PART I
CHAPTER I
SYNTHETIC ORGANIC INSECTICIDES.

The damage caused by insects to human property and health is enormous. Though several methods are possible for the control of insect pests, such as mechanical and biological control, the chemical method has been playing a vital part all along.

The older insecticides used were general poisons like cyanides, arsenates and tobacco. The discovery of the insecticidal properties of derris roots and pyrethrum flowers and their large scale use marked a great advance in the field of insecticides owing to their high toxicity to insects while being comparatively safe for human beings and domestic animals.

Studies on insecticides of vegetable origin led to efforts to discover simpler compounds having selective insecticidal properties. Earlier in this century thiocyanates (Murphy and Pest, J. Econ. Ent., 1932, 25, 123) and phenothiazine (I) (Campbell et al., ibid., 1934, 27, 1176) were introduced with considerable success. The highly toxic thiocyanates contain the -SCN group which is considered to liberate hydrocyanic acid in situ. Phenothiazine, on the other hand, is comparable to lead arsenate as a stomach poison but is not effective against flies and mosquitoes. Many compounds like para-dichlorobenzene were used as a protection for clothing against moths and certain dinitrophenols, 4:6-dinitro-ortho-cresol (II) and 2:4-dinitro-6-cyclohexyl phenol (III), are aphicidal, ovicidal as well as toxic to moths, but they are often highly toxic to plants.
Developing from the study of moth-proofing methods, the remarkable discovery of the most successful insecticides, viz. DDT, was made.

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\text{Chlorinated hydrocarbons.}
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DDT is the popular abridged name for 2:2-bis (para-chlorophenyl)-1:1:l-trichloroethane (IV). It was first synthesized by Zeidler (Ber., 1874, 2, 1180); Muller (Swiss Pat. 226180 (1940); U.S.Pat. 2,329,074 (1943) discovered its insecticidal properties. The laboratory as well as the commercial processes of synthesis are based upon the condensation between chloral and chlorobenzene in the presence of concentrated sulphuric acid. The technical product contains about 70-75 per cent of the p-p'-dichloro compound along with lesser amounts of o-p' and o-o'-isomers. The value of this insecticide has been established against house-flies, bed-bugs, mosquitoes, fleas and a variety of insect pests of agricultural crops.

The importance of the discovery of DDT not only lies in its intrinsic efficacy but also in its opening new fields of
insecticide research. Several compounds closely related to DDT have attained some importance as insecticides and are produced by an analogous reaction. For instance DDD or 2:2-bis-(para-chlorophenyl)-1:1-dichloroethane (V), is prepared by the reaction between chlorobenzene and dichloroacetal or dichloroacetaldehyde (Forrest et al., J.C.S., 1946, 333). It possesses certain special toxicological properties and finds application as a larvicide.

Another commercially important analogue of DDT is methoxychlor (2:2-bis-(para-methoxyphenyl)-1:1:1-trichloroethanes) (VI) which is produced from anisole and chloral (Stephenson and Waters, ibid., 1946, 339). It has been chiefly used as a residual insecticide to control house-flies since it has a faster knock-down effect. Further, methoxychlor is less toxic than DDT to vertebrates generally and less likely to be stored in fatty tissues and hence useful as a dairy-cattle insecticide.

Fluoro-DDT (DFBT) (VII) was produced in Germany during the war under the name Gix (Kilgore, Soap & Sanit. Chem., 1945, 21, 136). It has a higher vapour pressure than DDT and consequently a lesser duration of residual effect.

Of the dimethyl and diethyl analogues of DDT (VIII & IX) (Stephenson and Waters, loc.cit.); the latter is of the same general order of toxicity as DDT but is superior to it on account of its lower vapour pressure and ability to penetrate the waxy coatings of insects.

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\text{V} \quad \text{VI} \quad \text{VII} \quad \text{VIII} \quad \text{IX} 
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Mode of action of DDT.

The mode of action of DDT has been engaging the attention of several investigators. A generally accepted view is that there should be two specific groups in the molecule of a successful insecticide: (i) a toxophoric group and (ii) a lipoid solubilizing group. Läuger, Martin and Müller (Helv. Chim. Acta, 1944, 27, 892) considered that in DDT the lipoid solubilizing group is the trichloromethyl group (X) and the toxophore is the bis-(para-chlorophenyl)-methylenegroup (XI). However, the effectiveness of the various alkoxy and alkyl analogues of DDT make it evident that its toxicity is not uniquely explained by the presence of the bis-(para-chlorophenyl)-methylenegroup. Consequently, the opposite suggestion (Martin and Wain, Nature, 1944, 154, 512) has been made that para-chlorophenyl groups are really responsible for the lipoid solubility and trichloromethyl group for toxic action. This toxic action has been explained by Martin and Wain (loc.cit.) to be produced by the liberation of hydrogen chloride in situ at vital centres. This idea is not supported by the comparative study of the dehydrochlorination rates of DDT analogues and the insecticidal potency, as the two do not run parallel. But this may not rule out the validity of the explanation since there may be other factors such as steric configuration that control intensity of insecticidal action (Rienschneider and Otto, Z. Naturforsch., 1954, 9b, 95; Regers et al., J. Amer. Chem. Soc., 1953, 75, 2991; Gunther et al., Arch. Biochem. Biophys., 1954, 50, 504).

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\text{X} \quad \text{XI}
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\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl}
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Benzene hexachloride (BHC). This compound was first prepared by Faraday in 1825, but its insecticidal properties were discovered in Britain and France by Slade (Chem. & Ind., 1945, 314) and Raucort (La Nature, 1945, 3093, 325) respectively. BHC is an addition product of benzene and chlorine and is a mixture of six complex isomers. Of these the \(\gamma\)-isomer (XII), which forms 10-13 per cent of the crude product, is the principal insecticidal component (Metcalf, J. econ. Ent., 1947, 40, 522) and all the BHC formulations are therefore rated according to the \(\gamma\)-isomer content. It is remarkably stable towards oxidation and can be recrystallised from hot nitric acid without appreciable decomposition. BHC has been used successfully against a variety of insect pests of public health and agricultural importance.

BHC, like DDT, releases hydrogen chloride in the presence of alcoholic alkali. In this series also there is no correlation between the relative rates of dehydrochlorination of the various isomers and their toxicites to insects. This may be due to stereochemical factors which play an important part. According to Slade (loc. cit.) \(\gamma\)-BHC might act as an anti-vitamin in the case of meso-inositol as both were postulated to have the same stereochemical configuration. More recent evidence (Bijvoet, Rec. trav. chim., 1948, 67, 777; van Vloten et al., Nature, 1948, 162, 771) has, however, indicated that the configuration, of meso-inositol is \(\alpha\) as compared with \(\alpha\) for the \(\gamma\)-isomer and thus the \(\delta\)-isomer is the structural analogue.
Attempts have been made to prepare structural analogues of Y-BHC based on the reasoning that methoxy and ethyl analogues of DDT are good insecticides. But hexamethoxy cyclohexane (XIII) (McGowan, J. Soc. Chem. & Ind., 1947, 66, 446) and hexaethyl cyclohexane (XIV) (Stringer and Woodcock, Chem. & Ind., 1948, 110) are found to be relatively ineffective. It should, however, be noted that, unlike DDT analogues, these compounds do not have any chlorine atoms in their molecules which probably explains their lack of activity.

![Chemical Structure of Hexamethoxy Cyclohexane (XIII) and Hexaethyl Cyclohexane (XIV)]

**Aldrin and Dieldrin.** Several other compounds having high chlorine content have been made and used as insecticides. Aldrin (XV) and dieldrin (XVI) (Rohwer, Interdepartmental communique on Pest Control, Bur. Entomol. Plant Quarantine, Wash., Dec. 12 and 13, 1949) are the most toxic members of this group and are principally used against locusts and other agricultural pests. Dieldrin is a remarkably stable oxide and is produced by the oxidation of the former. Both are stable in the presence of acids and alkalies.

![Chemical Structure of Aldrin (XV) and Dieldrin (XVI)]

The corresponding endo, endo-isomer of aldrin is isodrin.
(XV a) which on oxidation with peracetic acid gets converted into the epoxide, endrin (XVI a). (Bluestone, U.S.Pat. 2676132 (1954). Both these compounds are less stable than aldrin and dieldrin.

![Chemical structure of endrin](image)

Chlordane (XVII a), also known as octachlor, is obtained by the chlorination of a dimer of cyclopentadiene (Kearns et al., J. econ. Ent., 1945, 38, 661). Technical chlordane has been found to contain another complex chlorinated hydrocarbon, heptachlor (XVIII) (ibid., 1949, 42, 127), whose toxicity is comparable to that of γ-BHC.

![Chemical structure of heptachlor](image)

Toxaphene (C_{10}H_{10}Cl_{8}) is a terpene derivative, prepared by chlorinating camphene to such an extent that the final product contains about 65 per cent chlorine (Stearns, Soap & Sanit. Chem., 1947, 23, 117 and 141). It is relatively slow in action and hence is used in admixture with a quick-acting insecticide (Parker and Beacher, Bull. Del. Bd. Agric. Stat. No. 264, Tech. Bull., 1947, 36, 26).

Chlorination of bornyl chloride (XVII a) in carbon tetrachloride with sunlight formed 2,6,7-trichlorocamphane (XVIII a), which has good insecticidal properties. (Desalbres and Roche, Chimie et industrie, 1948, 59, 236).
Phosphorus compounds.

Phosphate Insecticides having great potency were discovered during the Second World War. They are selective in action, the most important members being tetraethyl pyrophosphate (XIII), diethyl-para-nitrophenyl phosphate (E 600; para-oxon) (IX) and diethyl-para-nitrophenyl thiophosphate (E 605; parathion) (XI). They are described in detail in chapter V.

During the course of present work coumarin phosphates have been synthesised and found to be potential insecticides (see chapter V).

Pyrone derivatives.

Rotenone, which was isolated as early as 1902 (Nagai, J. Tokyo Chem. Soc., 1902, 22, 744), is the principal constituent of derris and is also the most important from the insecticidal point of view. Efforts of a number of groups of chemists led to structural formula (XIII) for rotenone (LaForge et al., Chem. Revs. 1933, 12, 181).
The pyrethrum flowers contain a mixture of pyrethrins which are contact poisons and exhibit a characteristic paralytic action on insects. They consist of mixtures containing esters of chrysanthemum-carboxylic acid (XXIII) and of the monomethyl ester (XXIV) of chrysanthemum-dicarboxylic acid with the keto-alcoholic pyrethrolones (XXV, R = -CH₂.CH=CH₂.CH=CH₂) and cineolones (XXV, R = -CH₂.CH=CH₂.CH₃) (Staudinger and Kuzicka, Helv. Chim. Acta, 1924, 7, 177, 201, 212, 377 and 448).

It is not very easy to decide which part of such highly complex molecules is the most reactive and is therefore to be considered in relation to combination with cell constituents. Läuger, Martin and Müller (Helv. Chim. Acta, 1944, 27, 892) have suggested that the unsaturated carbonyl groups (A) and (B) are responsible for a reaction or reactions with vital cell constituents which partly determine the insecticidal activity. This degree of reactivity may further be modified by other parts of the molecule, particularly by unsaturation.
Such groups occur very widely in nature in the form of \( \alpha \)- and \( \gamma \)-pyrone derivatives. In order to test the above suggestion a detailed investigation of chromones, flavones, flavonols, flavanones, chalcones, isoflavones and coumarins has been made by Seshadri and coworkers using fresh-water fish as a convenient test animal (Murti, Rao and Seshadri, Proc. Ind. Acad. Sci., 1947, 25 A, 22; Murti & Seshadri, ibid., 1947, 25 A, 333; Seshadri and Viswanadham, ibid., 1947, 25 A, 337; Murti, Rao and Seshadri, ibid., 1948, 27 A, 33; Narasimhachari and Seshadri, ibid., 1948, 27 A, 128). The simpler chromones and coumarins having the C\(_9\) skeleton have poor activity whereas the phenyl substituted compounds having the C\(_{15}\) skeleton are much more active. It was found that the presence of a large number of hydroxyl groups lowers toxicity whereas the methyl ethers are considerably more active. This can very easily be explained by the classical Overton-Meyer theory that the toxicity is also related to the relative solubility of the substance in oil and water and that as the fatty compounds will be accumulated at the plasma membrane narcotic action will be governed by the solubility of the narcotic in such fatty bodies (Lipoid theory) (Meyer and Hemmi, Biochem. Z., 1935, 277, 39; Ferguson, Proc. Roy. Soc. (London), 1939, B 127, 387). The simpler ethers, e.g. 7-methoxy flavone (XIVI), are found to be highly potent fish poisons. 7-Methoxy-8-allyl-2-methyl isoflavone (XIVII) (Seshadri et al., Proc. Ind. Acad. Sci., 1948, 27 A, 33), which has the carbon skeleton of the rotenoids, is one of the highly toxic compounds.
(compare allethrin (XXVIII) which also contains allyl grouping).

Compared with chromone derivatives, coumarins are far more easy to make. Among them the 3-phenyl coumarins, which have carbon skeleton similar to isoflavones, are the best (Seshadri and Varadarajan, ibid., 1952, 35 A, 75). For their preparation a simplified method, which is capable of introducing different substituents in the side-phenyl nucleus, has now been worked out (chapter III). Some of these compounds are strong as fish-poisons. On the other hand the partial methyl ethers of coumarins were found to have better insecticidal properties as compared with the corresponding hydroxy compounds or their methyl ethers (Sawhney and Seshadri, unpublished work). The experiments of Krishnaswami and Seshadri (ibid., 1942, 16 A, 231) show that the presence of a furan ring enhances this activity considerably; psoralen (XXIX), iso-psoralen (XXX) and karanjin (XXXI) may be considered to be illustrations of this type. Out of these furano-coumarins the angular type of compounds may be more toxic than the linear ones, e.g. iso-psoralen is more toxic than psoralen. 3-para-Nitrophenyl-psoralen (XXXII) has also been made for a similar investigation (chapter III). Further halogen derivatives of coumarins have also been investigated and the 3-chloro compounds, which are readily made by direct chlorination,
are found to have improved toxicity (Seshadri and Varadarajan, J. Sci. Ind. Res., 1952, 11B, 48).

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XXXI
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XXIX, \ R = H.
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XXXII, \ R = \text{para-nitrophenyl}
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