it is incorporated in the soil and the areas treated are irrigated.

Owing to its broad weed-killing range and to its residual activity of more than a year, metflurazon is also suitable for weed-control on industrial areas (Eder and Lavalleye, 1970).

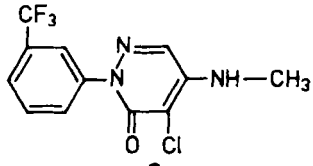
Metflurazon inhibits photosynthesis and prevents the development of chloroplastids in sensitive plants (Hilton *et al.*, 1969). The authors also report on their investigation of the mode of action of 4 pyridazinone herbicides on barley. Metflurazon and its phenyl- and unsubstituted amino analogues, structurally similar to pyrazon, also inhibited the Hill reaction and photosynthesis, but showed two further biological features: they resisted metabolic oxidation and inhibited chloroplast formation. The latter effect is similar to that of amitrol and dichlormate, but 100–1000 times stronger.

They established that CF_3 and dimethylamino substitutions are needed for the full effect. The action of analogues containing only one additional substituent is similar to that of pyrazon (Hilton *et al.*, 1969).

After treatment sensitive plants gradually discolour or bleach during the first few weeks without morphological changes. Sometimes the plants become red because of excessive autocyanine formation.

Hilton *et al.* (1969) found that the 50% Hill reaction inhibiting concentration of metflurazon is 4 mole/dm^3, a low value, but according to the investigations of Bartels and Hyde (1970) the primary cause of herbicidal action is in fact not the inhibition of photosynthesis, but the inhibition of carotenoid synthesis or of carotenoid accumulation (Bartels and Hyde, 1970). Practically, metflurazon is not toxic, its acute oral LD_{50} being 9100 mg/kg for rats.

The monomethyl analogue of metflurazon is norflurazon, 4-chloro-5-methylamino-2-(α,α,α-trifluoro-*m*-tolyl)pyridazin-3-one (**3**).



3

Herbicides with norflurazon as the active ingredient have been available commercially since 1971 under the trade names Zorial, Evital and Solicam in the form of WP or granules.

The range of action of norflurazon is similar to that of metflurazon, but it is a more potent herbicide. It can be used on cotton, stone fruits and cranberries at a rate of 1–4 kg active ingredient/ha. Its half-life in the soil is 21–28 days. It is susceptible to light.

According to the investigations of Strang and Rogers (1974) the major factors of the selectivities of metflurazon and norflurazon are the differences in absorption and translocation. In tolerant cotton the absorbed compounds are accumulated in the roots, while in sensitive soybean and maize significantly more herbicide is translocated to the shoots.

In sensitive soybean and maize metflurazon is rapidly demethylated to norflurazon, but this does not represent a detoxification mechanism, as norflurazon is more phytotoxic than metflurazon (Strang and Rogers, 1974).

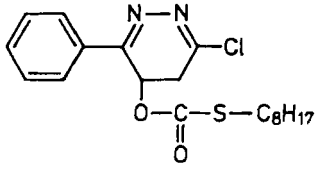
The biochemical mode of action of norflurazon was investigated by several workers (Böger and Schlue, 1976; Bartels and Watson, 1978; Devlin *et al.*, 1979).

It can be established from these investigations that unlike triazines and diuron, norflurazon damages the photosynthetic system of the plants. The main action is the blocking of carotenoid synthesis, as a result of which carotenoid precursors (phytoene and phytofluene) are accumulated because of the inhibition of dehydrogenation reactions.

Norflurazon is only slightly toxic to mammals, the acute oral LD_{50} for rats being 8000 mg/kg. LC_{50} for catfish and goldfish is 200 mg/l.

3-Phenylpyridazine derivatives have also a herbicidal action. The biological activity of this group has been investigated in the laboratories of the Chemie Linz AG. The precondition of good biological activity is a halogen, primarily chlorine, on the pyradizine ring in position 6, and a hydroxy, methoxy, acetoxy or ester group in position 4. The most potent derivatives are esters of the hydroxy group.

The compound found to have optimal selectivity, stability and herbicidal action is 6-chloro-3-phenylpyridazin-4-yl-S-octyl thiocarbonate, introduced under the code name CL-11 344, known by the common name pyridate (**4**).



4

The technical active substance is a brown, viscous oil, insoluble in water, and readily soluble in organic solvents. Pyridate is sensitive to hydrolysis.

Pyridate is a contact selective herbicide with foliar activity. It is effective for the control of annual broad-leaved weeds and some grassy weeds on cereals, maize, rice and some other crops at a rate of 1.0–1.5 kg active ingredient/ha. It has the advantage of killing efficiently some triazine-resistant weeds, such as *Galium aparine* and *Amaranthus retroflexus* in their early development (Discus *et al.*, 1976).

The mode of action of pyridate is probably the inhibition of the Hill reaction.

It is moderately toxic and has a slight skin irritating effect, its acute oral LD_{50} is 2000 mg/kg for rats, the LC_{50} (96 hours) for rainbow trout 81 mg/l. It is not toxic to bees.

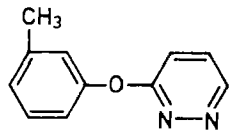
The 3-phenoxypyridazine herbicide group was developed by Japanese workers in the mid-1960s (Tamura *et al.*, 1956).

Takematsu *et al.* (1972), in their investigation of 3-phenoxypyridazines found that of substances mono-, di- and trisubstituted on the benzene ring with halogen, alkyl and alkoxy groups, those compounds with the best herbicidal activity contain an alkyl or halogen group in *ortho* position of the benzene ring. On tomato, cotton and Azuki beans an excellent margin of selectivity was exhibited by 3-(2-methylphenoxy)-, 3-(2,3-dimethylphenoxy)-, 3-(2,4-dimethylphenoxy)- and 3-(2,6-dimethylphenoxy)pyridazines.

For transplanted, submerged rice 3-(2-isopropylphenoxy)- and 3-(2-*n*-butylphenoxy)pyridazines showed a remarkable margin of selectivity, but 3-(2-methylphenoxy)pyridazine exhibited the highest herbicidal activity.

Jojima *et al.* (1972) investigated the relationships between the herbicidal activity of 3-phenoxypyridazines and the basicity of the N atoms of the compounds and the stability of their ether bonds. A good correlation was found particularly between the hydrolytic stability of the ether bonds and herbicidal activity.

A single member of the 3-phenylpyridazine group is available today commercially (e.g. 3-*o*-tolyloxypyridazine). It was introduced in 1970 by the Sankyo Chemical Ltd. under the trade name Kusikara®. Its common name approved by JMAF is credazine (**5**).



5

3-*o*-Tolyloxypyridazine is a stable crystalline compound insoluble in water and readily soluble in organic solvents.

It is a selective preemergence herbicide for soil application, particularly for the control of grassy weeds and several broad-leaved weeds. In Japan it is used in rice, potato, strawberry and pimento at a rate of 2–3 kg active ingredient/ha.

3-*o*-Tolyloxypyridazine is moderately persistent, in tolerant plants it is metabolised by the hydrolysis of the ether effect and glucosidation.

3-*o*-Tolyloxypyridazine is a compound of low toxicity. In rats peroral doses of 10 and 100 mg/kg are decomposed in 4 days by oxidative metabolism to unstable alcohol and carboxylic acid metabolites (Tanaka *et al.*, 1977). The acute oral LD_{50} for rats is 3090 mg/kg, for mice 569 mg/kg. It causes no dermal irritation. LC_{50} for carps is 62 mg/l.

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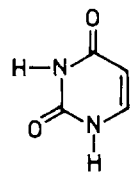
6.18 Uracils

Unsubstituted uracils have no herbicidal activity, but the growth-regulating action of certain substituted uracils has been recognised for some time (Ogolevets, 1960).

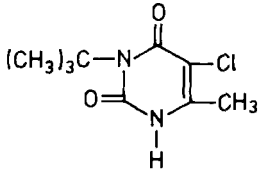


The strong herbicidal action of uracils substituted in positions 3,5,6 was first reported in the USA (Bucha *et al.*, 1962).

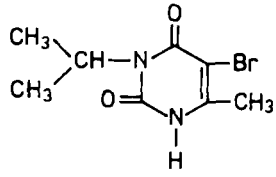
Most of the substituted uracils are total herbicides, but certain recently introduced derivatives have a selective action.

The first three compounds to attain importance in agriculture are: terbacil, 3-*t*-butyl-5,6-methyluracil **(1)**; isocil, 5-bromo-3-isopropyl-6-methyluracil **(2)** and bromacil, 3-*sec*-butyl-5-bromo-6-methyluracil **(3)**.

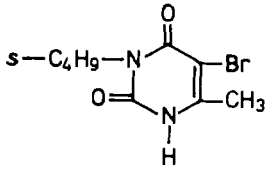
These substituted uracils may be prepared by several synthesis routes.



1



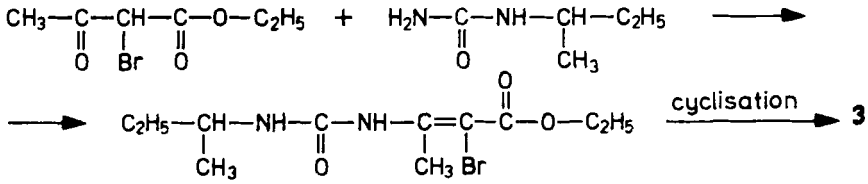
2



3

According to Bucha *et al.* (1962), the synthesis of isocil is effected by reacting isopropyl isocyanate with methyl 3-aminocrotonate to form methyl 3-(3-butylureido)crotonate, which is cyclised without isolation by heating in 6% sodium hydroxide. The uracil is then precipitated by acidification and brominated to give the end-product.

Bromacil may be prepared from bromoacetoacetic acid ethyl ester and *sec*-butyl urea in a two-step reaction according to the following scheme (Loux, 1962a,b):



Isocil and bromacil are soil-applied herbicides. Both block the Hill reaction and interfere with a step in the photosynthetic pathway close to oxygen evolution. This blocking may cause the accumulation of a phytotoxic product, possibly a reactive free radical. Though this particular antiphotosynthetic action is not in itself sufficient to explain the total phytotoxic action (Hoffmann, 1972), it is certain that the herbicidal action of substituted uracils is based on the inhibition of photosynthesis.

According to the investigations and data of Hoffmann *et al.* (1964), Hilton *et al.* (1964), Moreland (1967) and Hoffmann (1972), a concentration of 0.28–2 μ mole/dm^3 of the known substituted uracils is needed for the 50% inhibition of the Hill reaction.

Terbacil and bromacil do not inhibit the stem and root growth of higher plants in the dark, but inhibit the growth of *Chlorella* in light (Kratky and Warren, 1971).

Growth inhibition caused in *Chlorella* is a result of the inhibition of photosynthetic carbon dioxide fixation. It is proved by the experimental observation that

there is no growth inhibition in the dark in glucose nutrient solution, and, on the other hand, inhibition can be partly relieved by the subsequent addition of sugar (Hoffmann *et al.*, 1964).

Uracils are analogues of a very important building element of nucleic acids, pyrimidine, and thus might be incorporated in principle in nucleic acids. However, experiments of McGahen and Hoffmann (1963a,b) performed on desoxyribonucleic acids showed that bromacil is not incorporated in nucleic acids.

According to the investigations of Kecskés *et al.* (1974) in plants treated with lenacil (discussed later) and isocil, the level of RNA and DNA synthesis is diminished by 30%. In tolerant plants metabolism is more rapid, while in sensitive plants it is very slow. The main metabolite is 6-methyluracil.

Jordan *et al.* (1975) investigated in orange seedlings the metabolism of terbacil and found the following scheme of metabolism: terbacil 3-*t*-butyl-5-chloro-6-hydroxymethyluracil conjugation to *β*-glucoside.

Both herbicides are absorbed mainly through the roots and kill monocotyledonous and dicotyledonous weeds efficiently. Owing to their lack of selectivity, they are primarily used on industrial and non-crop lands at a rate of 10 kg active ingredient/ha.

Bromacil may also be used for selective weed control in citrus plantations at a rate of 1.6–3.2 active ingredient/ha against annual weeds, and at 3.2–8 kg/ha against perennial grassy weeds. Applied at the higher rate bromacil persists over more than a year.

Bromacil kills the shoots of yellow nutsedge *(Cyperus esculentus)* postemergence. In addition to the inhibition of vegetative growth, it also kills tuberous plants, rapidly exhausting their nutrients (Keeley and Thullen, 1974).

Bromacil is recommended preemergence in asparagus at a rate of 1.8–2.2 kg active ingredient/ha, and in raspberry after planting at 1.1 kg/ha for selective weed-killing.

Bromacil is very slightly soluble in water, so that much rain is needed for its activation. Its water-soluble formulation (Hyvar X–L) contains 21.9% bromacil lithium salt. It is incompatible with ammonium sulfamate, with the liquid formulations of aminotriazole, and with pesticides containing water soluble potassium salts.

Bromacil is mildly irritating to the skin, but does not sensitise. It is virtually nontoxic to mammals. Its acute oral LD_{50} for rats is 5200 mg/kg.

Terbacil (Sinbar®, Du Pont), introduced in 1966, is also used as selective weed-killer in sugar cane, apple and peach orchards, citrus plantations, established alfalfa and blueberry (Aitken and Arnolds, 1973; Meeklah and McRobb, 1973).

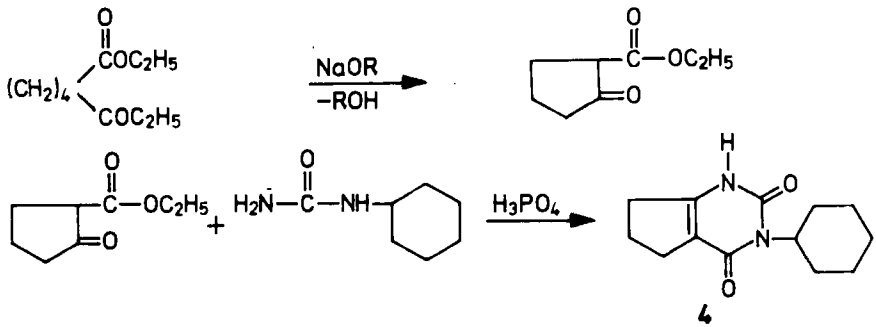
The recommended rate of terbacil in citrus plantations against perennial weeds (Johanson grass, Bermuda grass) is 4–8 kg active ingredient/ha, in the other crops 1–4 kg active ingredient/ha. The herbicidal action is first manifested in characteristic chlorosis, which is followed by necrosis.

Terbacil is practically nontoxic to mammals. Its acute oral LD_{50} for rats is more than 5000 mg/kg.

The adsorption of terbacil is in close correlation with the organic matter content of the soil. According to the investigations of Kratky and Warren (1973), to achieve the same herbicidal effect, 24 times as much terbacil was needed in a soil with 24% organic matter content as in a soil with 0.3% organic content.

Paulson (1975) gave a summary report on the investigations of the metabolism of terbacil in rats and dogs. Both herbicides are metabolised by several pathways (oxidation, dehalogenation, hydroxylation) and are finally evacuated from the organism in the form of conjugated metabolites.

Lenacil, 3-cyclohexyl-6,7-dihydro-1H-cyclopentapyrimidine-2,4-dione, also known as 3-cyclohexyl-5,6-trimethyleneuracil (**4**), is prepared by the condensation of ethyl-2-oxocyclopentane-1-carboxylate and cyclohexylurea with phosphoric acid, followed by boiling with sodium ethylate. From the sodium salt formed lenacil is precipitated by evaporation and acidifying (Sobeczensky, 1962a,b; Loux, 1965). 2-Oxocyclopentane-1-carboxylate may be made from adipic acid ethyl ester by Claisen reaction. The synthesis route is the following:



4

Lenacil is a stable, noncorrosive, crystalline compound with a melting point of 315.6-316.8°C. It is very slightly soluble in water (6 mg/l at 25°C) and organic solvents, with the exception of pyridine.

Lenacil is a selective root herbicide (Bucha *et al.*, 1962). In a way similar to bromacil and terbacil, its action is based on the inhibition of photosynthesis. It is used for preemergence or preplanting selective weed-control in red beet, sugar beet, spinach, strawberries and flax at a rate of 0.4–2.0 kg active ingredient/ha (Cussans, 1964).

Lenacil is not toxic to mammals, its acute oral lethal dose for rats is more than 10 000 mg/kg. It is degraded in the soil in one vegetative period.

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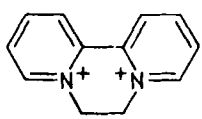
6.19 Quaternary ammonium salts

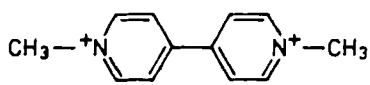
It has been known for some time that one group of surfactants, the quaternary ammonium compounds, are more phytotoxic than the anionic and nonionic types.

In 1954 at their research station in the Yealott's Hill ICI started a systematic research program to develop herbicides for practical purposes from the group of *o*-quaternary ammonium compounds. The first compound investigated was cetyltrimethyl ammonium bromide, which desiccates young seedlings in greenhouses at a rate of 15 kg/ha. This rate corresponds in field conditions to about 60 kg/ha, which would be uneconomical. By changing the length of the carbon chain attached to the nitrogen atom, a compound of only twice this efficiency could be attained.

The field of research was then extended to nontensioactive quaternary ammonium compounds, and in the reaction product of 2,2-bipyridyl, prepared for other purposes, with ethylene bromide a herbicide (diquat, **1**) was discovered which proved efficient in greenhouses at a rate of 125 g/ha (Brian *et al.*, 1958). This compound was followed by paraquat (**2**) (Jeater, 1963) and other isomeric bipyridyls and their substituted derivatives.



1
diquat cation



2
paraquat cation

In present agricultural use the 2,2′- and the 4,4′-bipyridyl diquaternary salts are prominent, the two most important are the quaternary salts of diquat and paraquat (Reglone® and Gramoxone®).

The carriers of herbicidal action are the 2,2′- and the 4,4′-bipyridyl cations, respectively; changing the quaternary group does not essentially change the herbicidal action.

Diquat and paraquat differ with respect to their biological action, although their chemical and physical properties are very similar. Characteristic is their ionic nature and excellent solubility in water. Their quaternary salts are stable and clear in acid and neutral solutions, but they form coloured complexes in strong alkalies, probably by the opening of one of the pyridine rings.

The reduction of diquat solutions gives a solution of an intense green colour. During the process a water-soluble, stable free radical is formed by the uptake of one electron. The free radical can be written in 18 possible resonance forms, and the odd electron can occupy any of the places in the nucleus. This delocalisation gives the free radical its stability.

The reduction, which can be carried out with sodium dithionite or zinc dust, is reversible, so that colourless diquat solution is formed again on shaking the solution with air.

Paraquat behaves similarly, giving on reduction a solution of an intense blue colour, which contains stable free radicals and is reconverted by oxygen to the basic compound.

This redox process of bipyridyls, as will be discussed later, is instrumental in the mechanism of their herbicidal action.

Diquat is used for general aquatic weed control, as a non-crop weed-killer for defoliation (preharvest top killer), for seed-crop desiccation and for the control of dodder (Cuscuta).

The rate of application for general aquatic weed-control is 2–4 kg active ingredient/ha, for non-crop weed control 0.5 kg/ha, for defoliation (of potato, alfalfa, etc.) 0.5–1 kg/ha, and for desiccation (of rice, maize, sunflower, oil flax, etc.) 0.4–0.5 kg/ha. The permissible residue is 0.5–2 ppm.

Paraquat is used for stubble cleaning, presowing and preemergence weed control, inter-row weed control of ploughed land, as a spray for subfoliar weed-control in maize, for inter-row weed-control in orchards, vineyards and tree nurseries, for pasture renovation and for total weed-control in non-crop areas. The rate of application is 0.4–1.5 kg active ingredient/ha.

The action of both herbicides can be increased by the addition of nonionic surfactants. Anion-active surfactants are incompatible with bipyridylium herbicides.

Activity investigations of substances derived from 2,2-bipyridyl prove that the pyridine rings of the molecule must lie in the same plane for a suitable herbicidal effect to be exerted.

With isomeric 4,4′-bipyridyl derivatives a substitution at any of the 4 carbon atoms adjacent to the linkage of the rings results in completely inactive compounds. Thus, coplanarity is here, too, a basic condition.

However, the complete inactivity of the quaternary derivatives of 2,3'-and 3,3'-bipyridyls shows that coplanarity, while necessary, is not the only condition for biological activity. These compounds, particularly the symmetric derivatives, are coplanar.

Michaelis and Hill (1933) showed that though the reduction of the quaternary salts of 4,4'-bipyridyl proceeds as a "two-electron" process, these compounds differ from other organic compounds in that the addition of the first and of second electrons proceeds at different, nonoverlapping electrode potentials. The first reaction product is the relatively stable free radical of intensive colour, formed by the addition of one electron.

The noncoplanar 4,4'-bipyridyl quaternary salts substituted at the carbon atom adjacent to the bond linking the rings cannot be reduced, which proves that biological activity is connected, at least in the first step, with a reduction process (Homer and Tomlinson, 1959; and Homer *et al.*, 1960).

In the case of the 2,3- and 3,3-bipyridyl derivatives there is no free radical formula, so the electron may occupy any position on the two rings; this may explain the absence of herbicidal action.

It is well known that the reducibility of a substance and the free radical formed as a result of reduction both depend on the redox potential. The more difficult the reduction of a compound, the more negative is the value of the redox potential. Of the bridge-form quaternary salts of 2,2'-bipyridyl the redox potential of diquat dibromide (E_o) is -349 ± 3 mV, while the redox potential of the 1,1'-trimethylene analogue, difficult to reduce, is -548 ± 3 mV. The difference in the two redox potentials is well reflected in their herbicidal activity.

The relationship between the limiting concentration in moles needed for the killing of the plants (T) and the redox potential (E_o) shows that the more negative the redox potential, the higher is the limiting concentration, that is the lower the phytotoxic efficiency.

The redox potential of diquat dibromide is -348 mV, and its limiting concentration for mustard is $1.5 \cdot 10^{-5}$ mole, while the redox potential of the homologue diquat trimethylene dibromide is -548 mV and its limiting concentration for mustard is $500 \cdot 10^{-5}$ mole.

However, the relationship between the actual herbicidal action and the redox potential of the compounds is not completely consistent. The redox potential of the quaternary diamyl salt of 4,4'-bipyridyl is nearly identical to that of paraquat; nevertheless, its limiting concentration is ten times that of paraquat. The redox potential of benzyl-viologen dichloride (1,1'-dibenzyl-4,4'-bipyridylium dichloride) is the same as that of diquat, but the compound has no herbicidal action. This irregularity is probably connected with the uptake by the plant.

Mees (1960) established through his experiments that bipyridyls have the characteristic property of acting more rapidly in light than in darkness. He concluded from this that energy needed for reduction is supplied by photosynthesis. Mees showed in further experiments that the presence of chlorophyll is also necessary for the exertion of the action, which is another indication of the

connection of their mode of action with photosynthesis. Mees determined by ingenious experimentation that, besides light and chlorophyll, oxygen is also needed for the exertion of phytotoxic action, demonstrating thereby the joint role of the three factors in biological action.

Another characteristic property of bipyridylium herbicides is their very strong basicity, so that by anion exchange the base exchange process takes place very easily with the cations of most of the clay minerals or with other ion exchange systems, such as ion exchange resins. This property is one of the most important and advantageous features distinguishing bipyridylium herbicides from other herbicides and ensuring their particular applicability.

Owing to ion exchange, bipyridyls are immediately inactivated on contact with most soils. Thus, ten times the practical foliar concentration can be applied on the soil without damaging plants growing in it.

Paraquat is more strongly adsorbed by the soil than diquat.

Two processes participate in soil adsorption. The first is a very strong, irreversible binding, not directly correlated with the concentration of the solution. These adsorptive bonds cannot be broken except by the complete destruction of the soil structure. The second process is a slower one in which the quantity of adsorbed herbicide is proportional to the concentration of the solution.

The base exchange capacity of most of the mineral soils is about 20 mole eq./100 g. Such soils are able to bind about 3.6% of paraquat. The base exchange capacity of sandy soils is 4 mole eq./100 g, corresponding to 0.75 w/w% of paraquat. Thus, a 1 cm layer of 1 hectare of soil can adsorb approximately 900–5000 kg of paraquat (Calderbank, 1966).

The adsorption process also proceeds in organic soils, but the situation is more complicated and not completely clear. Bipyridylium herbicides are strongly adsorbed and thus deactivated by organic soil. However, in peat soils, for example, adsorption is often slow or incomplete, so that residual action must be reckoned with (O'Toole, 1965).

Burns *et al.* (1973) investigated very thoroughly factors affecting adsorption and desorption of paraquat by the soil and the degradation of the paraquat adsorbed.

Diquat and paraquat are also strongly adsorbed on plant surfaces. Rain 30 minutes after spraying does not wash away the adsorbed herbicide.

The herbicides reaching the plant rapidly penetrate the green parts and destroy the tissues by contact action. Absorption, and consequently phytotoxic action, can be increased by nonionic surfactants. Concentrated paraquat solutions are more phytotoxic than dilute ones, and a spray applied in smaller droplets (100μm) is more phytotoxic than one of larger (300μm) drop size (McKinlay *et al.*, 1974).

Bipyridylium herbicides are absorbed only by the green parts of the plants and cannot penetrate phelloidal parts and woody bark. They can thus be selectively used in orchards and vineyards for weed-killing (Baldwin, 1963; Smith and Sagar, 1966).

Environmental conditions significantly affect the uptake and translocation of bipyridylium herbicides and thus their phytotoxic action. The quality and intensity

of light, the time of day of spraying and the moisture content of the air and soil are the main influences. Humid air and dry soil strongly increase the downward movement and thereby the destructive effect (Brian and Headford, 1968).

Calderbank (1968, 1972, 1976) wrote three excellent and exhaustive reviews on the chemistry and mode of action of bipyridylium herbicides.

Publications of Mees, Homer and Tomlinson in the 1960s on general herbicidal properties indicated that the phytotoxic action is connected with chlorophyll and light. The authors presumed, on the basis of the relationships between the reducibility of the single compounds and the phytotoxic action, that a reduction to a stable free radical occurs in the plant and that this free radical is responsible for phytotoxic action. The redox potentials of -0.446 and 0.346 mV of paraquat and diquat, respectively, are ensured by the reduction potential of light reaction I of photosynthesis (Calderbank, 1968).

The bipyridylium free radical is reconverted (oxidised) by the action of oxygen present in the leaf tissues, with the formation of hydrogen peroxide. Oxygen in the leaf tissue is formed during light reaction II by decomposition of water (Zweig and Avron, 1965).

In the biochemical process of photosynthesis bipyridylium compounds block the ferredoxinic photoreduction of NADP, thereby short-circuiting the electron current from NADP (Zweig *et al.*, 1965).

The formation of hydrogen peroxide has been demonstrated by Davenport (1963) and Davenport and Dodge (1969) in a chloroplast suspension treated with diquat. Reduction and oxidation of bipyridylium herbicides are cyclically repeated in the plant, so that catalytic quantities are sufficient to kill the plant.

Baldwin *et al.* (1968) showed experimentally that one paraquat molecule per one to two hundred chlorophyll molecules is sufficient to kill the plant. However, paraquat is not bound to some special site on the chlorophyll molecule.

But disturbance in photosynthesis leads to slow destruction and does not explain the very rapid phytotoxic action of bipyridylium herbicides, which in the presence of light, is manifested within hours by yellowing, wilting and necrosis.

Investigations of Merkle *et al.* (1965), Baur *et al.* (1969) and Harris and Dodge (1972) showed that the rapid physiological action of these herbicides can be attributed mainly to the destructive effect of peroxy radicals formed from hydrogen peroxide on the lipids of cell membranes.

The permeability of the cell membranes of leaf tissues is rapidly changed by bipyridylium herbicides, and this change proceeds independently of light conditions. The plasmalemma rapidly disintegrates, and chloroplast membranes swell, then burst. The other cell organelles also rapidly disintegrate, and finally only the components of the cell membrane and the granular substance of the cell nucleus remain in the cells (Baur *et al.*, 1969; Harris and Dodge, 1972).

Nonphotosynthetic tissues are only slowly attacked and disintegrated by bipyridylium herbicides, so this action is presumably not of primary importance for the mode of action (Bovey and Miller, 1968).

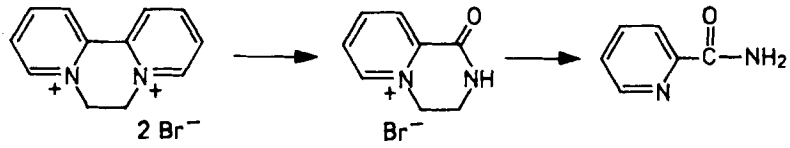
Bipyridylium herbicides also catalyse the noncyclic and cyclic phosphorylation reactions (Zweig, 1965; Jagendorf and Avron, 1968), but it is rather improbable that the inhibition of relevant $NADPH_2$ formation plays a role in their phytotoxic action (Corbett, 1974).

Bipyridylium herbicides also produce changes in other biological processes of plants. It has been shown experimentally that they have an effect on the respiration of plants, photosynthetic oxygen production and the intake of carbon dioxide and that they inhibit transpiration (Mees, 1960; Funderburk and Lawrance, 1964; van Oorschot, 1966; Dodge, 1971).

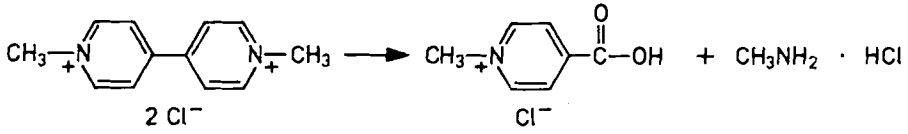
Bipyridylium herbicides are not metabolised by plants (Kearney and Helling, 1969).

Bipyridylium herbicides are broken down in the soil by microorganisms (Bayley and White, 1964; Bozarth *et al.* 1966; Funderburk and Bozarth, 1967; Calderbank and Tomlinson, 1968; Akhavein and Linscott, 1968).

In aqueous solution and adsorbed on silica gel diquat is decomposed by the action of the ultraviolet radiation of sunlight into tetrahydro-oxo-pyrido-pyrazonium bromide and then into picolin amide (Calderbank, 1968).



It is interesting that, on the other hand, paraquat does not undergo photolysis in aqueous solution (Slade, 1966), but adsorbed on silica gel or at the leaf surface, depending on the intensity of light, 25–50% is photolysed into 4-carboxyl-1-methylpyridinium chloride and methylamine within three weeks (Calderbank, 1968):



Diquat and paraquat cations are toxic to mammals. The nature of the anion does not affect toxicity. The acute oral LD_{50} of diquat for rats is 231 mg/kg, for dogs 100–200 mg/kg, and for cows 30 mg/kg. In long-term feeding experiments it causes, after 2–4 years, bilateral cataracts at daily levels of 20–50 ppm.

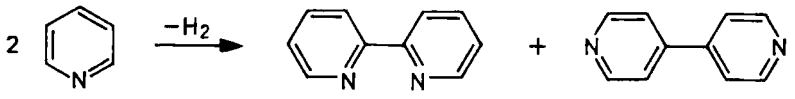
On longer contact it is absorbed through the skin. It may cause, even on brief contact, eye and skin irritation and damage to the nails.

The toxicity of paraquat exceeds by an average of 20–50% that of diquat (LD_{50} for rats is 150 mg), but does not cause cataract. Its irritating effect is the same as that of diquat.

In the concentrations used for aquatic weed control (diquat 1 ppm, paraquat 5 ppm) bipyridylium herbicides are not toxic to fish. The tolerance limit for the diquat cation is 6–12 ppm, for paraquat 125 pmm. The sensitivity of single fish species differs considerably. Owing to adsorption on mineral and organic colloids, rapid inactivation occurs in natural waters (Wurtz and Arlet, 1964; Howe and Wright, 1965).

Diquat and paraquat are not toxic to bees (Beran, 1970) and are harmless to earthworms. Bipyridylium herbicides have virtually no harmful side-effects on the microflora and microfauna of soils. They inhibit the growth of soil bacteria and soil fungi slightly but they have no significant effect on the microbes necessary for soil fertility. The same is true for the microarthropode fauna of the soil (Rodriguez-Kabana *et al.*, 1966; Calderbank and Tomlinson, 1968; Tu and Bollen, 1968; Wallnöfer, 1968; Mathur *et al.*, 1976).

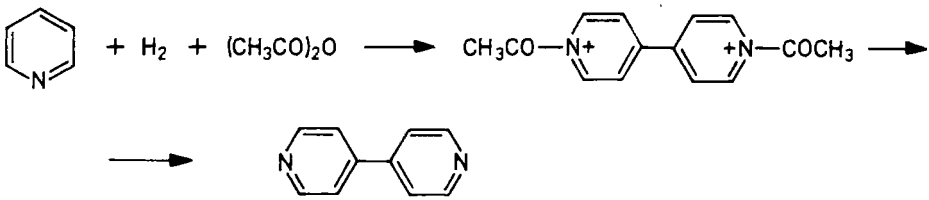
2,2′-Bipyridyl and 4,4′-bipyridyl are prepared industrially from pyridine by oxidative coupling according to the following reaction scheme:



The ratio of the isomers can be influenced by a change in reaction conditions. In the preparation of 2,2′-bipyridyl the oxidative coupling of pyridine is carried out over heated Raney nickel catalyst at 120–250°C. A product of 95% purity is formed at a yield of 60–70% (Brian *et al.*, 1956).

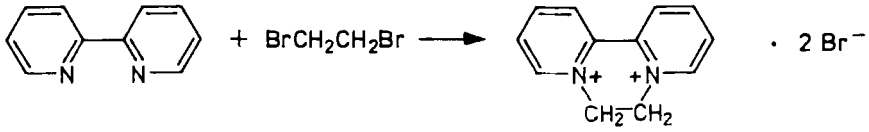
4,4′-Bipyridyl can be prepared from pyridine, forming first with sodium dispersed in liquid ammonia a transient pyridine radical, which is dimerised in the reaction mixture to 4,4′-tetrahydrobipyridyl. Its oxidation with air yields an end-product of about 90% purity.

4,4′-Bipyridyl can also be prepared from pyridine by the Dimroth reaction at a yield of about 60%. Pyridine is reduced in acetic anhydride with zinc dust to give amide, which is then oxidised and hydrolysed to 4,4′-bipyridyl of good purity.

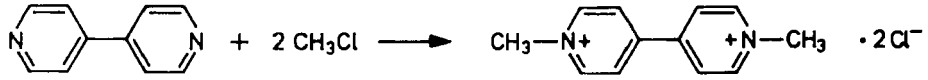


The water-soluble compounds with herbicidal activity can be prepared from 2,2′-bipyridyl and 4,4′-bipyridyl by alkylation.

The reaction of 2,2′-bipyridyl in aqueous medium and under pressure with ethylene dibromide gives 1,1′-ethylene-2,2′-bipyridylium dibromide (Fielden *et al.*, 1958):

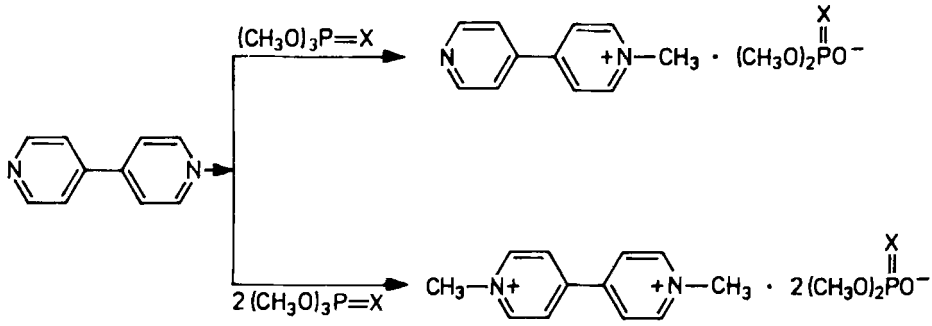


The alkylation of 4,4′-bipyridyl with methyl chloride gives 1,1′-dimethyl-4,4′-bipyridylium chloride (paraquat dichloride):



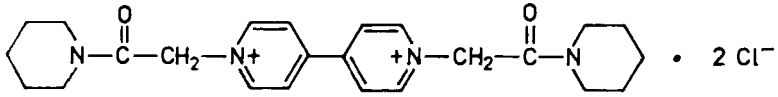
Paraquat dimethylsulfate has been prepared under the code number PP 148 by the alkylation of 4,4′-bipyridyl with methyl sulfate.

In the USSR the quaternary phosphate salts of 4,4′-bipyridyl, methylated on one or both of the nitrogen atoms, depending on reaction conditions, have been developed (Melnikov, 1971).



With the aim of increasing selectivity, the substituted derivatives of 4,4′-bipyridyl and their quaternary salts have also been synthesised.

1,1′-Bis(pentamethylene-carbamoylmethyl)-4,4′-bipyridylium dichloride, code number PP 407 (3)



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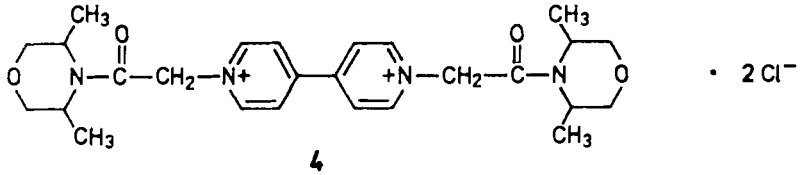
prepared by the condensation of monochloropentamethylene acetamide and 4,4′-bipyridyl, has been used with good effect against weeds resistant to 2,4-D.

1,1′-Bis(3,5-dimethylmorpholino-carbonylmethyl)-4,4′-bipyridylium dichloride (morphamquat dichloride, **4**) prepared by the condensation of monochloroacetic acid 3,5-dimethylmorpholide and 4,4′-bipyridyl (Fox, 1964; Fox and Beech, 1964) is effective as a lawn weed-killer on new grass or turf.



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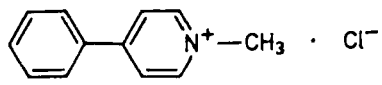
Due probably to their high production costs these herbicides have not gained widespread use.

Diquat dibromide and paraquat dichloride are crystalline substances that are stable in acid and neutral solutions but are hydrolysed by alkali.

Their aqueous solution are corrosive to metals, so formulations include corrosion inhibitors. The commercial products are aqueous solutions containing 140, 200 and 240 g/l of cations.

Schwartzbeck (1974) and Ahle and Cozart (1975) reported on a new phenylpyridinium herbicide with postemergence action.

Cyperquat, 1-methyl-4-phenylpyridinium chloride (**5**)



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is a water-soluble compound, specifically effective against purple and yellow nutsedge (*Cyperus rotundus* and *C. esculentus*) in the 6–9-leaf stage at rates of 2–4 kg/ha. It is tolerated by some ploughed land crops. In nontolerant crops it can be used for selective nutsedge-control by directed spray, as it does not act through the soil.

It is translocated relatively slowly from the leaves to the roots and tubers. Depending on temperature, light intensity and air and soil moisture, translocation proceeds in 4–8 days, the effect being manifested by chlorotic symptoms, which develop in 2–4 weeks into necrosis. Combined with other translocatable herbicides, such as 2,4-D, 2,4-DB or silvex, basipetal translocation and thus herbicidal action can be increased, and regrowth from tubers reduced.

The mode of action of cyperquat is unknown; presumably, being a bipyridylium herbicide, it inhibits photosynthesis.

The technical active substance is a strong poison, orally, dermally and by inhalation alike. The acute oral LD_{50} for rats is 35.1 mg/kg, the acute dermal LD_{50} is 23.7 mg/kg. The inhalation LD_{50} for rats is 34.6 mg/l.

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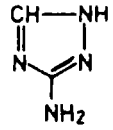
6.20 Azoles

Because this is a broad structural category, there are great differences among some of the herbicides discussed in this group with respect to composition and action. The patent literature contains reports on many compounds with herbicidal activity belonging to this group chemically, but so far only a few of them have gained ground commercially.

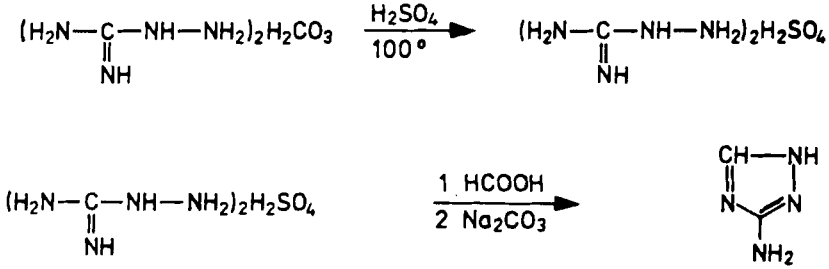
The herbicidal properties of the compound, 3-amino-1,2,4-triazole (amitrole, **1**), were first described by Behrens (1953). It was patented by Allen (1954) as a herbicide and plant growth regulator, and was introduced in 1955 by the Amchem Products Inc. under the trade name Weedazol®.



1

Amitrole is a white crystalline powder readily soluble in water in hot ethanol (280 g/l). It forms salts with acids and bases, behaves chemically as an aromatic amine, and is a strong chelating agent.

It can be synthesised by several routes. For industrial manufacture aminoguanidine is cyclised with formic acid in an inert solvent (Allen and Bell, 1946) according to the following reaction scheme:



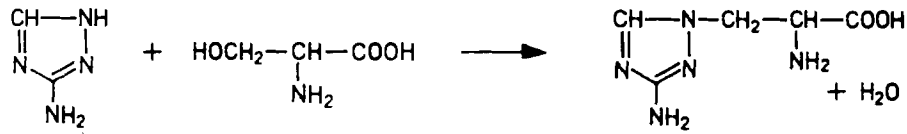
Amitrole is a nonselective herbicide, readily absorbed by the roots and leaves of the plant, and rapidly translocated in the xylem and phloem (Crafts and

Yamaguchi, 1960). Its action is synergised by the addition of ammonium thiocyanate. A similar enhancement of action can be obtained by the addition of surfactants.

Characteristic of its pattern of action is the transient red colouring, then the complete bleaching of the plants treated. Owing to its rapid translocation, it has proved to be an efficient herbicide for the killing of deep-rooted weeds. It is also used in combination with ureas and chlorotriazines.

The recommended rate of aminotriazole, depending on the prevailing weeds, is 2–20 kg active ingredient/ha. It is used in orchards after harvesting, on fallow land after harvest, 2–3 months before sowing, and in non-crop land. The biochemical mode of action of aminotriazole was investigated by several workers on yeasts, algae and higher plants (see the review by Carter, 1975). In higher plants the main action is the inhibition of carotinoid synthesis and of carotinoid accumulation. Thus, chlorophyll and probably other plastic components are photooxidised by sunlight. Moreover, amitrole irreversibly blocks several metabolic processes, such as amino acid and protein, nucleotide and nucleic acid, and riboflavine metabolisms, as well as catalase and other metalloproteine enzyme actions.

The degradation of amitrole in plants was investigated by Racusen (1958), Massini (1958, 1963) and Carter and Naylor (1959, 1961). During metabolism, glucose and protein adducts are formed without the opening of the amitrole ring, 3-(3-amino-1,2,4-triazole-1-yl)-2-aminopropionic acid (3-ATAL) being formed as main metabolite in the reaction with serine (Massini, 1963):



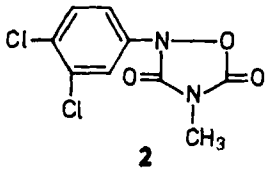
Amitrole rapidly disappears from the soil. According to the investigation of Kaufman *et al.* (1968) and Plimmer *et al.* (1967) degradation does not proceed by the biological pathway; this implies the opening of the amitrole ring and the formation of nontoxic products. However, microbial involvement cannot be excluded.

Investigating the metabolism of amitrole in animals, Fang (1964, 1966) found that amitrole fed to rats is evacuated in a few days in unchanged form, mainly in the urine.

In long-term feeding tests on male rats thyroid enlargement was observed in the experimental animals, from which a hazard of carcinogenity was concluded. However, on the basis of the investigations of Ashwood (1960) and Jukes and Schaeffer (1960) the carcinogenic effect could not be proved, because the thyroid enlargement observed during the feeding soon regressed after the termination of amitrole administration. Because of the suspected carcinogenic effect, the use of amitrole in fodder and food plant crops has been banned world-wide.

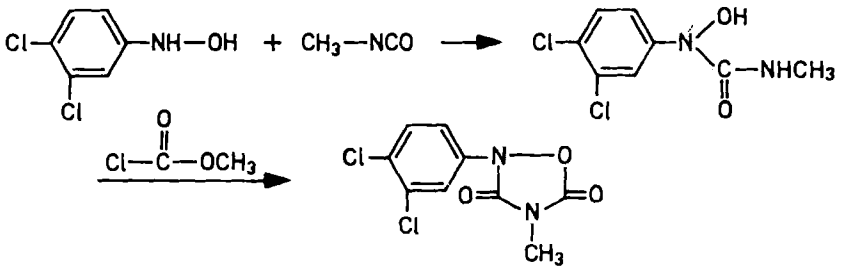
The acute oral LD_{50} of amitrole for rats is 1100–24 600 mg/kg.

The herbicide methazole, containing an oxadiazolidine ring, can be classed in the azole group. The herbicidal properties of this compound were first described in the 1960s. The composition of the compound, introduced under the code number VCS-438 is 2-(3,4-dichlorophenyl)-4-methyl-1,2,4-oxadiazolidine-2,5-dione **(2)** (Furness, 1970).



2

Methazole is a light tan solid prepared by two-step synthesis. In the first step the reaction of N-(3,4-dichlorophenyl)hydroxylamine with methyl isocyanate yields 1-(3,4-dichlorophenyl)-1-hydroxy-3-methylurea, which is cyclised with methyl chloroformate to methazole.



Methazole is a selective herbicide which can be used both as a residual soil herbicide and as a contact foliage-acting herbicide for the control of certain grasses and many broad-leaved weeds.

It is recommended for preemergence use in cotton, potato and garlic at a rate of 2–6 kg active ingredient/ha. It can be used as a directed spray on emerged weeds in cotton at a rate of 4–6 kg active ingredient/ha, in established vines, tea, stone fruits and citrus at 7–9 kg active ingredient/ha, on alfalfa established at least one year at a rate of 2 kg active ingredient/ha. Because of its low water solubility it has to be sprayed on moist soil to achieve efficient herbicidal action.

One of the advantages of methazole is its ability to kill efficiently in vines and orchards certain weeds that are difficult to control, such as *Sida spinosa* (prickly sida) and *Convolvulus* spp. (Butts and Foy, 1974a,b; Furness and Halawi, 1974).

According to the investigations of Jones and Foy (1972), in cotton methazole is translocated in the apoplast, and more methazole is absorbed and accumulated through the stem than in soil or foliar application.

Butts and Foy (1974a,b) found that the selectivity of methazole is based on the biochemical differences between sensitive and tolerant plants and depends heavily on the mode of application and the stage of development of the plant.

Because of its basicity methazole is strongly adsorbed in the soil, thus remaining in the upper layer of a few centimetres. Methazole is slowly degraded in the soil; its residual action must therefore be taken into consideration.

Methazole is rapidly metabolised in plants. The first metabolite, 1-(3,4-dichlorophenyl)-3-methylurea of the same phytotoxity as methazole, is then metabolised to 1-(3,4-dichlorophenyl)urea. The activity of the latter is one-twentieth of that of methazole (Jones and Foy, 1972; Dorough, 1974).

In the soil methazole is broken down according to the same scheme (Hoogstraten *et al.*, 1974).

Investigating the photodecomposition of methazole Ivie *et al.* (1973) found the following photoproducts: 3,4-dichloronitrobenzene, 1-(3,4-dichlorophenyl)-3-methylurea and two isomer dichloro-1-methyl-2-benzimidazolones.

Methazole is also metabolised relatively rapidly in mammals. The main metabolites are 1-(2-hydroxy-4,5-dichlorophenyl)urea glucuronide, 3-(3,4-dichlorophenyl)-1-methylurea and 1-(3,4-dichlorophenyl)urea in the free or in the glucoronide form (Gutenmann *et al.*, 1972; Dorough *et al.*, 1973, 1974; Atallah *et al.*, 1976).

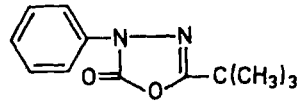
Methazole is moderately toxic to mammals. The acute oral LD_{50} for rats is 1350 mg/kg. It is mildly irritating to the skin and moderatly irritating to the eye. The subchronic (90-day) no-effect level is on the basis of rat feeding trials 50 mg/kg/day. Methazole is strongly toxic to fish, the LC_{50} (96-hour) for goldfish and rainbow trout being 3 mg/l.

Of the azole derivatives containing a diazole ring two new herbicides have been introduced in the last twenty years, and a few experimental herbicides are in the development stage.

The biological activity of oxadiazolone derivatives was first described in the research laboratories of Rhône-Poulenc.

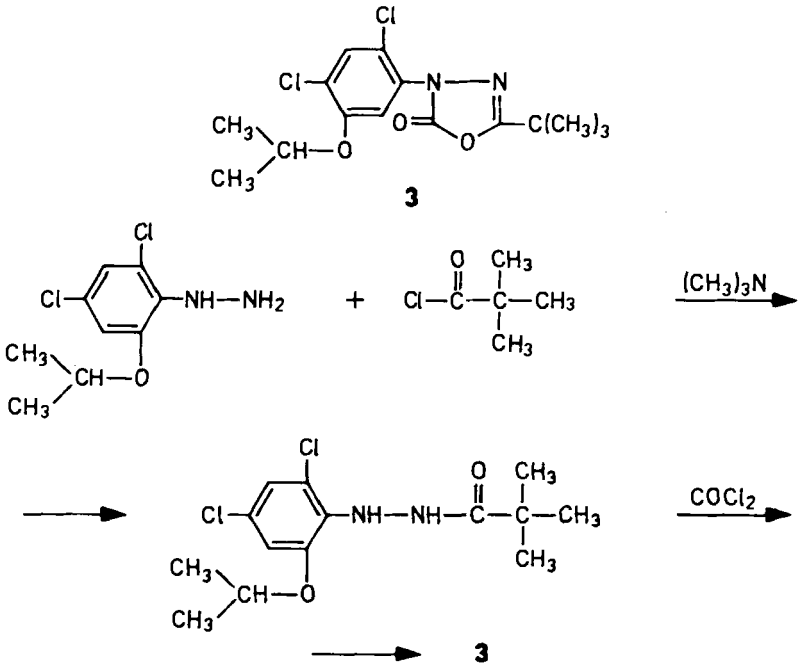
The compounds of the 3-alkylcarbamoyl-5-alkyl-1,3,4-oxadiazol-2-one group are insecticides, and the 3-phenylcarbamoyl-1,3,4-oxadiazol-2-one derivatives are fungicides, while the 5-*t*-butyl-3-phenyl-2-oxadiazolones are herbicides.

The last group is characterised by the following structural formula (Boesch and Metivier, 1963):



It was established within a short time that the herbicidal action can be increased by substitution in the phenyl group. Of the compounds containing chloro substituents on the phenyl ring in positions 2 and 4 and an alkoxy group in position 5 the most potent is 5-*t*-butyl-3-(2,4-dichloro-5-isopropoxyphenyl)-1,3,4-oxadiazol-2-one (oxadiazon, **3**), (Bourgaud *et al.*, 1969, 1970).

Oxadiazon can be obtained by the following synthesis route: pivaloyl chloride (trimethylacetyl chloride) is condensed with 2,4-dichloro-5-isopropoxyphenyl-



hydrazine, and the product is cyclised with phosgene (DOS 2039 397, Rhône-Poulenc, 1969).

Oxadiazon is a stable crystalline compound with a melting point of 90°C, insoluble in water and readily soluble in acetone, benzene, chloroforme. It is not corrosive.

Oxadiazon is a selective pre- and postemergence herbicide of medium persistence. Applied at a rate of 1–4 kg active ingredient/ha, it is effective for the control of several grassy and broad-leaved weeds.

It is used as premergence selective herbicide in rice at a rate of 0.6–1 kg active ingredient/ha (Perret and Simmonds, 1977). It has the advantage of killing the "problem" weed of rice, *Echinocloa crus galli.*

As preemergence herbicide it efficiently controls most of the broad-leaved weeds in soybean at a rate of 0.8–1 kg active ingredient/ha. In the case of strong grassy weed infection higher application rates are needed (Hunton and Cagnon, 1973, Hunton *et al.*, 1974).

Owing to its wide range of herbicidal action it is an effective weed killer in vineyards, orchards and woody ornamental plants at a rate of 4 kg active ingredient/ha preemergence or 2 kg active ingredient/ha postemergence. Oxadiazon is particularly advantageous in vineyards and orchards, where *Convolvulus arvensis* (bindweed) and *Calystegia sepium* infest the soil (Richardson *et al.*, 1976; Bailey and Simmons, 1979).

Oxadiazon alone is ineffective against *Stellaria* spp., and not sufficiently efficient against *Avena* spp., however, in combination with linuron these weeds, too, can be controlled. (Wilson and Hutchinson, 1970.)

The biochemical mode of action of oxadiazon is still little understood. According to the investigations of Kawamura and Hirai, 1976 and Kawamura *et al.*, 1976, in *Echinocloa crus galli* it acts on chloroplast ultrastructure, the nucleus and the cytoplasm.

Oxadiazon is absorbed by the roots and is translocated to the stem and the lower leaves, where it accumulates. Metabolism is slow, and several metabolites are formed. In rice mainly dealkylated metabolites and products oxidised in the side chain (alcohols or carboxylic acids) are formed, and the heterocycle is also opened. A very small quantity of metabolite, the derivative with the opened ring, reaches the ear (Ishizuka *et al.*, 1976).

Ambrosi *et al.* (1977) investigated the persistence of oxadiazon in the soil. After an incubation of 25 weeks 0.1–3.5% of the radioactivity could be detected in the form of CO_2, 0.5–1.1% in the volatile product, and 1.9–13.3% in the bound form.

At the recommended rate the half-life of oxadiazon is 80–180 days in the temperate zone.

Oxadiazon does not accumulate in mammals or birds. 95% of the herbicide administered orally is evacuated in unchanged form, while 5% is oxidatively metabolised into alcohols, carboxylic acids and phenol derivatives (Boesch *et al.*, 1974; Lefar and Gallo, 1974).

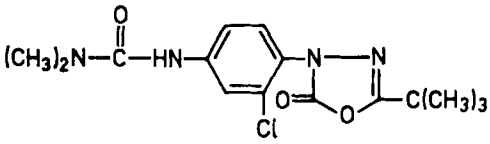
Oxadiazon is only slightly toxic to mammals. Its oral and dermal LD_{50} for rats is more than 8000 mg/kg. The no-effect level for rats and dogs is 25 mg/kg.

The homologue of oxadiazon, 5-isopropyl-3-(2,4-dichloro-5-propoxyphenyl)-1,3,4-oxadiazol-2-one was investigated as an experimental herbicide under the code number RP 20810 (Richardson *et al.*, 1976). The action of this compound is very similar to that of oxadiazon. Oxadiazon is somewhat more efficient for the control of annual grassy weeds, while RP 20810 is considerably more potent against *Stellaria media*. The two herbicides are equally effective against *Convolvulus* spp.

RP 20 810 is also selective mainly in broad-leaved crops. It is very well tolerated by large legumes, brassicas and carrot. It is a promising herbicide in peanuts and soybean.

RP 20 810 has a considerably briefer persistance in the soil than oxadiazon.

In 1974 Bourgaud *et al.* described the new oxadiazolone derivative of code number RP 23 465, dimefuron, 5-*t*-butyl-3-[2-chloro-4-(3,3-dimethylureido)-phenyl]-1,3,4-oxadiazol-2-one (**4**).

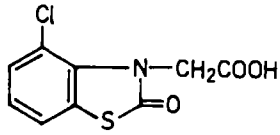


4

Dimefuron is a pre- and postemergence herbicide of high activity. At a rate of 4 kg active ingredient/ha it has a total effect, and it is very persistent at this rate. At a rate of 0.5–1.0 kg it selectively controls most of the annual broad-leaved and grassy weeds, with the exception of a few cruciferous weeds, in cereals, dormant alfalfa and legumes. Higher (2–3 kg) doses can be used in cotton, tea, cocoa, sugar cane and rubber plantations.

Dimefuron is of low toxicity to mammals.

The properties of this benzimidazole derivative benazolin, 4-chloro-2-oxobenzothiazolin-3-ylacetic acid **(5)** were described by Leafe (1964).



5

Benazolin may be prepared from 2-amino-4-chlorobenzthiazole, obtained by ring closure from *o*-chloroaniline and thiourea. 2-Amino-4-chlorobenzthiazole is converted into the 4-chloro-2-hydroxy compound, condensed with ethyl chloroacetate and hydrolysed to the endproduct.

Benazolin is a selective postemergence herbicide translocated in the phloem. Combined with phenoxy herbicides, such as MCPA and MCPB, 2,4-DB and 2,4-DP, it efficiently controls many broad-leaved weeds, particularly *Stellaria media* and *Galium aparine*, in undersown cereals and direct sown leys. Alone it is used against wild mustard, chickweed cleavers and oil seed rape at a rate of 0.9–2.5 kg active ingredient/ha (Shafer and Stobbe, 1973a, Rea *et al.* 1976). Used in the form of its water-soluble sodium or potassium salt it is not adsorbed in the soil and is rapidly leached.

The mode of action of benazolin is not known. Its retention and penetration are higher in sensitive plants, and the selective action can be attributed to this fact. It is rapidly metabolised in the plants and is also detoxicated by conjugation (Shafer and Stobbe, 1973b).

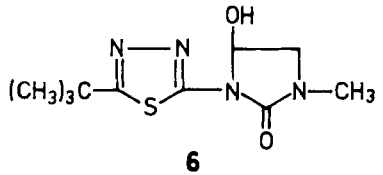
Benazolin is a slightly toxic compound. Its acute oral LD_{50} for mice, rats and dogs is 1000–3000 mg/kg. Subacute tests on rats showed that the no-effect level lies between 300 and 1000 mg/kg/day. The same value was found in chronic toxicity tests. Its aqueous solution is a slight irritant to the mucous membranes and the skin.

Recently the Velsicol Chemical Co. developed a herbicide containing two five-membered heterocyclic rings, which can be considered a substituted thiadizole or a substituted imidazolidinone. It was introduced under the code number VEL-5026 (Anderson, 1974). Its chemical composition is 3-(5-*t*-butyl-1,3,4-thiadiazol-2-yl)-4-hydroxy-1-methyl-2-imidazolidone (buthidazole, **6**).

Buthidazole is prepared in three steps from 2-amino-5-*t*-butyl-1,3,4-thiadiazole. In the first step it is reacted with carbonyl chloride. In the second, the intermediate formed is coupled with methyl (2,2-dimethoxyethyl)amin. In the third step this

product is heated with concentrated hydrochloric acid to yield buthidazole. The crystalline compound with a melting point of 133–134°C is slightly soluble (3–4 g/kg water) and more readily soluble in polar organic solvents.

Buthidazole is a residual herbicide for pre- and postemergence use. Owing probably to its poor water solubility, it is weakly absorbed in the soil, and thus is



6

washed by moisture into deeper soil layers (Furness *et al.* 1976). Buthidazole is readily absorbed through both the roots and the leaves and is rapidly translocated in the phloem and the xylem.

Buthidazole effectively controls most annual grasses and broad-leaved weeds. It is recommended at rates of 4–13 kg active ingredient/ha for total weed control in non-crop areas. Applied at a lower rate it can be used as a selective herbicide in maize, sugar cane and pineapple plantations. Depending on rainfall, the activity of buthidazole persists for 12–15 months.

Buthidazole is moderately toxic to mammals and fish. Its acute oral LD_{50} for albino rats is 1483–1581 mg/kg, the LC_{50} (96 h) is for bluegill 126 mg/l, for rainbow trout 74.7 mg/l (Anonym, 1979).

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6.21 Organophosphorus compounds

Organophosphorus pesticides became known and indispensable in agricultural use primarily because of their insecticidal action. More recently several groups of organophosphorus compounds with fungicidal action have been discovered as contact and systemic fungicides (see Section 5.2.4).

The first organophosphorus compounds with herbicidal action have been

introduced in the latter half of the 1950s. The first of these used in agriculture, S,S,S-tributyl phosphorotrithioate (**1**), was introduced in 1956 by the Chemagro Co. under the trade mark Defoliant®.

$$(CH_3—CH_2—CH_2—CH_2S)_3P=O$$

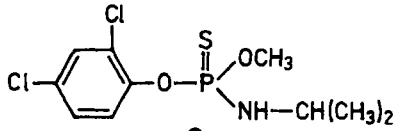
1

The liquid active substance, insoluble in water and readily soluble in organic solvents, is prepared by the reaction of phosphoryl chloride and butene-1-thiol in the presence of an acid acceptor.

The compound is strongly phytotoxic and is used for the defoliation of cotton at a rate of 1.0–2 kg active ingredient/ha.

Its acute oral LD_{50} for female rats is 325 mg/kg (Murphy and Du Bois, 1959), its acute dermal LD_{50} for rats 850 mg/kg.

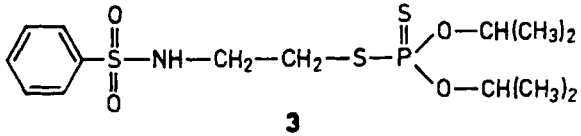
DMPA, O-(2,4-dichlorophenyl)-O-methyl-isopropyl phosphoroamidothioate (**2**), was introduced in 1958 (Zytron®).



2

DMPA is a preemergence soil herbicide which has been used in turf for the control of crab grass (*Digitaria* spp.), and in soybeans, peas, beans and onions against grass weeds (Roberts *et al.*, 1966), but it has been superseded today.

The representative of the phosphoridithioate ester group with herbicidal action is O,O-diisopropyl-S-(2-phenylsulfonylamino)ethyl phosphorodithioate (bensulide, **3**), which was developed by the Stauffer Chemical Co. and introduced in 1964 under the trade marks Betasan® and Prefar® (Hemphill, 1962).



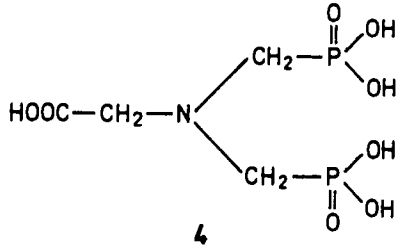
3

Bensulide is prepared by the condensation of N-(2-chloroethyl)-benzenesulfonamide and ammonium diethylthiophosphate. Bensulide is a moderately persistent preplanting and preemergence herbicide. It is used preemergence on established turf at a rate of 11–22 kg active ingredient/ha, and preplanting on cotton, cucurbites, brassicas and lettuce (Prefar®) at a rate of 2.3–7.0 kg active ingredient/ha. At high rates it persists for a year (Menges and Tamez, 1974).

Bensulide is moderately toxic, its acute oral LD_{50} for male albino rats being 770 mg/kg, its acute dermal LD_{50} 3950 mg/kg.

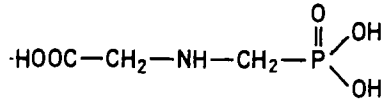
The first member of the phosphonate group, 2-chloroethylphosphonic acid, introduced under the trade mark Ethrel®, is a plant growth regulator with no herbicidal action.

The development of phosphonates with herbicidal properties came in the 1970s. The plant growth regulating action of N,N-bis(phosphonomethyl)glycine (glyphosine, **4**) was discovered in the research laboratories of the Monsanto Co. (Porter and Ahlrichs, 1972). This compound is used to accelerate the growth of sugar cane and to increase its sugar content.



4

N-phosphonomethylglycine (glyphosate, **5**) a compound closely related to glyphosine, was introduced as a herbicide in 1971 under the trade mark Roundup®, (Baird *et al.*, 1971).



5

Glyphosate can be prepared according to the method of Moeritzer and Irani (1966) by the reaction of orthophosphorous acid with formaldehyde and glycine in the presence of sulfuric acid.

Several processes for the preparation of glyphosate have been patented. In the process of Smith (1972) N-(phosphonomethyl)iminodiacetic acid, hydrolysed with a strong acid, gives glyphosate at a good yield and, as by-products, formaldehyde, glycolic acid and other decomposition products.

Glyphosate can be also prepared from N-(phosphonomethyl)iminodiacetic acid by oxidation or by hydrolysis in alkaline medium at good yields.

Glyphosate is a white, crystalline compound. Its solubility in water is 12 g/l, it is insoluble in organic solvents. In agriculture its mono-isopropylamine salt which is completely soluble in water, is used. The concentration of the formulation Roundup® is 480 g of glyphosate-isopropylammonium/l (360 g acid equivalent/l).

Glyphosate is a nonselective postemergence herbicide. Its range of herbicidal action is uncommonly wide—it is effective against mono- and dicotyledonous annual and perennial weeds. It is rapidly translocated from the leaves to the roots, rhizomes and stolons, so it is also efficient in the control of deep-rooted perennial grasses, such as *Agropyron repens, Cyperus aesculentus, Imperata cylindrica, Cynodon dactylon, Panicum* spp., *Sorghum halepense* as well as various broad-leaved perennial weeds, for example, *Convolvulus* spp., *Cirsium arvense, Plantago lanceolata, Rumex crispus, Solanum carolinense, Taraxacum officinale, Tussilago farfara* and *Urtica dioica.*

In contrast to other known herbicides, glyphosate is more efficient against older weeds, so it is to be used in the later growth stages. Its recommended rate is 0.7–5.6 kg active ingredient/ha. It is recommended, in addition to industrial and non-crop areas, for application as directed spray in orchards, vineyards, rubber, coffee, citrus, tea and oil palm plantations (Anonym., 1971; Kemmer, 1978; Kafadaroff *et al.*, 1977; Wurgler and Neury, 1977; Bailey, 1978; Richardson and Lynn, 1979, Franz, 1979).

The phytotoxic effect of glyphosate can be increased by additives enhancing absorption and translocation. According to the investigations of Wills (1973) the addition of various salts and surfactants to glyphosate does not increase its initial phytotoxicity, but increases the duration of effectiveness from 2 to 8 months. Of the cations K^+, of the anions PO_4^{3-} had the best effect.

Turner and Loader (1975) investigated on bean leaves the change of the phytotoxic action of glyphosate caused by ammonium sulfate and butyl acid phosphates (BAP = a mixture of dibutyl hydrogen phosphate and butyl dihydrogen phosphate). Both of the additives increased the phytotoxicity of glyphosate.

The investigations of Fiveland (1978) also showed an increase in potency on adding two- to fivefold quantities of ammonium sulfate to glyphosate, but only at low rates of glyphosate.

The joint action of glyphosate–ammonium sulfate composition against *Agropyron repens* has also been investigated at glyphosate rates from 0.72 to 1.44 kg active ingredient/ha, but the effect of ammonium sulfate was found to be inconsistent.

Kemmer (1978) investigated the effect of the herbicide Roundup® on stubble-field against *Agropyron repens* at application rates of 4-6-8 l/ha and found that the effect depends more on the time of application than on the dose. For optimal effect spraying must be done at least two weeks before ploughing.

Glyphosate is rapidly and strongly bound in the soil and thereby inactivated. Bonding to Al, Zn, Fe or Mn clay complexes and to organic soil constituents is strong. The simultaneous application of P_2O_5 considerably reduces the adsorption of glyphosate, indicating that P can compete for the bonding sites of glyphosate in the soil. The adsorption of glyphosate also depends on the pH of the soil, the adsorption of the herbicide being higher in acid soils (Sprankle *et al.*, 1973, 1975).

In the soil glyphosate is broken down by microorganisms. The end-product of degradation is CO_2, with aminomethyl phosphonic acid formed as intermediate product ($H_2N—CH_2PO(OH)_2$) (Torstenson and Aamisepp, 1977; Nomura and Hilton, 1977; Moshier, 1978).

The mode of action of glyphosate is not yet fully understood. Jaworski (1972) found in investigations on *Lemna gibba* and *Rhizobium japonicum* bacteria that glyphosate inhibits the biosynthesis of aromatic amino acids.

In the treated plants the biosynthesis of phenylalanine, more particularly the metabolism of chorismic acid, is inhibited. Similar conclusions were drawn by Roisch and Lingens (1974) in experiments with *Escheria coli*.

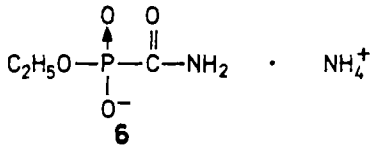
Tymonko and Foy (1978) found in soybean an inhibition of leucine incorporation and a general disturbance of protein synthesis in plants treated with glyphosate.

Some of the weed species, such as *Euphorbia esculenta, Equisaetum arvense, Hedera helix* and *Robia peregrina*, are resistant to glyphosate. (Gottrup *et al.*, 1976; Kafadaroff *et al.*, 1977).

Glyphosate is moderately toxic to mammals. Its acute oral LD_{50} for rats is 4320 mg/kg, its acute dermal LD_{50} for rabbits is higher than 7940 mg/kg.

The acute toxicity of the formulated product (Roundup®) for fish and aquatic invertebrates (LD_{50}, 96 hours) varies between 2.3 mg/l and 43 mg/l (Folmar *et al.*, 1979).

A new representative of the aliphatic phosphonate group is ammonium ethylcarbamoyl phosphonate (fosamin-ammonium, **6**).



6

The herbicide introduced under the code name DXP 1108 and protected by US Pat. 3 627 507 and 3 846 512 was first described by Zoebisch *et al.*, (1974).

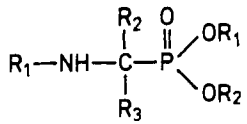
Fosamin-ammonium, prepared by the reaction of triethylphosphite, methyl chloroformate and ammonia, is a crystalline compound with a melting point of 175°C, readily soluble in water (at 25°C, 1.79 kg/kg water). It hydrolyses in dilute acid solution (Schwerdtfeger and Allison, 1976).

Fosamin-ammonium is a contact herbicide used in autumn before the shedding of leaves in non-crop areas at a rate of 6.8–13.5 kg active ingredient/ha with the addition of a surfactant, against deep-rooted weeds (*Convolvulus arvensis* and *Pteridium aquilinum*), and as a shrub killer. Spring application causes growth suppression and abnormal leaf growth.

On fruit trees it can be used at a rate of 0.24 kg active ingredient/ha against sprouts. Fosamin-ammonium is also recommended in coniferous plantations against decidous trees and shrubs. It does not act through the soil. The species *Malus* and *Prunus* are sensitive to fosamin-ammonium (Atkinson *et al.*, 1978).

Fosamin-ammonium is not toxic, its acute oral LD_{50} being 24 000 mg/kg for rats (Anonym, 1976).

Kramer *et al.* reported in 1974 on a new biologically active phosphoric acid ester group. Compounds with herbicidal activity can be characterised with the following general formula:



where R_1 = alkyl

R_2, R_3 = alkyl or cyclohexyl

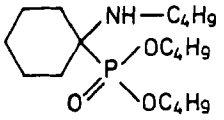
Of this group of compounds O,O-dibutyl-1-butylaminocyclohexyl phosphonate (aminophon, **7**) proved to be the most efficient.

Aminophon is primarily a defoliant and desiccant recommended at a rate of 7–8 l/ha for the destruction of potato and cotton haulm. It can also be used preemergence for the control of weeds in onions and legumes. It is rapidly translocated and metabolised in the plants, and does not move in the soil (Dedek and Partisch, 1976).

Aminophon is moderately toxic, its acute oral LD_{50} being 7000 mg/kg for rats; however, it is highly irritating to the skin. The no-effect level for rats in 130-day feeding tests is 1000 ppm.

Another phosphonoamidothioate group was developed by Soviet research workers (Melnikov *et al.*, 1974).

The most selective member of this group, introduced under the trade mark Isophos-3®, is chlorometyl O-(2-chloro-4-tolyl)-N-*sec*-butyl phosphonoamidothioate (**8**).



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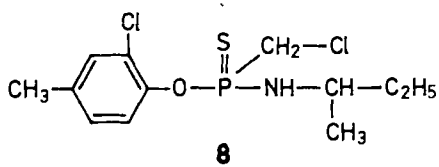
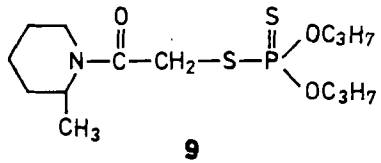


8

Isophos-3® is recommended in preplanting application mainly in rice at a rate of 1 kg active ingredient/ha. It is particularly effective against grassy weeds. It kills *Echinocloa crus galli* during the whole season. It is a strongly adsorbed by soils rich in humus. Depending on soil and climatic conditions, it is persistent for 30–100 days. It is metabolised in rice in 25 days, in *Echinocloa* in 40 days.

The acute oral LD_{50} of Isophos-3® for rats is 510 mg/kg.

Another representative of dithioesters is S-(2-methylpiperidinocarbonylmethyl)-O,O-dipropyl phosphorodithioate (piperophos, **9**).



9

Piperophos is a selective herbicide recommended for pre- and postemergence application in rice for the control of annual grassy weeds (Green and Ebner, 1972).

Piperophos is a colourless liquid, immiscible with water but miscible with organic solvents. It is absorbed by both the leaves and the roots and can therefore be used pre- and postemergence. Its action is specific against *Echinocloa crus galli*. Its effect can be enhanced by combination with dimethametryn (Nakasa and Dachler, 1976). In the tropics it is combined with 2,4-D.

The acute oral LD_{50} of piperophos is 324 mg/kg for rats, its acute dermal LD_{50} is more than 2150 mg/kg.

Aya *et al.* investigated in 1973 the biological activity of the O-alkyl-O-(substituted phenyl) phosphoroamidothiaotes. Derivatives containing the *o*-nitrophenyl group with halogen, lower alkyl or alkoxy substituents in *para*-position proved to be the most active.

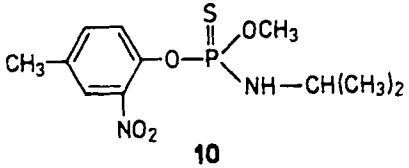
The most selective member of the group is O-methyl-O-(2-nitro-4-tolyl) isopropylphosphoroamidothioate (amiprofos-methyl, **10**).

Amiprofos-methyl is a selective preemergence herbicide. It does not inhibit germination but suppresses the growth of roots and shoots. Its main action is the inhibition of mitosis. Its action is selective in maize, cotton, rice and several garden vegetables.

Its acute oral LD_{50} for rats is 609 mg/kg.

A very close analogue of amiprofos-methyl has been developed by the Sumitomo Company (Ohkawa *et al.* 1975; Ueda, 1975).

The new herbicide is butamifos (**11**), O-ethyl-O-(6-nitro-3-tolyl) *sec*-butylphosphoroamidothioate.



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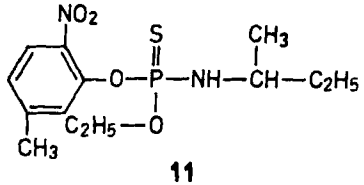

11

Butamifos is also a herbicide inhibiting mitosis (Sumida and Ueda, 1976). It disrupts the spindle apparatus in sensitive plants, so that mitosis is blocked in the metaphase.

Ohkawa *et al.* investigated in 1975 the difference in herbicidal action of the two optical isomers of the compound and found in *E. crus galli* a 3–4-fold, in rice a 3–6-fold difference in activity between the enantiomers.

Butamifos is selective in turnip, water melon and lettuce. Its half-life in the soil is 50–67 days.

Its acute oral LD_{50} is 630–790 mg/kg for rats.

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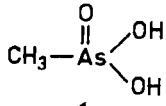
6.22 Organoarsenic compounds

Inorganic arsenic compounds were discussed in the chapter on inorganic herbicides. The use of organic arsenic compounds began in the 1950s in the USA. Even today several substituted arsenic acid derivatives are used only in the USA for total weed-control on non-crop land, on cotton and for turf treatment.
Methylarsonic acid (MMA, **1**) is a strong dibasic acid, readily soluble in water and in ethanol.



1

The monosodium salt (MSMA) and the disodium salt (DSMA) are used as herbicides.

DSMA is prepared according to the following reaction scheme.

$$As_2O_3 + 6NaOH \rightarrow 2Na_3AsO_3$$
$$Na_3AsO_3 + CH_3Cl \rightarrow Na_2CH_3AsO_3 + NaCH_3SO_4$$

An alternative route is methylation with dimethyl sulfate.

Both salts are very readily soluble in water and in methanol.

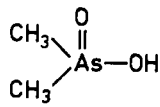
MSMA and DSMA are selective postemergence contact herbicides with some systemic action. A surfactant must be added to the nonformulated active substances, complete coverage by the spray being vital for adequate herbicidal action.

MSMA is recommended for the control of grassy weeds at the following rates: on cotton as directed spray 2–3 kg/ha; on sugar cane 3.0 kg/ha; in orchards, as directed spray 4–5 kg/ha, dissolved in 100–200 l water. Combined with 2,4-D or diuron it is used for non-crop areas and on turf.

DSMA is recommended on cotton, for turf treatment and for non-crop areas at a rate of 2–4 kg/ha for the control of grassy weeds.

Methylarsinic acid salts are moderately toxic and do not accumulate in animals. The acute oral LD_{50} of MSMA for albino rats is 900 mg/kg, that of DSMA 1800 mg/kg. The dietary no-effect level of the acid is 100 mg/kg. Practically, the two active substances are barely toxic to fish, LC_{50} (48 h) being for bluegill more than 1000 mg/kg, though the addition of surfactants increases this toxicity.

Dimethylarsinic acid (cacodylic acid, **2**) is prepared by the reduction of disodium methylarsonate with sulfur dioxid, followed by methylation.



2

It can also be prepared by Cadet's cacodyl reaction. In this method, cacodyl oxide first is prepared by the reaction of K- or Na-acetate with arsenic trioxide, and this is then oxidised with HgO or air to dimethylarsinic acid (Treffler, 1944).

The reaction scheme is the following:

$$4\,CH_3COONa + AsO_3 \rightarrow (CH_3)_2AsOAs(CH_3)_2 + 2CO_2 + 2Na_2CO_3$$
$$(CH_3)_2AsOAs(CH_3)_2 \xrightarrow[air]{HgO} 2(CH_3)_2AsOOH$$

Dimethylarsinic acid and its sodium and potassium salts are very readily soluble in water.

Dimethylarsinic acid is a nonselective, postemergence contact herbicide. It is inactivated by contact with the soil. It is used as a general weed-killer admixed with surfactants at a rate of 11–17 kg/ha, as a desiccant and defoliant for cotton at a rate

of 1.1–1.7 kg/ha, and for lawn renovation 5 days before reseeding at 11–17 kg/ha. It can also be used for killing unwanted trees by injection.

The acute oral LD_{50} of dimethylarsinic acid is 1350 mg/kg for rats. It is not irritating to the skin or eye.

Plants treated with organic arsenic compounds first show symptoms of chlorosis and then cease to grow. They gradually become brown and finally wither. Action develops slowly, increased temperature accelerating the action.

Both herbicides discussed are translocated in the plant. Cacodylic acid is translocated only apoplastically, while DSMA is translocated in the phloem in the assimilation stream (Long and Holt, 1959, Holt *et al.*, 1967; Sachs and Michael, 1971).

Arsenical herbicides are strongly adsorbed in the soil and thus resist leaching. Their frequent application and high rates may therefore cause arsenic residue problems.

The biochemical action of arsenic herbicides is primarily interference in phosphorus metabolism. They probably kill plants be the uncoupling of oxidative phosphorylation and by the blocking of the enzymes containing sulfhydryl groups.

Because of the present rigorous regulations of environmental protection it is expected that these types of herbicides will be replaced by new, nonpersistent compounds.

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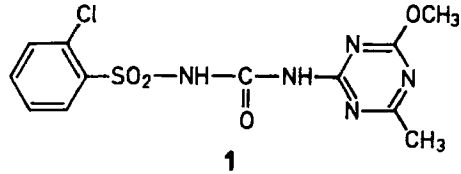
6.23 Sulfonylurea herbicides

Du Pont has recently developed a new group of selective herbicides, the sulfonylureas, from which three candidates have shown extraordinary activities: DPX 4189, DPX-T 6376 and DPX 5648.

DPX 4189, 1-(2-chlorophenylsulfonyl)-3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)urea (chlorsulfuron, **1**), (Levitt, 1978, 1979, 1980) is synthesised by adding an equivalent of 2-chlorobenzenesulfonyl isocyanate to a suspension of 2-amino-4-methoxy-6-methyl-1,3,5-triazine in acetonitrile (Levitt *et al.*, 1981). The compound is moderately soluble in acetone and acetonitrile. The sodium salt of chlorsulfuron has a solubility of 5–10% in water.



1

Chlorsulfuron is the active ingredient in Du Pont "Glean" Weed Killer. A very important feature of this new selective herbicide compound is its very high herbicidal activity at very low application rates. The compound controls most broad-leaved weeds in small grains at 10–40 g/ha. It is nonvolatile and is active due to uptake through both foliage and root system.

The first weed-control reports in cereals and fallow were published in 1979 (Hageman and Behrens, 1979; Miller and Nalewaja 1979). After the first summarised development report of 1979 (Levitt *et al.*, 1980) Palm *et al.* (1980) gave a world-wide review of the chlorsulfuron.

In the crop tolerance tests winter and spring wheat and barley have shown greatest tolerance to postemergence treatments. 70–100 g active ingredient/ha rates have commonly not reduced yield. Barley is sensitive to pre-emergence treatment. In Europe in the autumn winter wheat has shown no injury at 40 g active ingredient/ha preemergence of early postemergence. On winter barley autumn postemergence treatments up to 30 g active ingredient/ha are safe.

In the spring cereal belt of Canada and North Central United States 20–30 g active ingredient/ha as a postemergence treatment controlled adequately the typical broad-leaved weeds. These were *Cirsium arvense, Galium, Galeopsis, Chenopodium, Polygonum* spp., *Stellaria, Kochia, Amaranthus, Spergula, Solsola, Rumex, Matricaria* and all of the *Cruciferae* spp.

In the winter cereal belt in North America and Australia, similar rates also controlled *Helianthus, Erodium, Lithospermum, Amsinckia, Lamium, Oxalis* and *Emex*. At rates of 35–70 g active ingredient/ha early postemergence treatments controlled significantly *Lolium, Seteria* and *Poa*.

In Europe chlorsulfuron has demonstrated additive activity on *Alopecurus myosuroides* and has broadened the spectrum of neburon, chlortoluron, isoproturon, methobenzthiazuron.

Grass weeds have been more susceptible to treatments before emergence or early past *versus* late postemergence. In the FRG and UK chlorsulfuron was tested in winter cereals in combination with ioxynil, bromoxynil and MCPP by postemergence treatment to get a broader weed-control spectrum. The combination treatments gave good control against problem broad-leaved weeds as *Stellaria, Viola, Galium, Lamium, Veronica* and *Matricaria*.

Chlorsulfuron performed world-wide in the 1980 trials as well under cold as warm weather. Herbicidal effects develop fastest under good growing conditions. Under dry situation the weeds remain suppressed several weeks before death.

Chlorsulfuron is a residual soil herbicide. Its half-life in the soil is 1–2 months.

Degradation is by hydrolysis to inactive compounds. Some broad-leaved crops — as sugar beet, mustard and rape — are very sensitive to the usual small residues. Where these crops are grown in rotation, the rates to evaluate are 15–30 g active ingredient/ha as a preemergence treatment on winter wheat or as an early postemergence treatment on winter wheat or barley in the autumn.

Chlorsulfuron does not affect normally seed germination, but the subsequent seedling growth is severely inhibited in susceptible plants.

Death of treated plants is generally shown and is accompanied by chlorosis, necrosis, terminal bud death and vein discoloration.

Mode of action studies on isolated leaf cells and chloroplasts (De Villiers *et al.*, 1980) have shown that chlorsulfuron primarily affects the light-dependent part of the photosynthesis, but this occurs only when very high concentrations 10^{-4} mole/dm^3 and $5 \cdot 10^{-4}$ mole /dm^3 of the herbicide were used.

Ray (1980, 1982) studied numerous metabolic processes to determine the mode of action of this herbicide.

Continuous growth measurement studies on sensitive corn seedlings demonstrated that chlorsulfuron is a very strong and rapid inhibitor of cell division and plant growth. Already 0.001 ppm chlorsulfuron caused inhibition of root growth, while shoot growth was inhibited at 0.01 ppm. The reduction in growth is closely associated with the inhibition of plant cell division. This inhibition is rapid, occurring within 1–2 hours of treatment.

No significant effects were observed on auxin, cytokinin or gibberellin induced cell expansion. Photosynthesis, respiration, RNA synthesis and protein synthesis were uneffected at concentrations where the plant cell division is strongly inhibited.

The exact primary site of action of this herbicide is not known at present.

By the addition of nonionic surfactants to chlorsulfuron as 80% wettable powder its herbicidal performance can be increased. (Chow and Taylor, 1980).

Trials were made on seedlings of oil seed rape *(Brassica napus)*, chickweed *(Stellaria media)*, cleavers *(Galium aparine)*, mayweed *(Tripleurospermum maritimum)* and spurry *(Spergula arvensis)*, sprayed with chlorsulfuron at rates of 5–20 g/ha. Various concentrations of Agral (alkyl phenol ethylene oxide condensate), Atplus 300 F (polyoxyethylene sorbitane fatty acid ester), Citowett plus (alkylaryl polyglycol ether), Renex-36 (polyoxyethylene tridecyl ether), and Ethylans (nonyl phenol ethylene oxide condensates) were added to the spray solutions and the effects evaluated.

The enhancement of the herbicidal effect varies extensively depending on the type of the surfactants and the treated weeds.

Pot experiments were made to investigate the effects of known herbicide antidotes foi extending the selectivity of chlorsulfuron (Parker *et al.*, 1980).

The tolerance of maize to chlorsulfuron can be greatly increased by seed dressing with 1,8-naphthalic anhydride (NA) at 0.5%. Seed dressing with R 25788 (N,N-diallyl-2,2-dichloroacetamide) is less effective. NA has a safening effect on sorghum, rice at 5 g chlorsulfuron/ha. Wheat and barley are also well protected by NA to doses in excess of 100 g/ha active ingredient.

Chlorsulfuron has a low order of acute oral toxicity to rats. LD_{50} for fated male rats is 5545 mg/kg and for fasted female rats 6293 mg/kg. It is mildly eye-irritating and not skin irritating. The Ames test shows no mutagenicity.

The feeding of male and female rats for 3 months at dietary levels of 0, 100, 500 and 5000 ppm produced a decreased rate of body weight gain only in females at 5000 ppm, and slight hematologic and other clinical laboratory effects were observed at 5000 ppm (Levitt *et al.*, 1981).

The chemical name of DPX-T 6376 is methyl 2-[3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)ureidosulfonyl]benzoate (metsulfuron-methyl, **2**).
The first report on its chemical and biological properties has appeared in 1983 (Doig *et al.*, 1983).

DPX-T 6376 promises to be a useful herbicide in cereals. At rates of 4 active ingredient g/ha in spring cereals and 8 g active ingredient/ha in winter cereals it controls a broad spectrum of weeds.

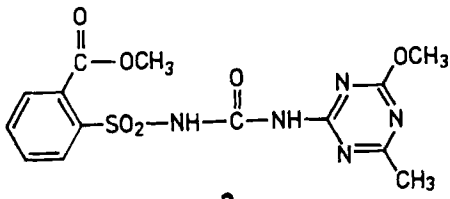
DPX-T 6376 has a different spectrum of activity from chlorsulfuron. It is more active on *Viola, Polygonum* spp., and *Veronica persica* while less active on *Galium aparine*. It controls certain grass weeds as *Apera spica venti* and *Lolium* spp.

Its mode of action is similar to that of chlorsulfuron. Within hours of uptake by the sensitive weeds there is a rapid inhibition of growth, then a yellowing, tissue necrosis and death.

In the soil DPX-T 6376 is broken down by hydrolysis and microbial degradation. Its half-life varies between one week and one month.

DPX-T 6376 has a low order of acute mammalian toxicity. The acute oral LD_{50} to male rats is 5000 mg/kg. It is mildly skin irritating to guinea pigs but is not a skin sensitiser. The product also shows low toxicity to fish and wildlife.

DPX 5648, methyl 2-[3-(4,6-dimethyl-1,3-pyrimidin-2-yl)ureidosulfonyl]-benzoate (sulfometuron, **3**) is a colorless solid with weakly acidic character, in respect of its herbicidal properties it is very similar to the previous two compounds.



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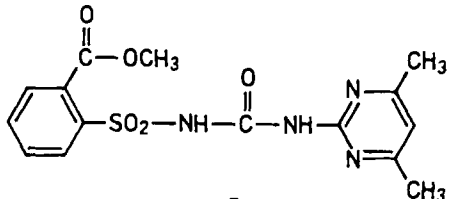

3

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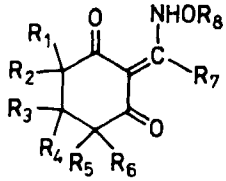
6.24 Other herbicides

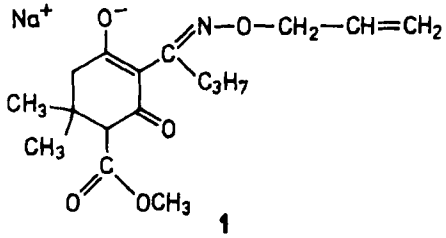
The nonsystemic miticide benzoximate was developed in Japan, in the research laboratories of the Nippon Soda Co. during the systematic investigation of hydroxamic acid derivatives. The herbicide alloxydim-sodium was prepared during the further development of compound with this skeleton.

Cyclohexane-1,3-dione derivatives of the following structure were synthesised:



Iwataki and Hirono (1978) found that the substituents of the cyclohexane ring and of the side-chain strongly influence herbicidal activity and selectivity. The cyclohexane ring is responsible for the postemergence activity of the molecule, the R_1–R_8 alkyl substituents for its selectivity.

The most selective compound of the series is methyl 3-(1-allyloxyimino)butyl-4-hydroxy-6,6-dimethyl-2-oxocyclohex-3-ene carboxylate (alloxydim-sodium, **1**).



1

The strongly hygroscopic compound is readily soluble in water, dimethylformamide and methanol. Formulations available are 75% WP (Fervin 20).

Alloxydim-sodium is a selective postemergence herbicide used for the selective control of grass weeds in dicotylenous crops, (such as) sugar beet, soybean, peas, cotton, peanut and rape at a rate of 0.5–1.5 kg active ingredient/ha (Hubl *et al.*, 1977; Takabayashi, 1977; Ingram *et al.*, 1978; Iwataki and Hirono, 1978).

To increase its effect against broad-leaved weeds it is used in combination with herbicides efficient for the control of such weeds. Used in tank mixture with phenmedipham, it hives total weed-control in sugar beet (Hubl *et al.*, 1977).

Alloxydim-sodium cannot be mixed with bentazon, the two herbicides being antagonistic (Iwataki and Hirono, 1978).

Poa annua is resistant to alloxydim-sodium (Quere *et al.*, 1977).

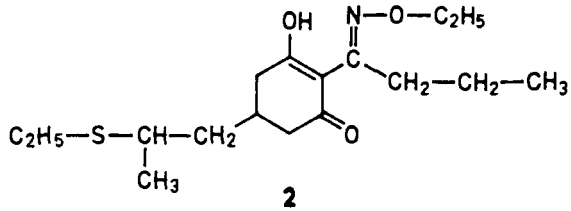
Soper (1978) found alloxydim-sodium efficient for the control of volunteer cereals in winter rape.

Alloxydim-sodium is not persistent, it is degraded in the soil and in plants in 1 month. During metabolism in the plant and in the soil the compound is decomposed to 2-oxazole derivative. In the soil it is eventually broken down by microorganisms to carbon dioxide.

Sensitive grass weeds rapidly absorb alloxydim-sodium, which is then rapidly translocated apoplastically and symplastically. Growth inhibition, chlorosis, antocyanide formation are manifested by the treated plant, and finally, necrotic wilt. The biochemical mode of action of the herbicide is not yet precisely known (Iwataki and Hirono, 1978).

Alloxydim-sodium is slightly toxic to mammals. Its acute oral LD_{50} for rats is about 2300 mg/kg.

The next selective herbicide belonging to the same chemical group as alloxydim-sodium with similar properties is NP-55, 2-(N-ethoxyiminobutyl)-5-(2-ethylthiopropyl)-3-hydroxy-2-cyclohexen-1-one (sethoxydim, **2**,). Its chemical, physical and toxicological data and its biological activity have been reported in 1980 (Ingram *et al.*, 1980).



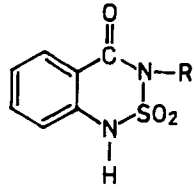
2

NP-55 is an odourless, oily liquid having a low vapour pressure and soluble in organic solvents. Water solubility at 25°C is 24.5 ppm.

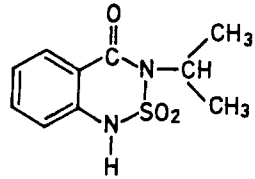
The biological activity has been evaluated in the UK over three seasons. The compound possesses both pre- and post-emergence activity, specifically against *Gramineae*. It controls at doses of 0.37 kg active ingredient/ha and 0.83 kg active ingredient/ha the annual and perennial grass weeds including *Avena* spp., *Alopecurus myosuroides*, volunteer barley, *Agropyron repens* and *Agrostis gigantea*.

NP-45 have shown a high level of selectivity in beets, crucifers, legumes and strawberries at doses between 0.32–3.3 kg active ingredient/ha. Acute oral LD_{50} on rats cca. 1500–2500 mg/kg, on mice cca. 6000–6500 mg/kg.

Fisher and his research group developed a new group of heterocyclic herbicides, the 2,1,3-benzothiadiazinon-(4)-2,2-dioxides, of the following general formula (Fisher, 1968):



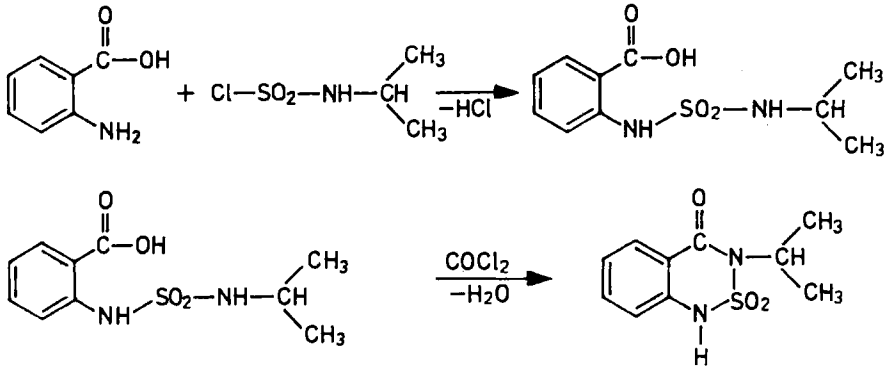
Those derivatives, in which R is an alkyl or cycloalkyl group with a short carbon chain are active. The most active member of the group is 2-isopropyl-2,1,3-benzothiadiazinon-(4)-2,2-dioxide, introduced under the common name bentazon (3).



3

Bentazon is a crystalline substance practically insoluble in water, but its sodium salt is readily soluble in water. The available formulation with bentazon as sole active ingredient is Basagran WL (BAS 3510H), a wetting powder containing 480 g active ingredient/kg. Combined formulations in aqueous solution are Basagran DP (250 g bentazon + 350 g dichlorprop-ethylamine) and Basagran MCPB (Basagran + MCPB).

According to patents of BASF, bentazon can be prepared in several ways. The synthesis of highest yield involves the reaction of anthranilic acid with isopropylsulfamoyl chloride, producing the intermediate product N-(isopropylsulfamoyl)anthranilic acid, which is then cyclised with phosgene (BASF, 1966/1971a and 1971b).



Isopropylsulfamoyl chloride can be obtained at a good yield by the reaction of isopropylamine hydrochloride with sulfuryl chloride in the presence of a Lewis acid catalyst ($SbCl_5$) in acetonitrile as solvent (Weiss and Schulze, 1964).

Bentazon is a contact selective herbicide for postemergence use mainly against dicotyledonous weeds. Many graminaceous crops, such as rice, maize and barley, most of the grass weeds and soybean are resistant to bentazon. Broad-leaved weeds and sedges are sensitive. Thus, bentazon is effective against pigweed (*Amaranthus* spp.)., common lamb's quarter (*Chenopodium album*), smartweed (*Polygonum pennsylvanicum*), false pimpernel (*Lindernia pyxidaria*), purple nutsedge (*Cyperus rotundus*), *Cyperus serotinus*, yellow nutsedge (*Cyperus esculentus*) and *Cirsium arvense* (Hendrick *et al.*, 1975).

The recommended rate of application of bentazon is 0.5–3.0 kg/ha, depending on the conditions of application. Its selective application in soybean has been reported by Luib and van de Weerd (1972), in cereals by Behrendt and Sipos (1969) and Menck and Behrendt (1972), and in rice by Mine *et al.* (1973) and Mine and Matsunaka (1974). Under flooded rice field conditions, bentazon exerts both a foliar and a root action. The effect of bentazon absorbed through the roots is slowly manifested, while when the preparation acts much more quickly in contact with the leaves. The temperature prevailing at the time of application has an important role in the development of phytotoxic symptoms. In hot weather the effect can be observed in 5–7 days, while in cold weather symptoms may appear only after weeks (Mine and Matsunaka, 1975).

The range of the herbicidal action of bentazon can be increased with hormone-type herbicides (MCPB, dichlorprop). Nalewaja and Pudelko (1975) found that the herbicidal action of bentazon in soybean can be increased by the addition of emulsifiable linseed oil (LO) and emulsifiable mineral oils.

Abernathy and Wax (1973) investigated the mobility and adsorption of bentazon in 12 different soils and established that bentazon, which possesses anionic properties in neutral solution, is not adsorbed on the soil, but moves with the water-front of the soil.

The primary mode of action of bentazon is the inhibition of photosynthetic CO_2-fixation by the plants (Mine and Matsunaka, 1973, 1975). A marked inhibition of CO_2-fixation develops rapidly both in resistant rice and in sensitive *Cyperus serotinus* after treatment with bentazon, but while tolerant rice recovers almost completely in 5 days, sensitive *Cyperus serotinus* does not recover.

Searching into the cause of the selectivity of bentazon, Mine *et al.* (1973, 1975) investigated the adsorption and translocation of the herbicide in sensitive *Cyperus serotinus* and in resistant rice. There is no substantial difference in either the absorption or in the translocation of the herbicide in the two kinds of plants. However, in rice 80% of the bentazon absorbed is metabolised in 24 hours and 85% is converted in 7 days to a water-soluble metabolite. The major metabolite formed in rice is 6-isopropyl-2,1,3-benzothiadiazinon-(4)-2,2-dioxide O-β-glucopyranoside. Only 5% of unchanged bentazon can be detected in rice, while in *Cyperus serotinus* 50-75% of the bentazon is present in unchanged form after 7 days.

Similarly, a large quantity of water-soluble metabolite is formed in resistant soybean, barnyard grass *(Echinocloa crus galli)* and in rice; thus, the cause of selectivity is the different measure to which sensitive and tolerant plants are able to metabolise, and hence detoxicate, bentazon.

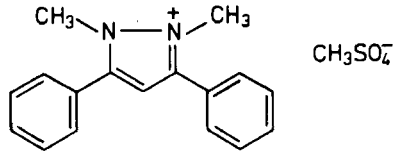
Investigations of Luib and van de Weerd (1972) on the metabolism of bentazon in rice and of Otto and Drescher (1971), Hayes and Wax (1973), Zaunbrecher and Rogers (1973) and Dahomey and Penner (1975) in soybean and bean led to essentially the same conclusions.

The photolysis of bentazon has been investigated by Eastin (1974) and by Nilles and Zabik (1975). According to the investigations of Eastin, during 288 hours of artificial illumination bentazon was converted into four volatile degradation products. Photolysis was the most rapid on irradiation with short wavelength ultraviolet light.

Eastin identified two degradation products by thin-layer chromatography: 2-amino-4-isopropylbenzamide and N-(isopropylsulfamoyl)anthranilic acid. Niles and Zabik, investigating the photolysis of bentazon produced by natural sunlight and by artificial illumination, established the oxidative formation of a dimer on the soil, presumably by the action of the transition metals in the soil. The other major degradation product is a compound formed by SO_2 elimination. A new quinazolin-3,4,4-on cyclic compound has also been detected as a degradation product.

Bentazon is moderately toxic to mammals, fowl and fish, its acute oral LD_{50} for rats being 1100 mg active ingredient/kg. The LC_{50} (96-hour exposure) for rainbow trout is 190 ppm. The LD_{50} for mallard ducks is 1600 mg/kg, for Japanese quail 720 mg/kg. It is not toxic to bees (WSSA, 1974).

1,2-Dimethyl-3,5-diphenylpyrazolium methyl sulfate **(4)**, known by the common name difenzoquat, was developed by the research workers of the American Cyanamid Co. (O'Hare and Wingfield, 1973).



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Difenzoquat methyl sulfate is a quaternary salt; the carrier of the herbicidal action is the 1,2-dimethyl-3,5-diphenylpyrazolium ion. It is very readily soluble in water, the pH of its 50% aqueous solution is 3.0–3.4. It is resistant to light and to acids but is decomposed by alkalies.

Difenzoquat methyl sulfate is a postemergence herbicide for the control of *Avena* spp. *(A. fatua, A. ludoviciana, A. sterilis, A. barbata* and *A. macrocarpa)* in wheat and barley, (Gruenholtz *et al.*, 1974; Winfield, 1974; Blank and Behrens, 1974; Weis *et al.*, 1974; Tafuro, 1974). Potatoes, sugar beet, beans, maize, lentils and several rye grasses are tolerant (Anonym, 1975).

Difenzoquat methyl sulfate is specifically effective only against *Avena* spp., for the control of other grass weeds and broad-leaved weeds it must be used in combination with other herbicides. It can be used in tank mixture with the esters of the following herbicides: 2,4-D, 2,4,5-T, MCPA, dichlorprop, bromoxynil, and ioxynil.

The efficiency of difenzoquat depends directly on the kind and concentration of the surfactant in the aqueous spray. The best wild oat control has been obtained with a nonionic emulsifier of alkyl polyglycol ester type, in a quantity of 0.5%, (in reference to the spray solution). In the factory formulation (Avenge) the proportions of the active substance and of the surfactant are adjusted to give the optimal effect in the recommended dose and the recommended quantity of spray solution. Avenge 200 contains 200 g of active substance plus 400 g of surfactant in each litre. Five litres of this solution is recommended for a 400 l/ha spray solution. Avenge 250 g contains 250 g of active substance and 200 g of surfactant in each litre, and its recommended dose is 4 in a 200 l/ha spray solution (Anonym, 1975).

The visible symptom of the herbicidal action of difenzoquat, withering of leaves, develops slowly, often in 3–4 weeks. However, the growth of wild oat is quickly halted, and often swelling, yellowing and necrosis can be observed in the basal stem area, indicating the translocation of the herbicide into the meristem. On the basis of the physiological symptoms observed, difenzoquat is primarily a mitosis poison, but it also affects other vital processes in wild oat.

The causes of its selectivity are yet unknown. It seems that only the *Avena* spp. are unable to detoxicate the herbicide taken up.

Difenzoquat is not metabolised in plants, soil or mammals. It is excerted by mammals in unchanged form in the urine and the feces. Difenzoquat does not accumulate in the tissues. In 3 months 50% disappears by chemical degradation from the soil.

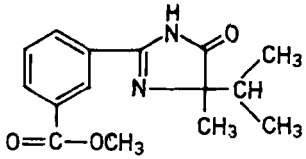
The acute oral LD_{50} of the technical active substance for albino rats is 470 mg/kg, the acute dermal LD_{50} for rabbits 3540 mg/kg.

Avenge is virtually nontoxic to wild fowl, the subacute LC_{50} for Mallard ducks being 10 388 ppm, for bobwhite quail 4640 ppm.

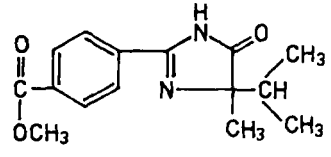
It is weakly toxic to fish, the 96-hour acute TL_{50} for bluegills being 696 mg/l, for rainbow trout 694 mg/l.

Toxicity to bees: the LC_{50} is 36.2 mg/bee (Anonym, 1975).

AC 222 293 (**5**) is a mixture of two isomeric imidazolin derivatives: methyl 3-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl) benzoate *(a)* and methyl 4-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl) benzoate (b), being developed by the American Cyanamid Co. (Shaner *et al.*, 1982).



(a)



(b)

5

AC 222293 is an odorless white crystallisne solid, with a melting point of 120–145°C. It is soluble in some common organic solvents. Water solubility (at pH 5.95 and 25°C) is 1360 ppm for the *m*-isomer and 850 ppm the *p*-isomer.

AC 222293 is a postemergence herbicide with good selectivity in wheat and barley. It is highly active on *Avena* spp., *Alopecurus myosuroides, Apera spica-venti* and several broad-leaved weeds such as *Sinapis arvensis* and *Polygonum convolvulus* (Kirkland and Shafer, 1982). The recommended dose against *A. fatua* varies from 0.4 to 0.82 kg active ingredient/ha.

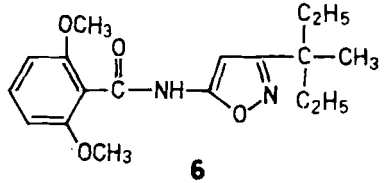
For optimal activity a nonionic surfactant is necessary. The optimal surfactant concentration, depending on spray volume, lies between 0.1 and 0.25% *(v/v)*, (Shaner *et al.*, 1982a,b).

AC 222293 is absorbed both through the foliage and roots of the plant and is translocated both in xylem and phloem.

Radiotracer studies have shown that the selectivity of AC 222293 on wheat cannot be attributed to the difference in translocation. Shaner and co-workers (1982) suggested that the mode of action of AC 222293 is similar to that of other wild oat herbicides as dichlofop-methyl, flamprop-isopropyl and benzoylprop-ethyl. In all the cases the herbicidal activity depends on the hydrolysis of the parent compounds to the free acids. This hydrolysis is more rapid in the susceptible weeds, than in wheat.

AC 222293 is of very low toxicity to mammals, its acute oral LD_{50} for rats is 5000 mg/kg. It is nonirritant to the rabbit eye.

The Eli Lilly and Co. recently discovered a new benzamide derivative herbicide. It is being developed under the code number EL-107, proposed common name benzamizole, N-[3-(1-ethyl-1-methylpropyl)-isoxazol-5-yl]-2,6-dimethoxybenzamide **(6)** (Huggenberger *et al.*, 1982).



6

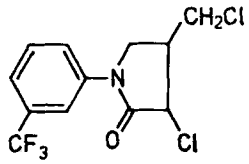
EL-107 is a white crystalline solid insoluble in water. The compound is stable in water between pH 5 to 9 but susceptible to photodegradation in aqueous solution.

EL-107 is a selective preemergence herbicide for the control of broad-leaved weeds in winter cereals. It has been field-tested in Europe at rates between 50–400 g active ingredient/ha. Applied at rates of 100–200 g active ingredient/ha EL-107 provided season-long control of *Matricaria* spp., *Stellaria media, Viola* spp., *Polygonum* spp. *Veronica* spp. and several other broad-leaved weeds. Its only effect on crop development is some reduction in lateral root production after applications in excess of 300 g active ingredient/ha for wheat, 400 g active ingredient/ha for barley.

EL-107 shows little mobility in soil. It is moderately persistent in the soil, under normal field conditions its half-life is 5–6 months.

EL-107 is of very low mammalian toxicity. The acute oral LD_{50} for rats is 10 000 mg/kg. It is not skin irritating, but causes slight conjunctivitis to rabbits.

R-40 244 is novel herbicide discovered and being developed by the Stauffer Chemical Company (Richardson *et al.*, 1979). Its chemical name is 1-(*m*-trifluoromethylphenyl)-2-chloro-4-chloromethyl-2-pyrrolidone (7) proposed common name fluorochloridone.



7

The technical product is a beige powder consisting of 30% *cis* and 70% *trans* isomers. It is insoluble in water, soluble in organic solvents. The purity of the technical compound is 90%.

R-40 244 is a preemergence herbicide against broad-leaved weeds in a number of crops. It controls many problem weeds such as *Amaranthus* spp., *Chenopodium album, Galium aparine, Polygonum* spp., *Sinapis arvensis* and *Solanum nigrum.*

R-40 244 shows good selectivity on carrots, potatoes, sunflowers, winter wheat, cotton, tree and bush fruits. European field trials carried out in potatoes, sunflowers and winter wheat (Pereiro *et al.*, 1982) indicate that rates of 0.5–1.0 kg active ingredient/ha are sufficient for a season-long control of broad-leaved weeds.

Mixtures of R-40 244 with appropriate grass herbicides such as linuron, trifluralin and terbutrine in sunflowers, linuron and metriburin in potatoes, chlortoluron and mitrofen + neburon in wheat show improved activity against grass weeds and several broad-leaved weeds.

R-40 244 is a powerful inhibitor of carotenoid synthesis (Devlin *et al.*, 1979, 1980; Sandman and Böger, 1981).

R-40 244 is weakly toxic to mammals. The acute oral toxicity for rats is 4000 mg/kg (male) and 3600 mg/kg (female). It is mildly skin irritant on rabbits.

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