STRUCTURE AND ACTIVITY IN SYNTHETIC INSECTICIDES

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General Considerations.—In considering relations between chemical constitution and biological activity, it is often difficult to correlate structure with effect when the measured biological response is the death of the organism. Death may result from many causes and the action of the poison may be indirect, with death ultimately resulting from the interruption of a complex dynamic system of delicately balanced biochemical reactions. Such difficulties increase with the complexity of the organism, and insects are much more complex than micro-organisms such as bacteria or protozoa. It is therefore not yet possible to correlate constitution and activity throughout the whole field of insecticides, where the chemical types vary from inorganic arsenic to complex molecules of diverse type such as rotenone, the pyrethrins, the chlorinated hydrocarbons, and the new phosphoric acid derivatives. A further complicating factor is the effect of the mode of presentation on the toxicity of the insecticide. Insecticides may be presented as fumigants, contact poisons, or stomach poisons. Contact poisons are absorbed by passage through the insect cuticle and sometimes also through the spiracles. Stomach poisons are so-called because they are eaten. A stomach poison may have relatively little activity as a contact insecticide. Furthermore, with contact insecticides, for example, the physical form may have a very great effect on the toxicity; factors such as the use and nature of a solvent or emulsifying agent, and the particle size of the dispersion greatly influence the result. There is also the question of insect specificity. These factors often render difficult the comparison of results obtained by different workers. In spite of the difficulties outlined above, there are, however, certain general principles which have emerged, particularly in relation to contact insecticides, and these will be briefly discussed, before proceeding to the treatment of the different chemical types.

It is a first essential of insect poisons, as indeed of all substances possessing biological activity, that they must be capable of absorption and translocation to a point at which the chemical reactions responsible for the toxic response may be initiated. (It should be said at this point that consideration is being given to genuine toxic effects, ruling out what might be termed the mechanical killing of insects, such as might occur by " drowning " through blockage of the spiracles.) Physicochemical properties may therefore play a dominant rôle and there may be a direct quantitative relation between toxicity and some physical constant. In such cases, there appears what J. Ferguson [1] has classified as " physical " toxicity, the outstanding characteristics of which in contact and fumigant insecticides are (i) the peak activity

[1] *Proc. Roy. Soc., B*, 1939, **127**, 387.

as an homologous series is ascended, and (ii) the equal molar toxicity of compounds of different chemical classes, provided that they have no very pronounced chemical reactivity. This may be illustrated by (*a*) the approximately equal molar toxicities to the grain weevil of vapours of toluene, ethylene chloride, and methyl alcohol, and (*b*) the approximately equal contact insecticidal action on blowflies of 2-hexylthiobenzthiazole, ethyl phenylmethylcarbamate, and dimethylaminoacetonitrile : in each chemical class physical properties play an important rôle. Where physical mechanisms predominate, two consequences follow. The first is that the toxicity may be greatly affected by the presence of a second organic substance, which may be an insecticidally inert solvent. This may either depress the toxicity or enhance it, and the latter effect is commonly referred to as synergy, and the substances producing it are called synergists. This will be referred to again later. The second consequence is that the toxicity may be highly specific—either specific to insects as distinct from other biological types or even affecting some insects and not others ; for Ferguson has pointed out that whereas in " physical " toxicants the chemical potentials (considering a particular biological response) of individual molecules lie very close together, the order of magnitude of the chemical potential is a characteristic of the organism. Specificity, of course, may result from other causes. Metabolite antagonism may be one of these and it is possible that phenomena analogous to those encountered in the study of inhibition of bacterial growth may ultimately be shown to be concerned with the action of insecticides.

It has been postulated as a working hypothesis that, in addition to the physical criteria mentioned above, a biologically active compound, *e.g.*, an insecticide, must be capable of combining with a vital cell constituent.[2] The union may be a firm one involving covalent bonds and having only a limited degree of reversibility. At the other extreme it may be a very loose union such as that due to hydrogen bonding, easily reversible and yet capable of disturbing the delicate balance of the normal biochemical reactions (*e.g.*, certain narcotics and other " physical " toxicants). There is a whole range of unions, of varying strength, between these two extremes, and it is necessary to include the unions of macromolecular species through a multiplicity of points of attachment by van der Waals forces, electrovalent links, hydrogen bonds, etc., which through stereochemical " fit " may add up to a considerable force. The two factors, physical and chemical, will be interdependent. Any particular molecular alteration may affect both the physical properties and the capacity for combination with all constituents, and such dual effects may be either mutually supporting or antagonistic so far as the final toxic effect is concerned. The nature of the cell constituent or constituents with which the insecticide combines is not likely to be the same for all types of insecticides, and its elucidation in individual instances can come only as the result of much more detailed biochemical investigations than have been attempted heretofore.

[2] W. A. Sexton, Soc. Exp. Biol. Symposium III, 1949, p. 1.

P. Läuger, H. Martin, and P. Müller [3] have put forward the general view that the activity of contact insecticides is associated with a grouping which is responsible for the toxic effect and a grouping which confers solubility in lipoids, and they have analysed the structures of a wide variety of contact insecticides from this standpoint. Although this theory is probably basically sound it appears to the Reviewer to be an over-simplification and to require modification (Ref. 4, p. 320). The view that one group in the molecule more than any other may be responsible for the particular chemical reaction within the organism which is the prime cause of its death may well be valid in quite a number of instances. This is the concept of the toxiphoric group. It is possible however that there may be other groups within the molecule which can enter into significant unions with cell constituents, and that such unions hinder the access of the molecule to the site at which the toxiphoric group would operate. Furthermore, the chemical reactivity of the toxiphoric group may be modified by molecular variation at other points. Thus although a series of insecticidal compounds may be seen to possess a common toxiphoric group, such as an unsaturated carbonyl system as exemplified by the Swiss workers, it does not follow that all compounds containing this group will be insecticidal. With regard to the conception of the lipophilic group, it is the lipophilic properties of the molecule as a whole which are relevant. These may on occasion be greatly modified by the introduction of a specific group, as for example the introduction of a long fatty chain in an alkyl thiocyanate, but it is not always possible to point to a specific group as being mainly responsible for fat solubility, a case in point being D.D.T.

It appears to the Reviewer that on present knowledge one could say of contact insecticides that they must contain a toxiphoric group which has rather a precise degree of chemical reactivity, enabling them to combine with a particular constituent of the insect thereby disturbing the normal biochemical sequence or initiating new processes which result in death. If their reactivity is too great, they may become immobilised by some reaction having no serious consequences for the insect before they can reach a vital centre. If they contain more than one such group, it is possible though not, of course, certain that the rival attractions of different receptor points within the organism may result in a diminished affinity for either (Ref. 4, p. 95). The molecule must have a degree of lipoid solubility, enabling it to penetrate the insect cuticle and possibly to pass other physical barriers before reaching the site of action.

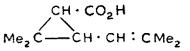
Although this article is primarily concerned with synthetic insecticides, some discussion of two classes of natural products, the pyrethrins and the nicotine alkaloids, is included for two reasons. First, although some of the compounds in these classes are of purely natural origin, quite a number have actually been synthesised. Secondly, when considering the mode of action of insecticides from the chemical standpoint, one must not differentiate

[3] *Helv. Chim. Acta*, 1944, **27**, 892.

[4] W. A. Sexton, " Chemical Constitution and Biological Activity ", E. & F. N. Spon, London, 1949.

between natural and synthetic compounds. Certain points which are brought out in connection with the pyrethrins and the nicotine alkaloids will be seen to have a general bearing on the relation between constitution and biological activity of synthetic insecticides.

Synthetic Analogues of Some Natural Products.—The natural pyrethrins are contact poisons which exhibit a characteristic paralysant action on insects. They consist of mixtures containing esters of chrysanthemum-carboxylic acid (I) and of the monomethyl ester (II) of chrysanthemumdi-carboxylic acid with the keto-alcoholic pyrethrolones and cinerolones. The pyrethrolones are stereoisomeric forms of (III ; R = CH_2·CH:CH·CH:CH_2),



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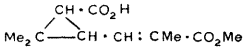
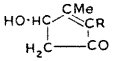


(II)

and the cinerolones are stereoisomeric forms of (III ; R = CH_2·CH:CH·CH_3).[5] In these, as in other complex molecules, it is not easy to decide which part of the molecule is the most reactive and which is therefore to be considered in relation to combination with cell constituents. Läuger, Martin, and Müller [3] have suggested that it is the *cyclo*propane ring, since it behaves like an unsaturated structure conjugated with the ester-carbonyl group. If, however, the pyrethrins are subjected to catalytic hydrogenation, it is



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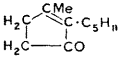


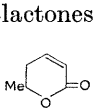
(IV)

not the *cyclo*propane ring which is attacked, for H. L. Haller and F. B. LaForge [6] obtained 3-methyl-2-*n*-amyl*cyclo*pent-2-en-1-one (IV) together with dihydro-derivatives of (I) and (II) : thus, hydrogenation splits the ester linkage. This is not surprising since the high reactivity of the system —X·CH_2·CH_2·CO— where X is a hetero-atom is manifest in the behaviour of such substances as aldols and Mannich bases. It seems likely therefore that this reactive group is responsible for a reaction or reactions with vital cell constituents which partly determine the insecticidal activity. The degree of reactivity may well be critical and this will undoubtedly be modified by the other parts of the molecule, particularly by the unsaturation. Tetrahydropyrethrin I, in which the C_5H_7 side chain has been reduced, has much lower insecticidal activity.[7, 8] Similarly, a synthetic " pyrethrin " made from the natural (+)-*trans*-chrysanthemum-monocarboxylic acid and the synthetic compound (III ; R = Bu) had low activity. On the other hand, compounds having high activity of the characteristic pyrethrin type have been synthesised by using compounds of type (III) in which R may

[5] F. B. LaForge and S. B. Soloway, *J. Amer. Chem. Soc.*, 1947, **69**, 186.
[6] *J. Org. Chem.*, 1937, **2**, 49.
[7] F. B. LaForge and W. F. Barthel, *ibid.*, 1947, **12**, 199.
[8] L. Crombie, M. Elliott, S. H. Harper, and H. W. B. Reed, *Nature*, 1948, **162**, 22.

be $CH_2{\cdot}CH_2{:}CH_2$, $CH_2{\cdot}CMe{:}CH_2$, $CH_2{\cdot}CH{:}CHMe$, or $CH_2{\cdot}CH_2{\cdot}CH{:}CH_2$. The compound derived from the first of these substituents and the natural isomeride of chrysanthemum-monocarboxylic acid was considerably more active than natural pyrethrins. Again, with (III; $R = CH_2{\cdot}CH{:}CH_2$) there was no difference in activity between the compounds obtained by esterification with the (±)-*cis*- and the (±)-*trans*-acid, although both compounds were somewhat less active than that derived from the (+)-*trans*-acid. Stereoisomerism, therefore, as in the nicotine series, plays a definite though not highly significant part. It would appear that the differences in activity amongst these synthetic compounds are a reflection of the part played by the physicochemical properties of the molecule, which probably determine its access to the site of the toxic reaction. The synthetic work mentioned here is described in recent papers by M. S. Schlechter *et al.*[9a] and by W. A. Gersdorf.[9b]

It may be remarked that the system —X·CH_2·CH_2·CO— is frequently found in natural compounds, including some with characteristic biological activities. Cocaine, ψ-pelletierine, and lobeline may be exemplified. The idea may be further extended if the principle of vinylogy is included, for —X·CH_2·CH_2·CH:CH·CO— will then be of equivalent reactivity, and this is contained in such substances as parasorbic acid (V), kawain (VI; R = —CH:CHPh), and mandarenin (VI; $R = CH_2{\cdot}CH_2Ph$).—In this way $\Delta^{\alpha\beta}$-unsaturated δ-lactones differ from unsaturated γ-lactones.



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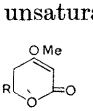
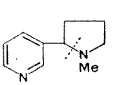


(VI)

Another feature of studies of pyrethrin derivatives deserves comment, and supports the conception that it is not the *cyclo*propane ring which gives to the molecule its unique biological properties. Esters of chrysanthemum-carboxylic acid with normal aliphatic C_{12-16} alcohols are as toxic to aphids as are the pyrethrins. Nevertheless their mode of action is probably quite different, for when these compounds are applied to cockroaches they do not produce the muscular paralysis which is the characteristic effect of pyrethrins.[10] Herein lies an illustration of the danger in comparing constitution with a biological response as vague as death. Similar difficulties obscure the consideration of nicotine.

Various alkaloids related to nicotine (VII) occur in solanaceous plants and are all powerful contact insecticides. These include both (+)- and



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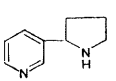

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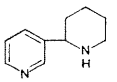


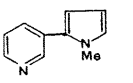
(XI)

[9] (*a*) M. S. Schlechter, N. Green, and F. B. LaForge, *J. Amer. Chem. Soc.*, 1949, **71**, 1517; (*b*) *J. Econ. Entom.*, 1949, **42**, 532.

[10] E. K. Harvill, *Contr. Boyce Thompson Inst.*, 1939, **10**, 143.

(−)-forms of nornicotine (VIII), and (−)-anabasine (IX), the optically inactive form of which (neonicotine) was first obtained by synthesis. There are some differences between the activities of these three substances and their stereoisomers, but their toxicities are of the same order of magnitude.

The effect of structural variations has been studied by alteration of both rings. In the work of C. H. Richardson and H. H. Shepard,[11] nicotyrine (X) and metanicotine (XI) had about one-tenth of the toxicity of nicotine to aphids, whereas dihydrometanicotine and 3-1′-ethylaminoethylpyridine (XII) had one-hundredth of this activity, while 3-1′-methylaminobutyl-



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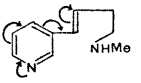

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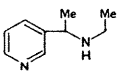

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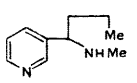

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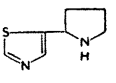

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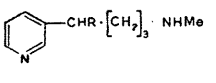


(XV)

pyridine (XIII) and 2-phenylpyrrolidine were still less active. The biological activity of the thiazole analogue (XIV) of nornicotine resembles that of nicotine, thus providing an example of the equivalence of the thiazole and pyridine rings.[12]

In determining what part of the molecule may be responsible for combination with cell constituents, it is of interest to consider some of the chemical reactions of nicotine, and particularly (as was done with the pyrethrins) its behaviour on hydrogenation. Reduction of nicotine with sodium and alcohol, or catalytically, results in fission of the molecule at the point indicated in formula (VII) and formation of hexahydro- and octahydrometanicotine.[13] Treatment of nicotine with acylating agents such as acetic anhydride or benzoyl chloride results in a similar rupture.[14] This would therefore appear to be the most reactive point of the nicotine molecule, and a suitable cell constituent RH, having an active hydrogen atom, might give rise to a product of structure (XV). If a similar reaction occurred with the relatively inactive compounds (XII) and (XIII), it would lead to loss of ethylamine and methylamine respectively, the adduct differing materially from the type (XV) by loss of the side-chain nitrogen atom. In dihydrometanicotine, also of low activity, the molecule contains no such reactive point, and such insecticidal activity as it possesses may be realised by an entirely different mechanism. In this connection it is of interest that

[11] *J. Agric. Res.*, 1930, **40**, 1007.

[12] H. Erlenmeyer and R. Marbet, *Helv. Chim. Acta*, 1946, **29**, 1946.

[13] F. Blau, *Ber.*, 1893, **26**, 628; W. Windus and C. S. Marvel, *J. Amer. Chem. Soc.*, 1930, **52**, 2543; J. Overhoff and J. P. Wibaut, *Rec. Trav. chim.*, 1931, **50**, 957.

[14] A. Pinner, *Ber.*, 1894, **27**, 1053, 2961.

insecticidal activity is shown by alkyl- and benzyl-substituted pyridines, and in the alkyl series there is maximum activity at propyl.

In metanicotine (XI) the extracyclic double bond is so placed that an additive reaction with a hypothetical cell constituent RH might well result (through the electromeric changes indicated) in addition of the group R, as with nicotine, at the carbon atom adjacent to the pyridine ring. Nicotyrine, as a pyrrole derivative, is highly reactive. Pyrrole derivatives have reactive hydrogen atoms in the α-positions, as exemplified by the addition to maleic anhydride to give α-pyrrylsuccinic acids.[15] 2-Phenylpyrrole affords a dimeride by linkage at the α(5)-position not bearing the phenyl group.[16] Nicotyrine has been insufficiently studied from this aspect, and the point at which it could combine with the hypothetical cell constituent RH under physiological conditions can hardly be foreseen.

In the group of compounds under consideration, physicochemical properties undoubtedly make an important contribution to the insecticidal effect. This might account for the large difference between nicotine and 2-phenylpyrrolidine, the removal of a basic centre being critical. (Compare the well-known effects of the basic side chains in synthetic antimalarial drugs.) On the other hand there may well be, in addition, significant differences in the chemical reactivity of these two compounds. The basic strength is probably a significant factor in regulating the degree of activity in this series, for L. C. Craig [17] found a relation between the dissociation constants of a series of pyrrolidine derivatives and their insecticidal activity, the weaker bases being the most toxic. This may be concerned with membrane permeability.

Organic Sulphur Compounds.—The insecticidal properties of the normal aliphatic thiocyanates are of considerable importance from both the theoretical and the practical viewpoint. The lower members have fumigant but little contact action and, as the series is ascended, maximum contact activity is shown between C_8 and C_{14}, and usually at C_{10} or C_{12}. The dominant feature of the lower aliphatic thiocyanates is the high chemical reactivity of the —SCN group. It is not surprising to find that they are toxic also to animals, to micro-organisms, and to green plants. This toxicity has been attributed by W. F. von Oettingen and his collaborators [18] to the liberation of hydrocyanic acid, for not only do animals poisoned by the thiocyanates exhibit symptoms of hydrocyanic acid poisoning, but the compounds yield this acid when in contact with minced liver. It is conceivable that the more reactive lower members are immobilised by reaction with some constituent of the insect cuticle, and hence cannot show contact insecticidal action, whereas, when they are used as fumigants, absorption is through the spiracles and there is no such impediment to penetration. The higher members of the series are less reactive and do not show the general toxicity of the lower members. The characteristic reactivity is however not lost, but only modified quantitatively, and one reaction of thiocyanates

[15] O. Diels and K. Alder, *Annalen*, 1931, **486**, 211.
[16] C. F. H. Allen, M. R. Gilbert, and D. M. Young, *J. Org. Chem.*, 1937, **2**, 227.
[17] *Iowa State Coll. J.*, 1931, **5**, 327.
[18] *J. Ind. Hyg. Toxicol.*, 1936, **18**, 310.

which may be significant is their hydrolysis, which is catalysed by the acetate of an organic base and proceeds according to the equation : [19]

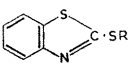
$$2RSCN + H_2O \longrightarrow RS{\cdot}SR + HCN + HOCN$$

It has been suggested (Ref. 4, p. 312) that the basic reaction on which the contact insecticidal activity of the higher fatty thiocyanates depends may be initiated by attachment of the —SCN group at one of the numerous salt-like linkages which are probably a feature of native proteins. Such an attachment might well serve to dislocate the balance of the biochemical processes, even though it might not result in liberation of hydrocyanic acid at the point of attachment. The normal aliphatic chains of appropriate length probably adjust, at the same time, the degree of reactivity of the —SCN group and the lipoid solubility which governs absorption through the cuticle. Many molecular variants of dodecyl thiocyanate have been examined and it is interesting to note that it is permissible to interrupt the normal aliphatic chain with oxygen atoms, or even with an appropriately placed benzene ring, without loss of insecticidal activity. This may be exemplified by $C_4H_9{\cdot}O{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2{\cdot}SCN$ and $PhO{\cdot}[CH_2]_3{\cdot}SCN$. The aromatic thiocyanates have not been subjected to the same degree of critical investigation as the aliphatic compounds and, although there are claims in the patent literature for activity of various aromatic compounds, notably those which also contain an amino-group, little can be found by way of quantitative data. A further feature of the aromatic thiocyanates is their phytocidal action, which obviously restricts their practical utility as insecticides. For references to the original literature R. C. Roark and R. L. Busby's review [20] should be consulted.

In the *iso*thiocyanate series the lower members, *e.g.*, methyl, ethyl, are active as fumigants but apparently not as contact poisons. There is a contrast with the thiocyanates, however, in the higher aliphatic region, for dodecyl *iso*thiocyanate has little or no contact activity. More attention has been paid to the aromatic *iso*thiocyanates and, although the literature contains insufficient data for the consideration of the effects of constitutional changes, α-naphthyl *iso*thiocyanate has been used commercially in fly-sprays.

High stomach-poison activity has been shown by reduced thiadiazines of the type (XVI), which are generally referred to in the early literature as carbothialdines.[21] They are readily obtained by reaction of a dithiocarbamic

(XVI)



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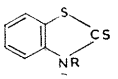


(XVIII)

acid $R'NH{\cdot}CS_2H$ with formaldehyde and a primary amine NH_2R. 2-Thio-3-phenyl-5-methyltetrahydro-1 : 3 : 5-thiadiazine (XVI ; R = Me, R′ = Ph)

[19] E. Hoggarth and W. A. Sexton, *J.*, 1937, 815.

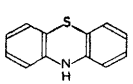
[20] " A List of Organic Sulphur Compounds used as Insecticides ", U.S. Dept. Agric., Bur. Entomology, 1935.

[21] W. H. Davies and W. A. Sexton, *Biochem. J.*, 1948, **43**, 461.

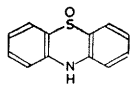
is considerably more toxic in a poison bait to locusts than is sodium arsenite. These compounds readily break down to *iso*thiocyanates, and this has been suggested as being associated with their insecticidal activity. In other words, a molecule of type (XVI) provides a method for presenting an *iso*-thiocyanate to an insect in what is, in effect, an altered physical form.

The finding of insecticidal activity in both thiocyanates and *iso*thiocyanates directed attention to other readily accessible compounds containing the —S·C·N— sequence of atoms.[21] 2-Mercaptobenzthiazole (XVII or XVIII ; R = H) was the starting point since, like thiocyanicacid, it could be alkylated at either the sulphur or the nitrogen atom. Contact insecticidal activity was found in both *S*- and *N*-alkylated derivatives and it was a characteristic in both series that the highest activity was found in the first three members, the activity decreasing thereafter as the molecular weight increased. In other words, the physical properties played a dominant rôle. It has already been pointed out that where physical properties play a dominant rôle there is likely to be considerable biological specificity. In conformity with this, it was observed that whereas the *S*-methyl compound (XVII ; R = Me) was quite highly toxic to blowflies, the *N*-methyl isomer (XVIII ; R = Me) was inactive. Against aphids, however, there was less difference in susceptibility, the tendency being towards greater toxicity with the *N*-methyl compound. It is of some interest to compare the chemical reactivities of three insecticidal compounds containing the —S·C·N— sequence. As already pointed out, the significant reactivity in the thiocyanates may be associated with the susceptibility to hydrolysis, *i.e.*, electron accession to the carbon atom of the toxiphoric group. The thiazole compound (XVII ; R = Me) is a weak base, that is to say it tends to donate electrons ; reactions requiring electron accession, *e.g.*, hydrolytic fission of the thiazole ring, require much more drastic conditions. The isomeric compound (XVIII ; R = Me) is neutral, though the fact that it gives a quaternary salt with methyl iodide indicates a capacity for electron donation. In those three compounds therefore the reactivities of the supposed toxiphoric groups vary both in nature and degree. Since they are all toxic to aphids, there are at least two possible inferences : (i) that they act by different mechanisms, and (ii) that, provided that there is the requisite degree of reactivity in the toxiphoric group, its nature may not be important. There is insufficient evidence to decide between them.

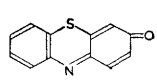
Although its main practical use is as an anthelmintic, the biological activity of phenothiazine (XIX) was first noted in its toxicity to mosquito larvæ. Later investigations showed that as a stomach poison it equalled lead arsenate in its toxicity to certain leaf-eating insects. It has no action as a contact spray against flies or aphids. In spite of its widespread use as an anthelmintic, surprisingly little is known of its mode of action.



(XIX)



(XX)



(XXI)

Chemically, its outstanding characteristic is its susceptibility to oxidation. Aerial oxidation, particularly in the presence of traces of iron or copper compounds, gives a bright green colour, probably a semiquinone form. Neutral or alkaline oxidising agents give the ψ-basic sulphoxide (XX), which is isomerised by acids to hydroxyphenothiazine, the leuco-compound of phenothiazone (XXI). Further oxidation leads finally to the red dye, thionol, the leuco-compound of which is excreted in the urine of animals which have consumed phenothiazine. The insecticidal activities of phenothiazine have therefore been attributed by various workers to its oxidation products. J. W. Zukel,[22] for example, suggested that the active agent is a conjugate of leucophenothiazone or leucothionol, which may act through inhibition of the important respiratory enzyme, cytochrome-oxidase. H. B. Collier [23] has observed the inhibition of various enzymic oxidation–reduction systems by the oxidation products, though not by phenothiazine itself. The evidence for the oxidation theory of the mode of action of phenothiazine is scanty and further work is obviously required. It would be informative, for example, to examine the insecticidal properties of phenothiazine derivatives in which certain critical positions such as the hydrogen atom of the imino-group, or the positions *para* to the imino-group, were blocked by methyl.

Amongst other organic sulphur compounds, various types are mentioned in the papers by Läuger [24] and Läuger, Martin, and Müller.[3] Dichloro-derivatives of diphenyl sulphide, sulphoxide, and sulphone, particularly the 4 : 4′-compounds, are stated to be active as stomach poisons, but no quantitative data are presented. Possibly activity is associated with the reactivity of one or both chlorine atoms. Certain aromatic sulphuric esters and sulphonamides are also active as stomach poisons, while the sulphonic acid group is made use of in various water-soluble textile-mothproofing agents in order to provide affinity for the wool fibre.

Chlorinated Hydrocarbons.—Various chlorinated derivatives of the lower aliphatic hydrocarbons have been known for a long time as insecticidal fumigants. Their activity is entirely governed by physical considerations, a fact which is brought out by Ferguson,[1] who quotes data relating to their toxicity to wireworms. These substances include chloroform, carbon tetrachloride, and trichloroethylene. Substances also included in the same category of " physical " toxicants are benzyl chloride, chlorobenzene, and *o*-dichlorobenzene, as well as chlorine-free substances such as dimethylaniline, pyridine, and carbon disulphide. The practical significance of these materials is however exceeded by the modern chlorinated hydrocarbon contact insecticides, the study of which started with the well-known substance 1 : 1 : 1-trichloro-2 : 2-di-*p*-chlorophenylethane (D.D.T.) (XXII, see Table I). Läuger, Martin, and Müller [3] suggested that the activity of D.D.T. was associated with the lipoid-solubilising properties of the CCl_3 group and the toxic effect of the *p*-chlorophenyl residues. Quite apart from

[22] *J. Econ. Entom.*, 1944, **37**, 796.
[23] *Canadian J. Res., B*, 1940, **18**, 345; 1942, **20**, 189, 284.
[24] *Helv. Chim. Acta*, 1944, **22**, 71.

the general point already made concerning the apportioning of the solubility properties to one substituent group in the molecule, it is extremely doubtful whether the Swiss workers were correct in assigning the toxic rôle to the *p*-chlorophenyl groups. A different viewpoint was early expressed in a suggestion by H. Martin and R. L. Wain [25] that insecticidal activity was associated with the ability of the molecule to lose hydrogen chloride, giving the unsaturated substance (XXIII), the hydrogen chloride liberated *in situ* being responsible for the toxic action. Since then a great deal of work has been carried out on compounds analogous to D.D.T. and it is clear that the position is not so simple as was first suggested. It has been pointed out by more than one investigator that the ability to liberate hydrogen chloride does not always run parallel with insecticidal efficacy, nor are the compounds with highest lipoid solubility always the most insecticidal. Some of these difficulties are discussed by S. Kirkwood and P. H. Phillips [26] and by J. R. Busvine.[27] The results may be reviewed afresh in the light of the hypothesis that activity is due to the correct balance of two different, but probably interdependent, sets of factors, the ability of the molecule to react with a vital cell constituent and the modification of this reactivity, or the regulation of transport of the molecule, by its physical properties. The contact insecticidal activities of some D.D.T. analogues are given in Table I, the assessment of activity being based on the studies of various investigators who used several insect species. Although some of the compounds show marked species selectivity, which is itself an indication of the importance of physicochemical factors, the results are mainly taken from data obtained on flies [27, 28] and they are therefore considered to provide a valid basis for considering the effects of structural variation. In the table, "high" signifies an activity not less than $\frac{1}{10}$ that of D.D.T., "moderate" $\frac{1}{50}$ — $\frac{1}{10}$, "low" $\frac{1}{50}$ — $\frac{1}{100}$, and "very low" less than $\frac{1}{100}$.

The loss of hydrogen chloride on thermal decomposition or on hydrolysis points to the grouping $CH{\cdot}CCl_3$ as being the most reactive chemical centre of the molecule and therefore as the one most likely to constitute the point of attachment to, or reaction with, the hypothetical vital cell constituent. Table I also contains data obtained by S. J. Cristol [29] for the relative reactivities of certain of the compounds towards alcoholic alkali. The first five compounds contain the grouping $CH{\cdot}CCl_3$ and it will be seen that *p*-chloro-groups are not essential for activity. The differences in activity between the individual members of this group of five are consistent with what is to be expected from the variations of physical properties brought about by the substituent groups. This is further supported by the fact that in the alkoxy- and alkyl-substituted types (XXIV) and (XXV) activity is known to decrease as the homologous series is ascended. At the same time

[25] *Nature*, 1944, **154**, 512.
[26] *J. Pharmacol.*, 1946, **87**, 375.
[27] *J. Soc. Chem. Ind.*, 1946, **65**, 356T.
[28] S. Kirkwood and J. R. Dacey, *Canadian J. Res., B*, 1946, **24**, 69; G. T. Barry and R. Boyer, *ibid., B*, 1948, **26**, 511; H. C. Browning *et al.*, *ibid., D*, 1948, **26**, 282; R. Domenjoz, *Helv. Chim. Acta*, 1946, **29**, 1317.
[29] *J. Amer. Chem. Soc.*, 1945, **67**, 1494.

TABLE I

Contact insecticidal activity of analogues of D.D.T.

		Insecticidal activity.	Relative rate constants [29] for alkaline hydrolysis at 70°.
	$p\text{-}C_6H_4F\cdot CH(CCl_3)\cdot C_6H_4F\text{-}p$	High	303
XXII	$p\text{-}C_6H_4Cl\cdot CH(CCl_3)\cdot C_6H_4Cl\text{-}p$	High (D.D.T.)	2480
	$p\text{-}C_6H_4Br\cdot CH(CCl_3)\cdot C_6H_4Br\text{-}p$	Very low to flies; high to lice and bed-bugs	3470
XXIV	$p\text{-}MeO\cdot C_6H_4\cdot CH(CCl_3)\cdot C_6H_4\cdot OMe\text{-}p$	High	9·18
XXV	$p\text{-}C_6H_4Me\cdot CH(CCl_3)\cdot C_6H_4Me\text{-}p$	Moderate	10·9
XXVI	$C_6H_5\cdot CH(CCl_3)\cdot C_6H_5$	Very low	36·9
XXIII	$p\text{-}C_6H_4Cl\cdot C(=CCl_2)\cdot C_6H_4Cl\text{-}p$	Very low	
XXVII	$p\text{-}C_6H_4Cl\cdot CH(CHCl_2)\cdot C_6H_4Cl\text{-}p$	High	567
XXVIII	$p\text{-}C_6H_4Cl\cdot CH(CH_3)\cdot C_6H_4Cl\text{-}p$	Moderate	
XXIX	$p\text{-}C_6H_4Cl\cdot CCl(CCl_3)\cdot C_6H_4Cl\text{-}p$	Very low	
XXX	$p\text{-}C_6H_4Cl\cdot CH(CF_3)\cdot C_6H_4Cl\text{-}p$	Low	
	$p\text{-}C_6H_4Cl\cdot CH(OH)\cdot CCl_3$	Moderate to low	
	$p\text{-}C_6H_4Cl\cdot CH(OMe)\cdot CCl_3$	Low	
	$p\text{-}C_6H_4Cl\cdot CH(OAc)\cdot CCl_3$	Moderate	
XXXI	$p\text{-}C_6H_4F\cdot CH(OH)\cdot CCl_3$	High	
XXXII	$p\text{-}C_6H_4Cl\cdot CH(CCl_3)\cdot C_6H_4Cl\text{-}o$	Very low (moderate to lice)	37·1

it is to be noted that there are some big differences in chemical reactivity, for example, between (XXII) and (XXIV) which both have high insecticidal activity. The very low toxicity of 1 : 1 : 1-trichloro-1 : 2-diphenylethane (XXVI) is perhaps surprising but need not be excluded from consideration on a physical basis. Removal of one of the aliphatic chlorine atoms (in XXVII) still leaves high activity, as the same capacity for chemical reactivity (manifested in the ability to liberate hydrogen chloride) remains, though at a somewhat reduced level. The fact that 1 : 1-di-*p*-chlorophenylethane (XXVIII) shows moderate activity is difficult to explain, as here the characteristic chemical reactivity has been completely removed. It is very difficult to assess the significance of a moderate degree of toxicity in an individual compound chosen from a large group, because it is always possible that, when the structure departs too far from the general pattern, the molecule may show activity by virtue of some entirely different mechanism. All that can be said about (XXVIII) therefore is that more critical biological experiments are required in order to decide whether it should properly be considered as belonging mechanistically to the D.D.T. class. With the other three compounds in which the characteristic reactivity of the $CH{\cdot}CCl_3$ system has been modified, there is a very low level of activity. These are (XXIII) in which the reactivity of the chlorine atoms will be reduced by the unsaturation, (XXIX) where replacement of the remaining aliphatic hydrogen atom eliminates reactivity typified by the ability to lose hydrogen chloride, and (XXX) where the reactivity will be reduced by the substitution of fluorine for chlorine. In these three compounds it must also be borne in mind that the structural alterations leading to reduced chemical reactivity will also affect physical properties, which may contribute to the reduced toxicity. The substitution of CCl_3 in D.D.T. by CBr_3 should enhance reactivity rather than reduce it,[29] yet the compound is relatively non-toxic. This may be a physical effect. On the other hand, if the compound is too reactive it may be immobilised by reaction with some cell constituent before it can reach the site at which it might initiate a toxic response. Four compounds, having only one aromatic nucleus, are included in the table, and all retain the $CH{\cdot}CCl_3$ system. It may be considered significant therefore that one of these compounds (XXXI) shows high activity. It seems that in this molecule there have appeared physical properties which appropriately balance the chemical reactivity.

It is clear that neither the lipoid-solubility theory, nor the chemical-reactivity theory is sufficient to explain the behaviour of the D.D.T. analogues, and that a combination of the two is necessary. What seems to be essential is the combination within the molecule of an appropriate degree of chemical reactivity, not too low and not too high, with the correct physical properties. In regard to the nature of the physical properties necessary to ensure activity, it can be said with some degree of certainty that fat solubility is essential, if only because of the necessity of penetrating the lipo-protein layers in the insect cuticle. Once this penetration is accomplished, however, there may be other factors which are significant, and one of these may be stereochemical, being concerned, as suggested by Busvine,[27] with association

with some enzyme or other macromolecule. In this connection, it is interesting to note [30] that flies which have through breeding become resistant to D.D.T. are also resistant to the stereochemically similar methoxy-analogue (XXIV) but not to chlorinated hydrocarbons of different molecular pattern such as γ-benzene hexachloride (hexachloro*cyclo*hexane), " Chlordane ", or " Toxaphene ". The low activity of (XXVI) may perhaps, in this sense, be partly associated with the lack of *p*-substituents, as also may be the relative inactivity of the D.D.T. isomer (XXXII), although both these substances, as well as the highly insecticidal methoxy-compound (XXIV), have reduced reactivity compared with D.D.T.

Since the commercial introduction of D.D.T. as an insecticide, several other chlorinated hydrocarbons of comparable potency have been discovered. The first of these was obtained by the addition of chlorine to benzene, and of the mixture of stereoisomers obtained the γ-isomer alone was of outstanding effectiveness.[31] This isomer was believed to have the same configuration as *meso*inositol and it was suggested that the insecticide might owe its activity to interference with some vital reaction involving *meso*inositol. Antagonism was indeed demonstrated by using certain micro-organisms,[32] but inositol did not have any effect on the toxicity of γ-benzene hexachloride to greenhouse thrips.[33] Moreover, *X*-ray investigations have recently shown that γ-benzene hexachloride is not isomorphous with *meso*inositol,[34] and it would appear that the evidence for the significance of *meso*inositol in the insecticidal action of γ-benzene hexachloride is not substantial. The evidence quoted above on the susceptibility of D.D.T.-resistant flies to γ-benzene hexachloride suggests that its mode of action may be different from that of D.D.T. By analogy it is well known in the field of trypanosomiasis that drug resistance acquired as a result of exposure of the organisms to an individual trypanocide is exhibited against trypanocides of the same chemical class, but not against trypanocides of different types. This is generally considered to be a manifestation of the existence of more than one toxic mechanism. If a trypanosome has characteristics which render it resistant to arsenicals, it is not necessarily resistant to the heterocyclic quaternary salt type which acts on different centres. Although there is no evidence of cross-resistance between D.D.T. and benzene hexachloride, it is quite possible that the two compounds share certain, though not all, the characteristics necessary for insecticidal activity. They are alike in having lipoid solubility, which probably facilitates passage through the cuticle, the primary phase of absorption. They have the same type of chemical reactivity, as manifested by their ability to lose hydrogen chloride, and hence they have a similar capacity for combination with cell constituents. Their most

[30] G. W. Barber and J. B. Schmitt, *J. Econ. Entom.*, 1949, **42**, 287 ; J. Keiding and H. van Deurs, *Nature*, 1949, **163**, 964.

[31] R. E. Slade, *Chem. and Ind.*, 1945, 314.

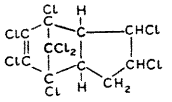
[32] S. Kirkwood and P. H. Phillips, *J. Biol. Chem.*, 1946, **163**, 251 ; H. W. Buston, S. E. Jacobs, and A. Goldstein, *Nature*, 1946, **158**, 22.

[33] R. L. Metcalf, *J. Econ. Entom.*, 1947, **40**, 522.

[34] G. W. van Vloten *et al.*, *Nature*, 1948, **162**, 771.

marked difference is in molecular shape, which perhaps determines affinity for separate macromolecules.

Much of what has been said about γ-benzene hexachloride can be applied to two other products which have high contact insecticidal activity. "Chlordane",[35] obtained by the chlorination of the dimer of *cyclo*pentadiene, may be represented by (XXXIII), the stereochemistry of which has not yet been investigated. "Toxaphene",[36] a chlorinated terpene derivative, shares with "Chlordane", γ-benzene hexachloride, and D.D.T. the property of lipoid solubility and the ability to liberate hydrogen chloride on hydrolysis.

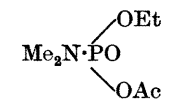


(XXXIII)

Organic Derivatives of Phosphoric Acid.—Although some attention had been paid by Swiss workers [3] to organic phosphorus compounds in connection with the mothproofing of textiles, the most important observations on their general insecticidal activity were made in Germany during the war. Detailed accounts of this work, including preparative methods, are to be found in the reports of allied missions to Germany,[37] but it is convenient to summarise here the salient points and to include references to work carried out since the war.

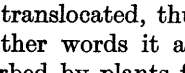
The starting point was apparently the strong fumigant activity of methanesulphonyl fluoride, and systematic alteration of this molecule, first by replacing the sulphur atom by other groupings, led to the discovery that fluorobisdimethylaminophosphine oxide (XXXIV) and ethyl *O*-dimethylamino *O*-acetoxyphosphonite (XXXV) had marked toxicity to aphids. The latter compound, moreover, had the property of being absorbed by plants

(XXXIV.)

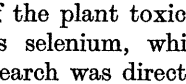


(XXXV.)

and translocated, thus rendering other parts of the plant toxic to insects. In other words it acted systemically, as does selenium, which can be absorbed by plants from the soil. Further research was directed towards obtaining the maximum insecticidal effect and reducing to a minimum the mammalian toxicity, while at the same time improving the stability to water, particularly in the presence of lime. The use of pyrophosphoric acid derivatives led to an increase in activity, and bisdimethylaminophosphonous anhydride (XXXVI) proved to be very useful as a plant systemic ("chemotherapeutic") insecticide (see ref. 38 for details of tests recently conducted



(XXXVI.)



(XXXVII.)

[35] C. W. Kearns, L. Ingle, and R. L. Metcalf, *J. Econ. Entom.*, 1946, **38**, 661.
[36] L. A. Stearns *et al.*, *ibid.*, 1947, **40**, 79.
[37] B.I.O.S. Final Reports, 714, 1095, 1808.
[38] W. E. Ripper, R. M. Greenslade, and L. A. Lickerish, *Nature*, 1949, **163**, 787.

in England). Another very active contact insecticide was the so-called hexaethyl tetraphosphate, a mixture in which the active ingredient is probably tetraethyl pyrophosphate (XXXVII) (cf. J. W. Hansen [39]). This compound also has systemic properties,[40] as also has the compound (XL) referred to later.[41] As a device to improve the stability to lime, the group PS was substituted for PO, both in the pyrophosphoric series mentioned above, and in the phenol derivatives described below.

The view has been expressed by G. Schrader [37] that the insecticidal activity is associated with an anhydride structure based on phosphoric acid, the second molecule being either phosphoric acid or another acid such as hydrogen fluoride, methanesulphonic, or acetic acid. Marked activity is found where the second molecule is an enolic substance such as ethyl acetoacetate [giving diethyl 1-carbethoxyprop-1-en-2-yl phosphate (XXXVIII)], and particularly when *p*-nitrophenol is employed. *p*-Nitrophenyl diethyl phosphate (XXXIX) was known as " E.600 " and the corresponding thiophosphate (XL) as " E.605 ". The latter has been developed commercially

$(EtO)_2PO{\cdot}O{\cdot}CMe{:}CH{\cdot}CO_2Et$ (XXXVIII.)

$(EtO)_2PO{\cdot}O{-}C_6H_4{-}NO_2$ (XXXIX.)

$(EtO)_2PS{\cdot}O{-}C_6H_4{-}NO_2$ (XL.)

both in England and America (where the name " Parathion " has become attached to it). For a synthesis, see J. H. Fletcher *et al.*[42] Table II, taken

TABLE II

Toxicity to aphids of some phosphoric acid derivatives

	Concn., %.	Kill, %.		Concn., %.	Kill, %.
$(EtO)_2PO{\cdot}O{\cdot}C_6H_5$ . . .	0·2	50–80	$EtO{\cdot}PMeO{\cdot}O{\cdot}C_6H_5$ . . .	0·2	80
$(EtO)_2PO{\cdot}O{\cdot}C_6H_4{\cdot}NO_2$-*p* .	0·005	100		0·05	50
$(EtO)_2PO{\cdot}O{\cdot}C_6H_4{\cdot}NO_2$-*o* .	0·005	100	$EtO{\cdot}PMeO{\cdot}O{\cdot}C_6H_5Me{\cdot}NO_2$-*p*(-*o*)	0·005	100
$(EtO)_2PO{\cdot}O{\cdot}C_6H_4{\cdot}NO_2$-*m* .	0·2	70			
$(EtO)_2PO{\cdot}O{\cdot}C_6H_4Cl$-*o* . .	0·2	100	$EtO{\cdot}PMeO{\cdot}O{\cdot}C_6H_4Cl$-*o* .	0·05	100
	0·05	50		0·005	80
$(EtO)_2PO{\cdot}O{\cdot}C_6H_4Cl$-*p* . .	0·2	100	$EtO{\cdot}PMeO{\cdot}O{\cdot}C_6H_4{\cdot}CO_2Et$-*p*	0·05	100
	0·05	90	$PrO{\cdot}PMeO{\cdot}O{\cdot}C_6H_4Cl$-*p*. .	0·2	100
	0·02	50		0·05	95
$(EtO)_2PO{\cdot}O{\cdot}C_6H_4{\cdot}CO_2Et$-*p*	0·2	95	Me_2N / EtO > $PO{\cdot}O{\cdot}C_6H_4{\cdot}NO_2$-*p* .	0·005	0
	0·05	90			
$(EtO)_2PO{\cdot}O{\cdot}C_6H_4{\cdot}CO_2Et$-*o*	0·05	100	$(Me_2N)_2PO{\cdot}O{\cdot}C_6H_4{\cdot}NO_2$-*p* .	0·05	100
				0·02	50
$(EtO)_2PS{\cdot}O{\cdot}C_6H_5$ . . .	0·2	50			
$(EtO)_2PS{\cdot}O{\cdot}C_6H_4{\cdot}NO_2$-*p* .	0·001	100			

[39] *J. Econ. Entom.*, 1947, **40**, 600.
[40] P. W. Zimmerman and A. Hartzell. *Contr. Boyce Thompson Inst.*, 1947, **15**, 11.
[41] D. D. Questel and R. V. Connin, *J. Econ. Entom.*, 1947, **40**, 914.
[42] *J. Amer. Chem. Soc.*, 1948, **70**, 3943.

from data provided in ref. 37, illustrates some of the effects of structural variation on insecticidal activity. A polar influence of the substituents in the benzene ring is discernible, for example, in the contrast between the effect of *m*- versus *o*- and *p*-nitro-groups in the first four compounds. Substitution of a dimethylamino- for an ethoxy-group evidently reduces the activity considerably, but replacement of one ethoxy-group by methyl, or of PO by PS, does not materially affect the activity. For a proper assessment of the significance of structural variation, however, it would be necessary to examine more compounds and to secure more accurate biological data.

The phosphoric ester insecticides appear to act on the nervous system, and they share with the very poisonous di*iso*propyl fluorophosphonate the capacity for irreversible inhibition of the important enzyme, cholinesterase, which is intimately associated with the mechanism of nerve-impulse transmission.[43, 44]

Miscellaneous Chemical Types.—Before the discovery of the chlorinated hydrocarbon and phosphoric ester types of contact insecticides, a very wide search was made amongst organic compounds, both naturally occurring and synthetic, for substances which might replace existing insecticides. The latter had certain inherent disadvantages. The arsenic compounds and nicotine alkaloids were poisonous to mammals, while the derris products and pyrethrins required a biological test for standardisation of quality. Many useful compounds were discovered, some of which have already been described in the section dealing with organic sulphur compounds. Certain others will be mentioned here, but first a few words must be said on the phenomenon generally known as synergy.

It frequently happens that when two substances are employed in admixture in a contact insecticidal spray, the toxic effect is greater than the sum of the contribution to be expected from the individuals. This has shown up particularly where one of the components is pyrethrin, and the literature contains many examples of so-called synergists for pyrethrins. There are two possible explanations. The first is physical, postulating an increase in permeability of the insect cuticle caused by the presence of the synergist which thus renders a greater proportion of the toxic material accessible to the body of the insect. This has been illustrated experimentally by H. Hurst,[45] who showed that blowfly larvæ were unaffected by either alcohol or kerosene but were rapidly killed by immersion in a mixture of the two solvents. The kerosene assisted penetration by the alcohol. This was confirmed and extended by V. B. Wigglesworth [46] to other pairs of solvents. The latter author found that penetration of pyrethrins was assisted by oleic and other fatty acids. Thus, by this physical mechanism, the effective activity of a contact insecticide can be improved by admixture with a second substance which is itself insecticidally inert. The second possible explana-

[43] K. P. Dubois and G. H. Mangun, *Proc. Soc. Exp. Biol. Med.*, 1947, **64**, 137.
[44] K. B. Augustinson and D. Nachmansohn, *J. Biol. Chem.*, 1949, **179**, 543.
[45] *Trans. Faraday Soc.*, 1943, **39**, 390.
[46] *Nature*, 1941, **147**, 116; *Bull. Entom. Res.*, 1942, **33**, 205.

tion is that, if two insecticides having different modes of action are used in admixture, insects which are only partly affected by the one may succumb to the effects of relatively small doses of the other. In this way a synergic effect may be apparent. The characteristic response of an insect to pyrethrins is rapid paralysis ("knock-down"), from which the insect may recover if the dose is not too great. Most of the synergists developed for use with pyrethrins do not show this characteristic effect though they may have toxicity themselves. It is possible that, if an insecticide mixture contains just sufficient pyrethrins to paralyse the flies, the affected flies become more susceptible to the toxic action of the second component.

One of the earliest of the commercial synergists for pyrethrins (for use in fly-sprays) was *N-iso*butylundecenamide (XLI).[47] It was later shown

$$CH_2{:}CH{\cdot}[CH_2]_8{\cdot}CO{\cdot}NHBu^i$$
(XLI.)

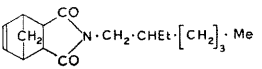
$$CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CO{\cdot}NHBu^i$$
(XLII.)

$$CH_3{\cdot}[CH_2]_2{\cdot}CH{:}CH{\cdot}[CH_2]_4{\cdot}CH{:}CH{\cdot}CO{\cdot}NHBu^i$$
(XLIII.)

that certain related higher aliphatic amides having insecticidal properties similar to those of the pyrethrins occur in plants. Thus the substance affinin (XLII) is obtained from the roots of a Mexican plant originally characterised as *Erigeron affinis* D.C., but later defined as *Heliopsis longipes* (A. Gray) Blake.[48] Related to this is herculin (XLIII), obtained from the bark of the Southern prickly ash *Zanthoxylum clava-herculis* L., and also certain other naturally occurring compounds referred to by M. Jacobson.[49] Affinin and herculin differ from *N-iso*butylundecenamide in that they have marked paralysant and toxic properties by themselves, whereas the last substance is useful mainly as a synergist for pyrethrum.[50] It is possible that the unique properties of the two natural products are associated with a special feature of their chemical reactivity, such as might be provided by the unsaturation occurring $\alpha\beta$ to the carbonyl group, and the point calls for further investigation.

Another amide (XLIV) having synergic properties with pyrethrum against houseflies has recently been developed commercially in America.[51]

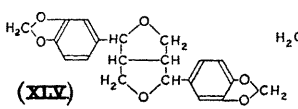
Sesamin (XLV), the active principle of oil of sesame, has little insecticidal action by itself but is a powerful synergist for pyrethrum. This activity is apparently governed more by the nature of the substituents in the benzene ring than by molecular shape, for various stereoisomers of sesamin are equally effective, while replacement of the methylenedioxy-group by two



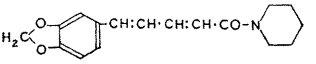
(XLIV.)

[47] A. Weed, *Soap*, 1935, **14**, No. 6, 133.
[48] F. Acree, M. Jacobson, and H. L. Haller, *J. Org. Chem.*, 1945, **10**, 236, 449; 1947, **12**, 731.
[49] *J. Amer. Chem. Soc.*, 1948, **70**, 4234.
[50] A. Hartzell and H. I. Scudder, *J. Econ. Entom.*, 1942, **35**, 428.
[51] A. Hartzell, *Contr. Boyce Thompson Inst.*, 1949, **15**, 337.

methoxy-groups destroys the activity.[52] Piperine (XLVI) differs from sesamin in that it is markedly toxic to houseflies by itself, besides showing synergy with pyrethrum.[53] The results with these two compounds have stimulated a wide investigation of compounds containing the methylene-

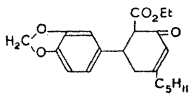


(XLV.)

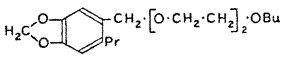


(XLVI.)

dioxy-group, many of which proved to be insecticidal either alone or by synergy with pyrethrum. Outstanding compounds appear to be (XLVII) and (XLVIII) which are powerful synergists.[53, 54]



(XLVII.)



(XLVIII.)

(LIII.)

Nitriles of α-amino-acids have been studied by A. D. Ainley and W. A. Sexton,[55] who found in this class several substances having high contact insecticidal activity. There was marked specificity of action against different insects, and the insecticidal properties were very largely governed

PhMeN·CHR·CN (XLIX.)

$[—CH_2·NMe·CHR·CN]_2$ (L.)

by the physical properties of the molecule. Among the most toxic to aphids were (XLIX) and (L; R = *n*-hexyl), the latter being at least as active as *n*-dodecyl thiocyanate. Although these compounds can give rise to hydrogen cyanide under certain conditions of hydrolysis, this is not believed to be the mode of action. Rather, it has been suggested that they may react with a cell constituent bearing some such group as amino by addition at the cyano-group or by displacement of the substituted α-amino-group.

The insecticidal properties of certain fluorine compounds were discovered in Germany during the war.[37] Methanesulphonyl fluoride $MeSO_2F$ was found to have fumigant activity equivalent to that of ethylene oxide, but raising the molecular weight in the aliphatic series, or the use of aryl groups in place of methyl, lowered the toxicity. Low activity was found also in aryl esters of fluorosulphonic acid $F·SO_2·OAr$. The most interesting substances emerged from a systematic evaluation of derivatives of 2-fluoroethyl alcohol. Certain esters and urethanes derived from this alcohol were very

[52] H. L. Haller, F. B. LaForge, and W. N. Sullivan, *J. Org. Chem.*, 1942, **7**, 185.
[53] E. K. Harvill, A. Hartzell, and J. M. Arthur, *Contr. Boyce Thompson Inst.*, 1943, **13**, 87.
[54] M. E. Synerholm and A. Hartzell, *ibid.*, 1945, **13**, 433; M. E. Synerholm, A. Hartzell and J. M. Arthur, *ibid.*, 1945, **14**, 79; H. Wachs, *Science*, 1947, **105**, 531; H. O. Schroeder, H. A. Jones and A. W. Lindquist, *J. Econ. Entom.*, 1948, **41**, 890.
[55] *Biochem. J.*, 1948, **43**, 468.

toxic to aphids on spraying, amongst the most active being the acetals (LI) and (LII). Not only were they very toxic to aphids, but (LI) showed to a remarkable degree the property of being absorbed by the plant and translocated, thereby rendering all parts of the plant poisonous to insect pests.

$CH_2(O{\cdot}C_2H_4F)_2$ (LI.)

$CH_2(O{\cdot}C_2H_4{\cdot}O{\cdot}C_2H_4F)_2$ (LII.)

There is nothing known concerning the mode of action of these substances as insecticides. B. C. Saunders [56] has discussed the relations between structure and mammalian toxicity in related fluorine derivatives, and two points are worthy of note. First, that in the most toxic compounds the fluorine atom is firmly bound and, secondly, that toxicity seems to be associated with the capacity for oxidation to fluoroacetic acid.

The insecticidal and ovicidal properties of dinitro-*o*-cresol (LIII ; R = Me) have been known for over twenty years and this substance has had extensive practical use. More recently, higher homologues have been investigated, and the compound in which R = *cyclo*hexyl has proved to be not only a more powerful insecticide than the cresol derivative but also apparently less toxic to animals and less phytocidal.[57, 58] J. F. Kagy [58] examined the toxicity to silkworm larvæ (stomach-poison test) of the series in which R varied from C_1 to C_8, including both *n*-alkyl groups and *cyclo*pentyl and *cyclo*hexyl groups : in the *n*-series, toxicity increased to a maximum at C_6 or C_7, the C_8 compound falling back to the level of the C_4 compound. Although the *cyclo*hexyl was less toxic than the *n*-hexyl compound, it was still much more toxic than the methyl compound. The influence of physical properties is clear. No study has been made of the chemical mode of action of these dinitrophenols, but it is possible that they have a mechanism related to that whereby 2 : 4-dinitrophenol exerts some of its biological effects, though the latter is a less potent insecticide than dinitro-*o*-cresol. In this connection it is of interest to note recent evidence [59] that dinitrophenol prevents phosphate uptake in an enzymic oxidation of glutamine and apparently uncouples phosphorylation from oxidation.

[56] *J.*, 1949, 1279.
[57] A. M. Boyce *et al.*, *J. Econ. Entom.*, 1939, **32**, 432.
[58] *Ibid.*, 1941, **34**, 660.
[59] W. F. Loomis and F. Lipmann, *J. Biol. Chem.*, 1948, **173**, 807.