PESTICIDE CHEMISTRY

Introduction

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.

Plant Pathogens

The pathogens of plant diseases are microorganisms - fungi, bacteria and viruses. Proliferating within the host plant and interacting with the host, they act mainly by

a) producing toxic substances which inhibit the activity of essential enzymes of the host, **or**

b) producing enzymes themselves which are able to degrade important components of the host.

Pest, Insects and Weeds

.Animal pests, particularly insects, damage the host plant either

a) directly by feeding on it, **or**

b) indirectly by spreading viral diseases.

Weeds compete on arable land, thereby depriving crops of sunlight, air, water, soil and nourishment.

Pesticides

Pesticides are the agents that are used to control pests such as fungi, bacteria, insects, rodents, mites, weeds etc. Pesticides having quick action and broad spectrum of activity are very important part of agriculture and household. Most pesticides show their effect through contact and are either respiratory or stomach poisons to the target organism. They usually attack specific sites in the insect, such as nervous system resulting in knock-down, lack of coordination, paralysis and death.

Pesticides are classified based on their application. Thus, microbicides act against microbial pests, zoocides against animal pests and herbicides against weeds.

Amongst 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 the development of efficient bactericides for plant protection.

Amidst the 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.

Conventional insecticides act chiefly on the insect nervous system. Classification of these insecticides is based on their chemical nature: compounds of natural origin, arsenic compounds, chlorinated hydrocarbons, organophosphorus compounds, carbamates, etc.

Novel anti-insect agents are classified according to their mode of action, but this biological subdivision, at the same time, represents chemical grouping. The most important categories are insect growth regulators, chemo-sterilants, pheromones and anti-feeding 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 chemicals which control weeds harmful to crops. They are classified in two ways. According to their mode of application, they are foliar herbicides and soil herbicides, and according to their time of application, pre- and post-emergent herbicides.

Pesticides are, in general, capable of harming all forms of life i.e. both targeted as well as non-targeted species. They may have diverse ecological effects ranging from long term to short-lived effects or chronic to acute toxic effects.

Pesticides may have different fates due to different components of the environment such as soil, air, water, and biota. The products sometimes lead to various deleterious effects on environment and public health.

Biopestcides

The harmful effects of chemical pesticides on human health and the environment initiated the search for the alternatives to the chemical pesticides.

Biopesticides are biochemical pesticides that are naturally occurring substances which control pests by non-toxic mechanisms. They are derived from natural materials such as plants, microbes (bacteria, fungus, viruses, and protozoa), and animals which can abate and/ or control the pests.

Followings are reasons for the choice of the biopesticides over chemical pesticides.
1) They are less harmful than conventional pesticides and less environment load (eco – friendly).
2) They are designed to affect only one pest (target specific).
3) Small doses of biopesticides are effective against pests.
4) They are biodegradable and non-persistent.

Natural pesticides are made by some organisms usually for their own defense, or are derived from a natural source such as plant, animal, bacteria, and certain mineral etc. Study has shown that some plants contain chemical constituents that are toxic to insects and pests.

Various botanical pesticides are already in use for the conventional, sustainable and integrated pest management. Neem based pesticides are one of the most important botanical pesticides used widely in India for agricultural pest management followed by pyrethrum, and Eucalyptus oil based pesticides.

Some Biopesticides

Rotenone disrupts energy metabolism causing blockage of ATP synthesis in the mitochondria. Nicotine inhibits and competes with neurotransmitter by binding to acetylcholine receptors at the nerve synapses. Pyrethrins exert their toxic effect by disrupting the sodium and potassium ion exchange process, which interrupt the normal transmission of nerve impulses. Azadirachtin is an antifeedant and growth disruptor.

Pesticide Research and Development

Presently the estimated number of 'pesticides' in the business is about a thousand. But the goal of an 'agricultural revolution' is to have separate pesticide for each individual crop, each individual plant disease, and in general, for each risk/benefit situation.

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

2) Another approach toward diminishing environmental contamination by chemicals is the development of new active substances, which are less volatile and are degraded more rapidly or are more readily absorbed by soil particles.

3) Rapid advances are necessary for the development of compounds with specific action on harmful insects eliminating side-effects on non-target organisms as far as practicable.

Search for new compounds is of utmost importance to combat against the acquired resistance of pests/insects to various kinds of available pesticides due to changes in the ecosystem for various reasons and applications of 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 radically alter crop protection.

It may be of interest to mention the some of the criteria recommended by the EPA for reduced-risk pesticides because they are important guiding principles in the development of new pesticides.

<u>The pesticide:</u>

Must have a reduced impact on human health and very low mammalian toxicity;
May reduce effects on non-target organisms (such as honey bees, birds, and fish);
May exhibit a lower potential for contamination of groundwater;
May require less number of applications ;
May have a new mode of action;
May have a high compatibility with integrated pest management;
Has increased efficacy.

In the meantime, plant protection must be handled efficiently and safely with the imperfect pesticides of today, carefully balancing the aspects of maximal yield and maximal safety.

Structure-Activity-Relationship (SAR) study

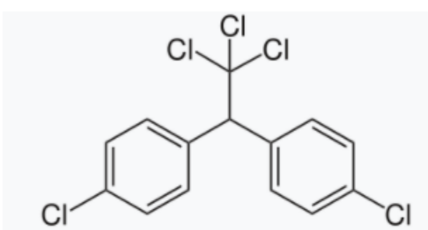
For the development of a new pesticide which would be more efficacious in agriculture/household application, target oriented SAR study is important for a pesticide chemist.
The structure–activity relationship (SAR) is the relationship between the chemical structure of a molecule and its biological activity.
The analysis of SAR enables the determination of the chemical group responsible for evoking a biological effect in the target organism.
This allows modification of the potency of a bioactive compound by changing its chemical
structure. Pestici
de chemists use the techniques of chemical synthesis to insert new chemical groups into those molecules and test the modified product for their biological effects.

Organochlorines

Organochlorines are the group of chlorinated hydrocarbons that are extensively used as pesticides. These pesticides were first introduced in the 1940s in Australia and later on widely popularized during 1950s to 1960s.They are the most widely used pesticides at the time of the Green Revolution. The reason for its wide-scale adoption worldwide is that it is of low cost and has a broad spectrum of activity against most of the insects that prevail in fields as well as in household.

Organochlorines were prohibited to use since 1970 and nowadays it is banned in developed countries. Organochlorines were banned due to the fact that it belongs to the class Persistent Organic Pollutants (POPs) and shows bioaccumulation in the food chain. These pesticides are insoluble in water but soluble in organic solvents, fats & oils and thus it can be ingested into human body via fish, dairy products & other fatty foods.

DDT (Dichloro-diphenyl-trichloroethane)

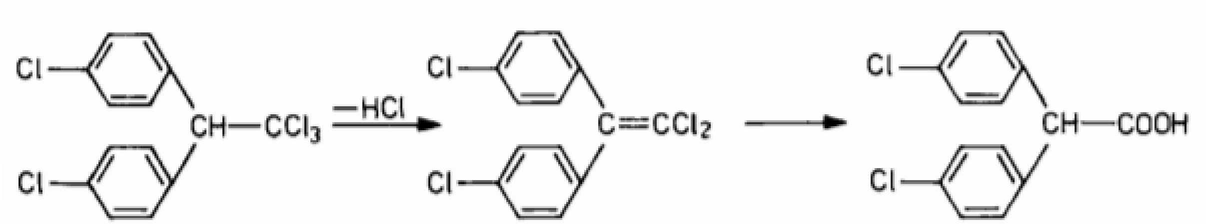


Uses:

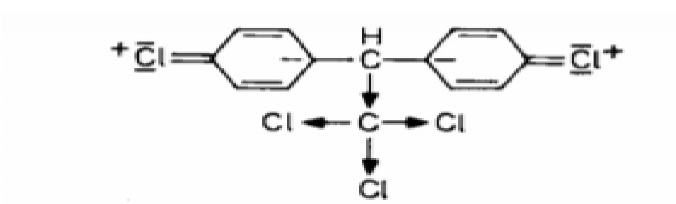
DDT was first made in 1874. Its insecticidal properties were discovered in 1939 by a Swiss chemist, Paul Hermann Müller.
It is widely used as insecticide, strongly toxic to many species of agricultural insect and pests. Probably no chemical made by man, not even penicillin, streptomycin and the sulphonamides, saved so many lives as has DDT. The reason for this is that it was, for a time, outstandingly successful in controlling the vectors

of organisms responsible for such mortal and debilitating diseases as malaria, typhus and yellow fever.

Mode of action:
DDT is resistant to light, atmospheric oxygen and weak inorganic acids, but is rapidly decomposed to the biologically inactive compounds by the action of high temperature or strong ultraviolet light with consequent elimination of hydrochloric acid.



The toxic action exerted by DDT to insects was presumed to occur due to the trichloromethyl moiety which, by dehydrochlorination, releases hydrochloric acid into the vital centre of the organism. Later, it was found that dehydrohlorinability showed little relationship with its toxicity character.
It is now accepted that the absorbability and permeability factors, due to lipoid solubility of the compound, predominate over dehydrochlorinability.
Owing to the strong electron-withdrawing effect of the three chlorine atoms of the trichloromethyl moiety, the central carbon atom acquires a positive charge, and the molecule can take up the following structure.



It was experimentally observed that under the action of DDT, the nerve fibre of the insects releases more L-leucine than normal. L-Leucine is a neuro-active substance.
It was suggested that 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.

DDT may also act by inhibiting the Na+, K+ and Mg2+ ATP'-ases.
DDT inhibits pyruvate oxidation and phosphorylation reactions in the mitochondria of certain insects.

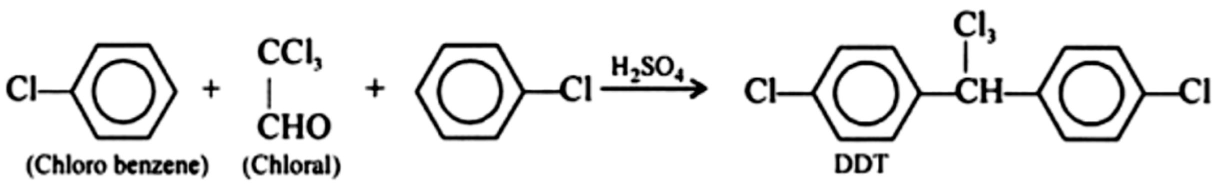
SAR studies:

Electron-donating substituent(s) on the p,p'-positions are the most efficient. Alkyl or alkoxy substitutions render the derivatives biodegradable.
Transfer of substituent(s) to the m-position slightly decreases efficiency.
Transfer of substituent at o-position of benzene ring strongly decreases efficiency and o-substitutions at both phenyl rings inactivate completely. Experiments show a definite correlation between the insecticidal efficiency and the free rotatability of the benzene rings. Because of their spatial disposition, substituent(s) in the o-position(s) suspend the possibility of free rotation of the benzene rings and, consequently, also the bioactivity.
Moieties with relatively large π-values such as hydroxyl, furyl, carboxyl or amino groups render a DDT type molecule nontoxic due to poor penetration capability through the lipid sheath of the nerve.
The gradual replacement of chlorine atoms in the aliphatic group with methyl groups, and with alkyl group bearing electron withdrawing group yields compounds with a wider safety margin

Special feature:

In the course of the prolonged use of DDT, certain insect strains became resistant to the original doses. It is due to the presence of DDT-dehydrochlorinase enzyme in those insects. DDT-dehydrochlorinase causes detoxification of DDT.
DDT is a nerve poison for warm-blooded organisms including humans. Due to its lipid solubility and chemical stability, DDT is accumulated in fat tissues of human. Lipophilic molecules often enter fat tissues more or less readily but, once inside, have difficulty in escaping.
DDT is still in use in developing and under-developed countries mainly for low manufacturing **cost**.

Synthesis:



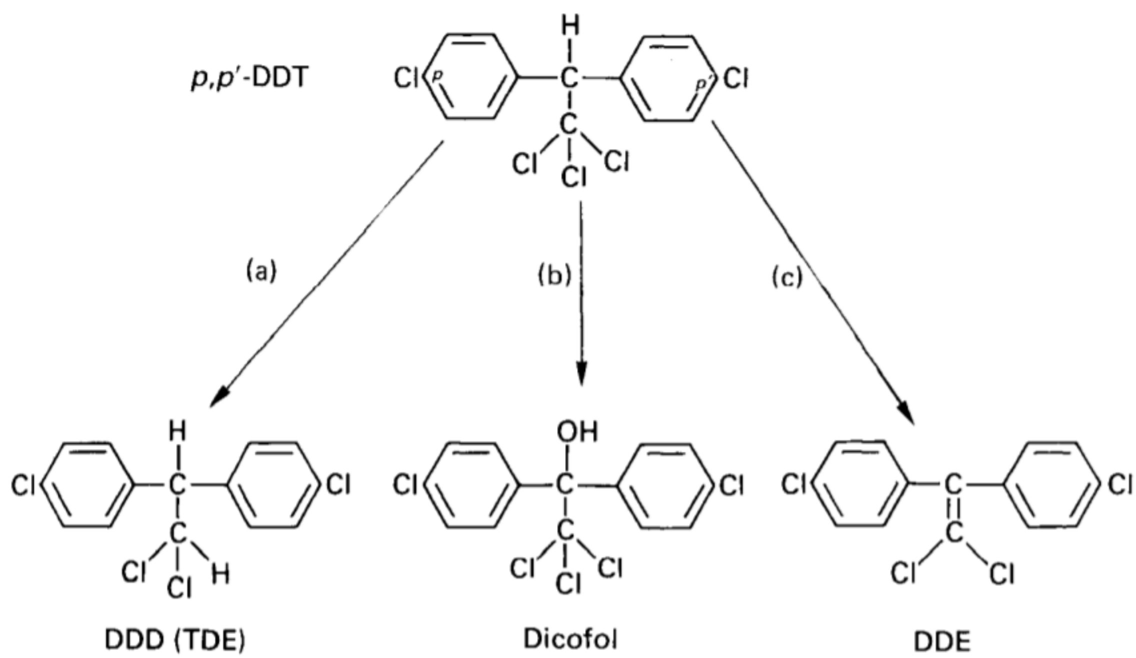
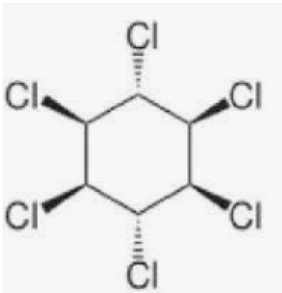


Figure 6.6 Metabolism of DDT. (a) Reductive dechlorination: by anaerobic liver + NADPH, by dead tissues and by some microorganisms. (b) Oxidation: by some insects, e.g. *Drosophila*. (c) Dehydrochlorination: by most insects, birds and mammals (the three pathways are not mutually exclusive)

Gammaxene (gamma-Hexachlorocyclohexane, γ-HCH)



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 hexachlorocyclohexanes, Linden was the first to separate each of the isomers in 1912. In 1936, Bender discovered the insecticidal properties of hexachlorocyclohexanes.

Uses:

Among the various isomers formed, the discovery, that γ-isomer of BHC (benzenehexachloride) is the carrier of insecticidal properties, was made in 1945. BHC isomers differ substantially from one another with respect to their solubility in organic solvents. This enables their separation by fractional crystallization.
γ -isomer is 50-10000 times as active as the α- and δ-isomer, depending on the insect species, while the β- and ε-isomers are practically inactive.
Before purification, the technical material contains about 13 per cent of the γ-isomer, some 68 per cent of two α- isomer and small quantities only of the β-and δ- isomers.
Purification of active isomer is important because the β-isomer, which is without insecticidal effect, accumulates most easily in various organisms.
It is used both against soil pests and household insects. It acts as contact and stomach poison, and owing to its volatility, also as a fumigant. Gammaxene is often inhaled by the users while it's handling.
It is used as a pharmaceutical treatment for lice and scabies.

Mode of action:

γ –Hexachlorocyclohexane (γ-HCH) is essentially a neurotoxin. But its effect on the CNS remains uncertain.

It increases the levels of dopamine and of N-acetyldopamine in the cerebral ganglion of the cockroach. In mammalian brain, receptors for neurotransmitter γ-aminobutyric acid (GABA) are primary targets for γ-HCH. GABA is also present in invertebrates, both in the nervous system and in the skeletal muscles. It is postulated that γ-HCH inhibits GABA-induced chloride ion uptake, with the effect that the inhibitory neurotransmitter action of GABA is blocked, leading to CNS excitation and convulsions.

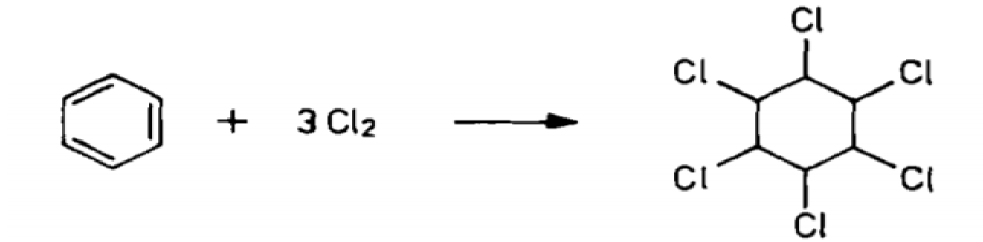
It is also observed that γ-isomer is the good electron acceptor. When hydrogen served as the electron donor, stepwise reductive dechlorination of the γ-HCH occur leading to cyclohexane as final product. Biological activity can be explained on the basis of the disruption of electron transfers during the metabolic process of mitochondria.

Its molecular diameter (8.5 Å) enables it to enter lipoprotein interspaces and cause distortion of the pore space affecting excitation of the nerve impulse.

Special feature:

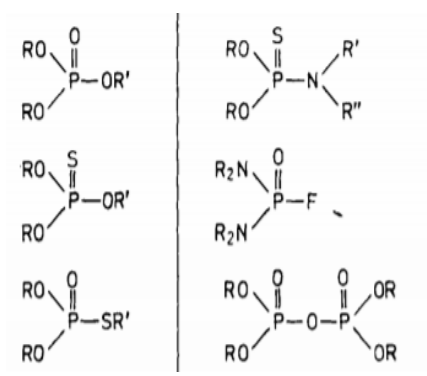
Transformation of γ-isomer to α- isomer has been reported to occur in plants and microorganisms but probably does not occur in mammals. Instead, a series of reactions occur in which double bonds or hydroxyls are inserted into the molecule and chlorine atoms (with or without accompanying hydrogen atoms) are removed. Such reactions may involve enzyme glutathione-S-transferase in combination with other enzymatic and non-enzymatic reactions. The outcome is the formation of a variety of chlorinated cyclohexane, cyclohexene and phenolic derivatives. Formation of glutathione conjugates has been indicated. It is probably from such compounds that the mercapturic acid and thiochlorophenols, identified in some insects, have been derived.

Synthesis:



Organophosphates

Most of the phosphorus-containing insecticides are not 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.



Organophosphates are known during early thirties of the last century. However their toxic effect on human was kept secret to prevent its use in chemical warfare during World War II. It was later found that, in addition to their toxicity to warm-blooded animals, some of the organophosphorus compounds are toxic to insects. Partly for this reason, and partly because of the anticipated peaceful intentions after the World War ll, research on phosphorus compounds was directed to the development of pesticides active against agricultural insects and pests.
Scope of phosphorus ester insecticides with respect to efficiency, duration of action, toxicity, range of activity etc. for crop protection is very broad. Their

importance has been further augmented when the detrimental properties of the chlorinated hydrocarbon insecticides, such as their accumulation in the environment and their persistence in human organisms, become apparent.

Mode of action:

Organophosphates act on warm blooded animals by irreversible inhibition of acetylcholine esterase activity during nerve impulse transmission. They
a) mimic acetylcholine esterase;
b) bind with its receptors by competitive inhibition process forming phosphate esters with the enzyme ;
c) disable the enzyme to cleave acetylcholine resulting in its accumulation;,
d) block the nerve impulse transmission process.

[Neural impulses from a nerve cell to another nerve cell via synapse or to a muscle cell via neuromuscular junction are transmitted by the mediation of acetylcholine. The function of acetylcholinesterase is to hydrolyze acetylcholine when muscle function ceases, and thereby to restore the state of rest. Hydrolysis of acetylcholine results in inactive choline and acetic acid from which, upon new neural impulses, acetylcholine is reformed by the enzyme choline-0-acetyltransferase with participation of ATP and CoenzymeA]

However, action of phosphorus esters in insects is not clear. Though the presence of acetylcholinesterase has been established in insects, it is not yet clear whether the enzyme plays a role in their neural activity. As an example, presence of seven acetylcholinesterase isoenzymes in the housefly has been indicated but they vary markedly in their sensitivity to phosphorus esters. It seems probable that for insecticidal action due to organophosphates, other mechanism also play an important role besides the blocking of acetylcholinesterase.

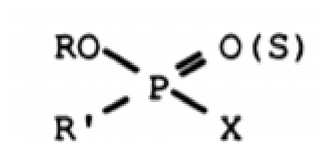
SAR studies:

Phosphorothiolates, as insecticide, show higher efficiency of several orders of magnitude than that of phosphates. This so called "thiolo effect" is explained as that the 100^0 valence angle of the P-S-C bond provides better steric conditions for linkage to the enzyme than the 109^0 angle of the P--O--C bond.

Methyl esters are found to be less toxic than ethyl esters. In insects, glutathione-S-alkyl-transferase enzyme uses glutathione as co-factor to facilitate O-dealkylation of organophosphates, thereby causing detoxification of the molecule and reducing the duration of action. O-demethylation is a facile process.

Special feature:

Among the insecticides containing a phosphorus atom, there are relatively few derivatives of phosphonic acid containing P--C bond. The insecticidal activity of these compounds appears to be largely a function of the reactivity of the molecule. The general structure of organophosphorus insecticides can be drawn as shown when R is methyl or ethyl, R' is either methoxy, ethoxy, ethyl, phenyl, amino, substituted amino or aklylthio and X is an appropriate leaving group.



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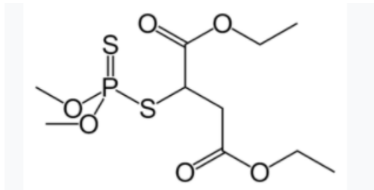
Since P-C bond is thermodynamically very stable, reactivity vis-à-vis biological activity of phosphonate insecticides mainly depends on the nature of the leaving group. Chirality at the phosphorus atom of alkanephosphonodithioate esters has a significant effect on their biological activity.

Organophosphorus insecticides generally undergo natural degradation enhanced by presence of humic substances, microorganisms etc. in soil.

Organophosphosphates are found to have a residual effect in food products and cause health hazards. It was found that residue recovered from different food products is high, such as, 88% of methyl parathion from tomato.

Since the inhibition is irreversible, small doses of residual insecticide from food products ingested in human body may produce neurotoxic symptoms even though the insecticide itself may not accumulate.

Malathion

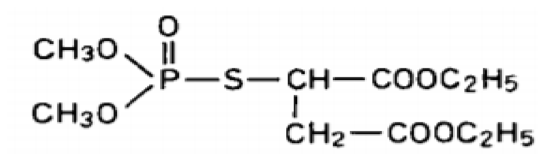


Uses:

Malathion is a dithiophosphate ester that has found use both as an aerial insecticide and clinically as a mitocide for topical treatment of lice infestations of the hair and scalp. Of all the phosphorus ester insecticides, it is the least toxic to warm-blooded animals.

Mode of action:

Mode of action of malathion may be same as of phosphorus esters, i.e. inhibition of acetylcholinesterase. In this case the 'leaving group' is a succinic acid ester. Malathion is metabolized in insects due to enzymatic oxidation to its oxo-analogue, malaoxon. This process may be termed as 'bioactivation' since the oxo



product is able to phosphorylate acetylcholinesterase more efficiently than malathion. The reason may be that, 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.

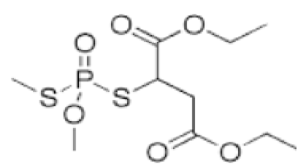
SAR studies:

The process of oxidation of malathion in mammals is slow. Actually the metabolism of malathion in warm-blooded animals proceeds via another route. One of the two ester bonds of malathion is hydrolyzed by the enzyme <u>malathionase</u> present in warm blooded animals. This metabolite is virtually

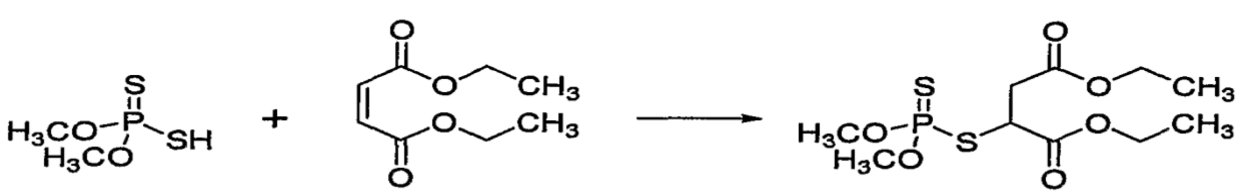
nontoxic. This enzyme is missing from insects sensitive to malathion. This explains the selective action of malathion towards insects.
The substrate specificity studies of malathionase indicated that carboxyesters with longer carbon chains is hydrolyzed more easily by the enzyme than those with short carbon chains.
The stereospecific aspect of the enzymatic action is shown by the fact that *d*-isomers are hydrolyzed more easily than *l*-isomers, and fumaric acid derivatives than maleic acid derivatives.

Special feature:

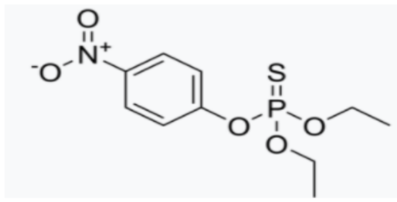
Extent of environmental poisoning by malathion may be detected from accumulated acetylcholinesterase in fish brain since the conversion of malathion to its oxo derivative is the dominant metabolic process in fish.
Various impurities increase the toxicity of malathion itself. Isomalathion, which possesses a malaoxon-like P=O group is an example of such a potentiating substance. This compound may be formed from thion-thiol rearrangement of malathion during storage in presence of sunlight.



Synthesis:



Parathion('Folidol')

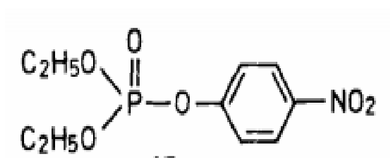


Uses:

Parathion acts as a contact and stomach poison. The range of action of parathion is very broad; in this respect it is foremost among the phosphorus ester insecticides. Spraying with parathion at blossom time is not permitted.
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.

Mode of action:

Mode of action of parathion is characteristic of phosphorus esters, i.e. phosphorylation of acetylcholinesterase. Facile release of 4-nitrophenol as the leaving group, may also contribute to its effectiveness as insecticide. Parathion is also bio-activated by oxidation of the P=S group to paraoxon in insects and vertebrates.



The strong insecticidal and acaricidal effect of paraoxon is linked with high toxicity. It is not used in agriculture. In ophthalmology, it is used as a miotic agent.

SAR studies:

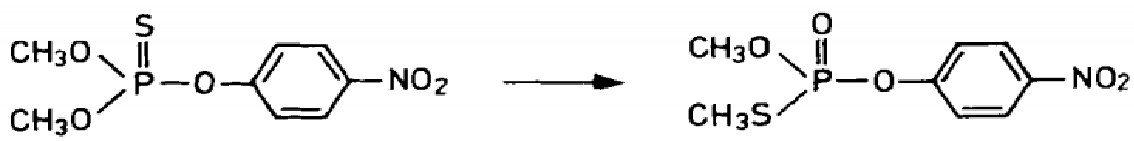
Presence of nitro group and similar electron-withdrawing substitution viz.-SO_2CH_3, halogens etc. at 4-psition of aromatic ring is important for activity.
The amino analogue of parathion is biologically less active than the unchanged parathion, but it is more stable to hydrolysis..

The ethyl groups of two phosphorothioate functionalities may by sequentially replaced by methyl group(s). The dimethyl phosphorothioate derivative is known as methyl parathion. The two methyl analogues possess similar insecticidal properties as parathion with lower toxicity to warm-blooded animals.
Both methyl analogues are detoxified easily via demethylation of a P-O-CH_3 linkage by glutathione-S-methyl transferase, whereas parathion does not readily de-ethylate in this manner. Parathion is principally degraded by oxidative rupture of the P-0-phenyl linkage by an NADPH-dependent oxidase.
Introduction of an extra methyl group into the **3-**position of the aromatic ring considerably decreases toxicity, while it does not alter the insecticidal effect much. Introducing a methyl group into the ring increases the hydrophobic nature of the molecule and also increases the affinity to the active site of the enzyme. The enzyme may be inactivated due to the methyl group but the inactivation rate is slowed. The net result on acetylcholinesterase, therefore, remains the same.
Toxicity is reduced due to substitution of chlorine atom at **3** position on the aromatic ring maintaining the activity.
One important aspect is that the presence of a methyl group increases and a chlorine atom decreases the stability towards oxidative hydrolysis of the respective compounds.
The transfer of the chlorine substituent from position **3** to position **2** on phenyl ring results in a slight decrease in insecticidal and toxic effects.
4-Nitro group on aromatic ring of methyl parathion may be replaced by –SCH_3 group. The compound is strongly toxic.
Sequential introduction of methyl group(s) at 3-position(s) of phenyl ring with **4-** methylthio substitution decreases toxicity towards warm-blooded animals.

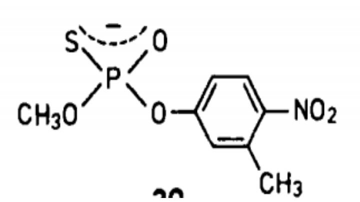
Special feature:

Parathion undergoes thion-thiol isomerisation at high temperatures.

However, the isomerisation pathway is different for Methyl parathion,



For amine catalyzed isomerisation, the following structure may be the intermediate when amine is alkylated forming onium salt with an ambident



anion. The latter is realkylated on the sulfur atom regenerating the amine. Preparations containing parathion are turned brown by the action of strong sunshine, may be due to the formation of small amount of thion-thiol rearrangement product and some types of decomposition products.

Synthesis:

Parathion is synthesized from diethyl dithiophosphoric acid $(C_2H_5O)_2PS_2H$ by chlorination to generate diethylthiophosphoryl chloride $[(C_2H_5O)_2P(S)Cl]$, and then the chloride is treated with sodium 4-nitrophenolate (the sodium salt of 4-nitrophenol).

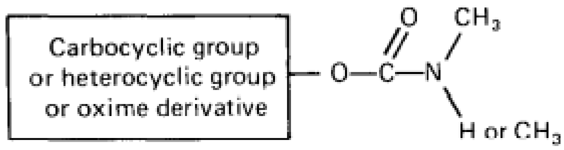
$$2\ (C_2H_5O)_2P(S)SH + 3\ Cl_2 \rightarrow 2\ (C_2H_5O)_2P(S)Cl + S_2Cl_2 + 2\ HCl$$

$$(C_2H_5O)_2P(S)Cl + NaOC_6H_4NO_2 \rightarrow (C_2H_5O)_2P(S)OC_6H_4NO_2 + NaCl$$

Carbamates

Uses:

Carbamates, used as insecticides, are esters of aromatic and heterocyclic hydroxy derivatives of N-methyl- and N,N-dimethylcarbamic acids.



The carbamate pesticides were introduced in 1956 and became instantly popular at that time. Carbamates are strongly toxic to a wide range of insect pests. They have low mammalian toxicity as well as low oral and dermal toxicity and show broad spectrum of insect control. They have wider adaptability as garden, lawns and household insecticides.

They generally act quickly. Duration of their action varies considerably.

Synthetic Methodology:

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.

Mode of action:

The mode of action is very similar to that of organophosphorus. It binds with acetylcholinesterase receptors by competitive inhibition process and disables the acetylcholine esterase enzyme to cleave acetylcholine.

But the only difference is that the binding is reversible in case of carbamates while it is irreversible in case of organophosphorus. Thus carbamates are less toxic than organophosphates.

[Cleavage of acetylcholine by acetylcholinesterase (AChE) enzyme gives choline and acetylated AChE. As long as the enzyme is acylated, it cannot bind another molecule of acetylcholine; the enzyme is in an inactive state. The acylated enzyme then undergoes rapid hydrolysis to regenerate the active form of AChE and a molecule of acetic acid. Experiments indicate that regeneration of active AChE by hydrolysis of the carbamylated enzyme, formed due to the reaction between carbamates and AChE, is much slower than hydrolysis of the acetylated enzyme. Phophorylated AChE is quite stable to hydrolytic condition. The values are mentioned here; the half-life for acetylated enzyme is ~0.2 milliseconds, same for methyl carbamylated enzyme is ~15 minutes and for diethyl phosphates are ~8 hours. Based on the duration of action, carbamates are referred to as reversible inhibitors of AChE whereas organophosphates are mentioned as irreversible inhibitors.]

SAR studies:

It was 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. N-aryl derivatives of carbamate are used as herbicide and they follow a different mode of action.

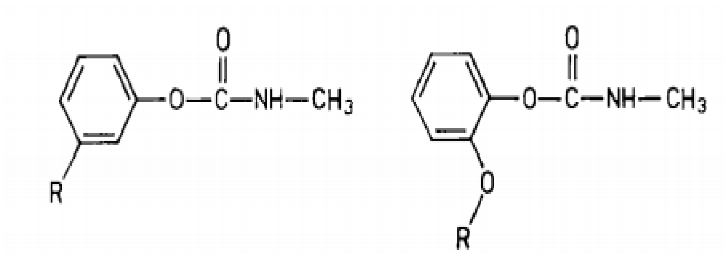
Similarly when the alkyl substituents on the carbamoyl group increased in size from *N*-monomethyl- to *N*,*N*-dimethyl-, *N*-ethyl-*N*-methyl-, or *N*,*N*-diethyl-, the decarbamoylation rate constants for carbamylated AChE decreased by 4-, 70-, and 800-fold, respectively. This may be due to the result of active site distortion, particularly in the acyl pocket of the active site.

Aryl carbamates are superior to alkyl carbamates as AChE inhibitor, because they have better affinity for AChE and, therefore, carbamylate AChE more efficiently. This is to be expected because phenoxide anions are more stable and, hence, are better leaving groups than alkoxide anions.

Possible involvement of π-π interactions in binding them to the enzyme is also suggested since aryl carbamates are ~ 1000 times as active as its cyclohexyl analogue.

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. .

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.



Several aryl N-methylcarbamates have been developed in which the phenyl group is substituted by a sulfur containing moiety and similarly with a nitrogen containing side chain to the phenyl group. Both types of compounds show very broad spectrum of activity.

It is observed that anticholinesterase activity of phenyl N- methylcarbamates containing a dithiolane substituent on aromatic ring is ten times that of the dioxolane analogues lacking sulfur. 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.

Heteroaromatics N,N- dimethylcarbamates have been proved to be efficient primarily against plant lice and aphids.

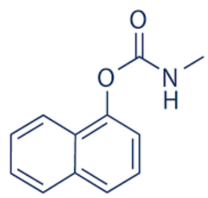
Aryl N-methylcarbamate containing a phosphate ester group has not surpassed the efficiency of parent carbamate containing no phosphate ester group. This conforms to the pharmacological experience that the presence of two biologically active groups within a molecule mutually weakens the efficiency, presumably because the attractions, acting in the direction of the various functional groups of the site of action, mutually compensate each other.

Special feature:

Carbamate insecticides were found to be comparatively lesser persistent in nature as they are relatively unstable in the environment and liable to degradation within weeks or months.

In most animals, the primary attack on most carbamates involves oxidative N-demethylation or ring hydroxylation due to a NADPH-dependent mono-oxygenase. Such attacks weaken the molecule and enable enzyme-catalysed hydrolytic changes to occur much more rapidly as secondary events. It is possible to decrease the rate of detoxification (and thus to increase toxicity and persistence) of the carbamate pesticide by the simultaneous use of a methylene-dioxyphenol synergist.

Carbaryl



Uses:

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 to insects than DDT.

A very advantageous property of carbaryl, compared with other carbamic acid esters, is its low toxicity to warm-blooded organisms

Side effects:

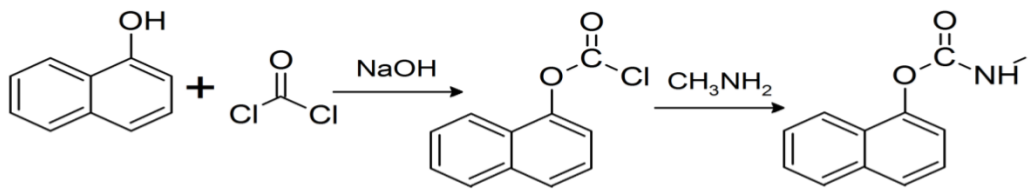
The chief danger to mammals associated with the use of carbaryl (and probably some other carbamates) arises from the ease with which it is absorbed through the skin. It is absorbed into the human forearm some 10 times faster than compounds such as parathion and gammaxene.

Special feature:

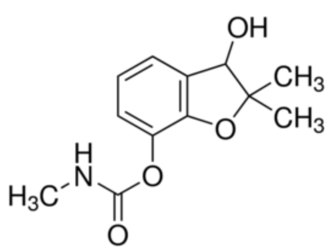
Carbaryl is converted oxidatively to 4-hydroxycarbaryl and 5,6-dihydro-5,6-dihydroxycarbaryl by monooxygenase and also hydrolytically to 1-naphthol.

Synthesis:

1-naphthol can be treated with excess phosgene to produce 1-naphthylchloroformate, which is then converted to carbaryl by reaction with methylamine.



Carbofuran



Uses:

Carbofuran is a systemic insecticide, acaricide and nematocide with a very broad spectrum of action. Carbofuran had a major advantage that the insects were incapacitated sufficient rapidly to prevent effective feeding.
It is toxic to warm-blooded organisms. This disadvantage is somewhat counterbalanced by its rapid decomposition in plant organisms.
It is used mainly for seed treatment against smut and diseases of vegetable seeds.

Side effects:

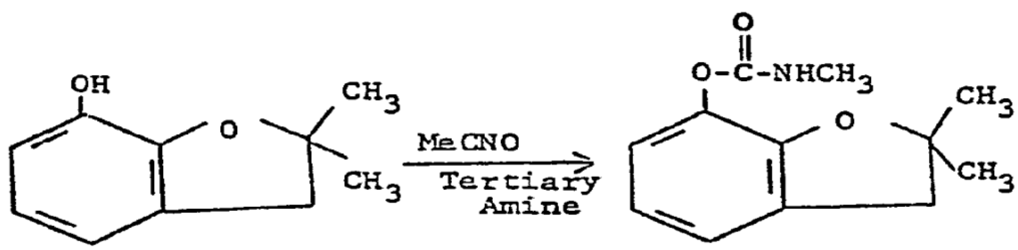
Carbofuran is some 50 times more poisonous to vertebrates than is carbaryl. It must therefore be handled with care, although its dermal toxicity is reported to be low.

Special feature:

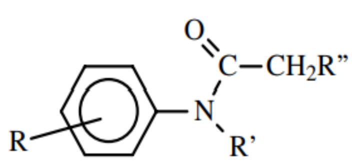
The most important metabolites of carbofuran are 3-hydroxycarbofuran and 3-ketocarbofuran. Both are highly toxic but their hydrolysis products, which contain no carbamoyl group, are not toxic.

Synthesis:

It is manufactured by the reaction of methyl isocyanate with 2,3-dihydro-2,2-dimethyl-7-hydroxybenzofuran.



α-Chloroacetanilides



R is often one or two alkyl groups, R' may have various structures, and in the herbicides, R'' is chlorine in accordance with the name α-chloroacetamides.

Uses:

Chloroactanilides are herbicides.
Herbicides are generally of two types. viz. pre-emergent and post emergent.
Pre-emergence weed killers are used before you see the weeds. The chemicals do not interfere with germination but rather they stop the formation of new root cells in baby weed plants.

Post-emergents attack weeds after they have shown their ugly little heads. The "post" part of this type of herbicide refers to the fact that it is used on already existing weeds.

Mode of action:

Experimental observations suggest that α-chloroacetanilides act upon some aspect of cell division or growth. The effect is, however, almost certainly indirect and possibly involves some (as yet unknown) step in protein synthesis.
One possibility is their ability to bind covalently to enzymes, coenzymes, or metabolic intermediates containing sulfhydryl (-SH) groups, thus preventing germination and seedling growth of the weeds. The chlorine atom of α-chloroacetanilide herbicides is activated by the adjacent carbonyl group, so chlorine easily reacts with nucleophiles, and hence with thiol groups.

Some results have confirmed a close connection between the metabolism of various α-chloroacetanilides and the levels of glutathione or of its transferase. It is suggested that exposure of a plant to α-chloroacetanilide 'stress' results in some sort of feedback system that leads to the production of more glutathione and of its transferase; should this occur, the consequence is that chloroacetanilide could stimulate its own destruction in plants.

SAR studies:

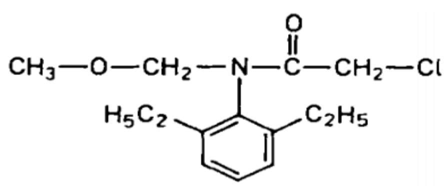
It seems that the most important pre-condition of activity in this group of compounds is the unsubstituted chloroacetyl group.
Substitution of chlorine for another halogen atom or pseudohalogen considerably reduces the herbicidal action.
Alkyl substitution in the methylene group results in completely inactive compounds.
Substitution of two or three chlorine atoms at the α-carbon atom similarly stops herbicidal action.

It has been observed that any second substituent on amide nitrogen 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 bonded to amide nitrogen. Increased polarity of the hydrocarbon chain on this carbon strongly reduces activity, and this phenomenon becomes particularly marked if the non-polar carbon - carbon triple bond is substituted by a polar carbon - nitrogen bond. Result(s) of other polar substituent(s) are similar. Any -CH_3 or -Cl substitution on the benzene ring reduces pre-emergence activity as a herbicide.. This, however, does not hold true for 2,6-substituted compounds.

Side effects:

Chloroacetanilides are reported to be substantially toxic at high doses. On prolonged exposure, it causes skin irritation and allergic reaction to eyes also.

Alachlor



Uses:

Alachlor is a selective pre-emergence soil herbicide.

Mode of action:

Absorbed alachlor inhibits the growth of the shoots and roots and lateral root development of sensitive plants. The biological mode of action of alachlor is probably the inhibition of protein synthesis.
Treatment of maize seedlings with alachlor raises the levels of glutathione in the roots.

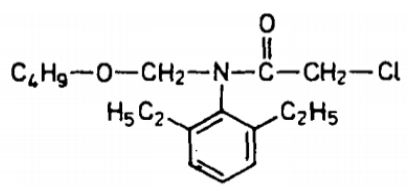
Side effects:

Alachlor is a nonvolatile crystalline substance; the technical product is viscous oil. Though alachlor is nontoxic to mammals, the emulsifiable concentrate and alachlor granules occasionally cause allergic skin reactions.

Special feature:

With its poorer solubility in water it needs sufficient soil moisture to exert its action and irrigation must be used in a dry spring to obtain a satisfactory herbicidal action.

Butachlor



Uses:

Butachlor is a pre- and early post-emergence selective herbicide for the control of grass weeds and a few broad-leaved weeds.

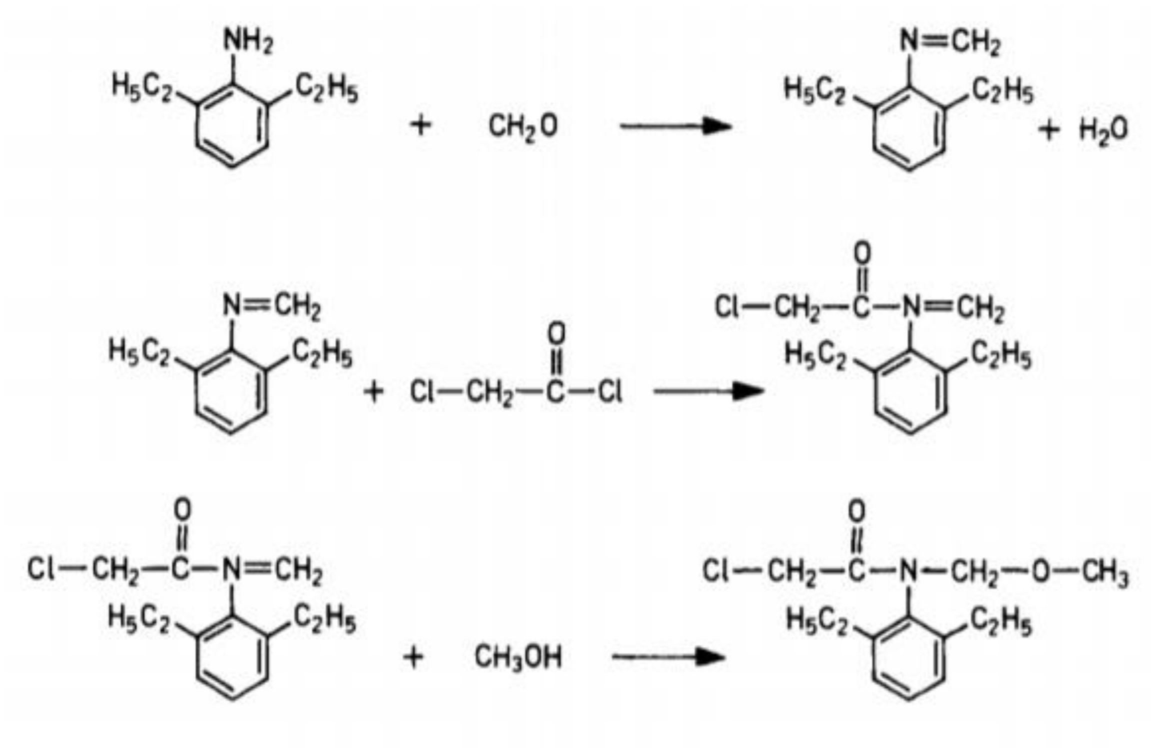
Side effects:

Butachlor is moderately toxic to mammals and is a mild eye and skin irritant.

Special feature:

Butachlor is less soluble in water than alachlor by one order of magnitude and thus needs higher soil moisture to exert a suitable herbicidal action.

Synthesis of Alachlor



Butachlor is the butyl homologue of alachlor.

Quinone

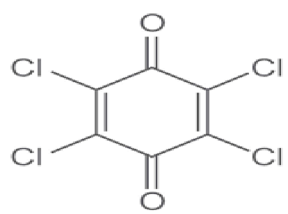
Uses:

It is found that quinones, napthoquinones are the most toxic to fungi and bacteria. These are followed in decreasing order by phenanthroquinones and anthraquinones. Halogenation, primarily chlorination, increases fungitoxicity, and at the same time decrease phytotoxicity; pesticides used in agriculture are therefore chlorinated derivatives of quinones .

Mode of action:

The mode of action of chlorinated quinones is based on their reactivity, occurring primarily with enzymes containing sulfhydryl groups. The quinone ring behaves as conjugated ketone and at the site of the reactive chlorine atom a thioether bond is formed with the sulfhydryl group.
Moreover, quinone may have also an oxidizing effect.

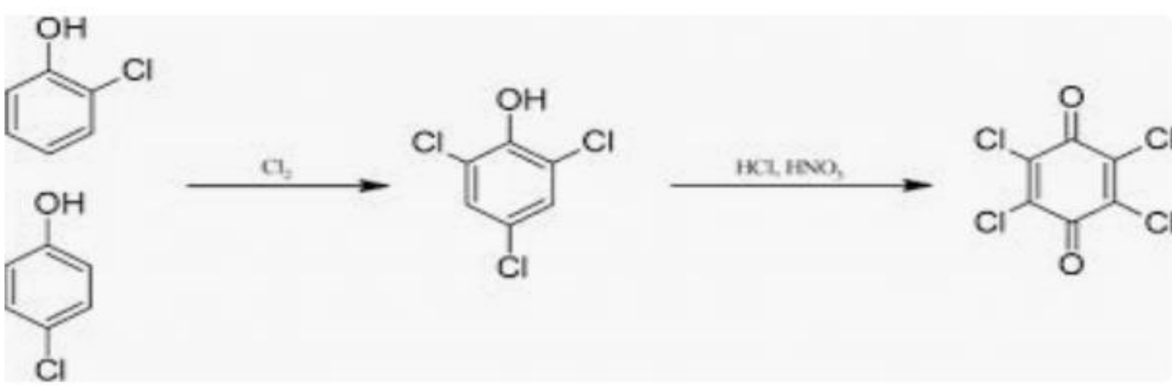
Chloranil



Uses:

Chloranil is used mainly for seed treatment against smut and diseases of vegetable seeds.
Use of chloranil as a foliage fungicide is limited because it decomposes partly by hydrolysis and partly photochemically and sublimes in hot weather.

Synthesis:



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