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THE CHEMISTRY OF PESTICIDES

Walter R. Benson
Food and Drug Administration

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Pesticide Branch, Division of Food Chemistry, Bureau of Science
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INTRODUCTION

This review is limited to the structures and a few reactions of the pesticides—mainly insecticides—that affect mammalian systems and that are the subject of papers by other authors in this monograph. There is no attempt to give a complete review of the chemistry of pesticides. It is intended only to show the breadth and depth of pesticide chemistry through the use of examples. With proper use of the references, and of the papers by Crosby, Freed and Montgomery, and Owens in this monograph, the reader will be able to find information for other chemicals.

NOMENCLATURE

Pesticides or economic poisons are defined in the Federal Insecticide, Fungicide, and Rodenticide Act as ". . . any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any insects, rodents, nematodes, fungi or weeds or any other forms of life declared to be pests; any substance or mixture of substances intended for use as a plant regulator, defoliant or desiccant." Thus, the classification of a pesticide could be made by first naming the living system that it controls and then listing functional groups wherever possible. This is generally the form that we have used, as shown in TABLE 1.

However, this is not the only system used. For example, the U. S. Tariff Commission first classifies synthetic organic chemicals according to whether they are cyclic. Pesticides are classified further by the living system controlled, and finally by categories containing similar organic functional groups. Some authorities classify pesticides alphabetically and then give the crops upon which they can be used. Another arrangement is to list, first, the crop or livestock to be protected; second, the pest that usually attacks it; and third, several pesticides for the control of each pest. In one classification, pesticides are listed in the chronological order in which their tolerances were established. They have also been grouped according to their pharmacologic action (e.g., cholinesterase-inhibiting pesticides) or by the way they can be analyzed (e.g., gas chromatography). These classifications are summarized in TABLE 2. Recognition of the classification systems used by various groups is the first step toward understanding the complex chemical reactions involved.

In any list of pesticides, a name must be used for each agent. However, many names are used today for the individual chemical or the mixture of chemicals. The chemical name usually describes one compound and, if general enough, several isomers, as well. However, this name is often cumbersome and awkward for discussions and reports. Therefore, abbreviations and common names have been adopted. Agreement to use one name is not always unanimous.

There is another nomenclature problem, since very few chemicals are prepared and used in their pure state. When chemicals are diluted with materials to increase their effectiveness, they are said to be formulated, and their names change once more. The new name depends on such factors as the concentration, the diluent,

TABLE 1

CLASSIFICATION OF PESTICIDE CHEMICALS[4,41]

I. Fungicides
  A. Inorganic compounds containing
    1. Copper
    2. Mercury
    3. Chromium
    4. Zinc
    5. Other metallic compounds
    6. Sulfur
  B. Organic compounds
    1. Dithiocarbamates
    2. Phthalimides
    3. Karathane
    4. Dodine
    5. Quinones
    6. Pentachlorophenol
    7. Others

II. Herbicides
  A. Inorganic compounds — $NaClO_3$
  B. Organic compounds
    1. Petroleum fractions
    2. Arsenicals
    3. Phenoxy type
      a. 2,4-D
      b. 2,4,5-T
      c. other phenoxy and related
    4. Phenylureas
    5. Carbamate (thiol, N-phenyl)
    6. Dinitrophenols
    7. Triazines
    8. Benzoic acids
    9. High bromine content
    10. Phosphorus (aliphatic phosphites, phosphates)
    11. Amides
    12. Quaternary salts
    13. Other organics

III. Insecticides (see TABLE 3 for specifics)
  A. Inorganic
    1. Arsenicals — Paris green
    2. Others — $NaAlF_4$ (cryolite)
  B. Botanicals and derivatives
    1. Nicotine
    2. Pyrethrum
  C. Biologicals
    B. thuringiensis
  D. Petroleum
  E. Synthetic organic compounds
    1. Chlorinated
      a. aldrin-toxaphene group
      b. lindane and isomers (BHC)
      c. DDT group
    2. Phosphorus (with and without sulfur)
      a. aliphatic phosphates and phosphonates
      b. vinyl phosphates
      c. aromatic phosphates and phosphonates
      d. pyrophosphates
    3. Carbamate
      a. N-methylcarbamates — Sevin®, Bux®
      b. N,N-dimethylcarbamate—Dimetilan®
    4. Others

IV. Miticides (see TABLE 3 for specifics)
  A. Sulfites, sulfones, sulfides, sulfonates
  B. Dinitrophenols
  C. Kelthane®
  D. Others

V. Fumigants
  A. Space and product — HCN, CH_3Br
  B. Soil type — $CH_3N=C=S$, $BrCH_2CH_2Br$

VI. Defoliants and desiccants
  Phosphites, H_2SO_4

VII. Rodenticides
  A. Anticoagulants
    Coumarins
  B. Other
    1. Fluoroacetamide
    2. 1-Naphthyl thiourea

VIII. Other
  A. Plant growth regulators — 1-naphthylacetic acid
  B. Repellents (insects, birds) — allyl isothiocyanate

TABLE 2

CLASSIFICATION OF PESTICIDES WITH EXAMPLES

Classification System	Example
1. Plant or animal controlled	Broad leaf plant, Norway rat
2. Functional chemical group	$C-Cl$, $ArO-\underset{\overset{\|}{O}}{C}-\underset{\overset{\|}{H}}{N}-CH_3$
3. Alphabetical listing by name	Aldrin to zineb
4. Crop, livestock, or surface usually protected	Potatoes, cattle, or freight cars
5. Pharmacological action	Inhibition of cholinesterase

6. Others
    a. Systemic or nonsystemic
        or
    b. Method of analysis
	
	Insecticide
	Fumigant
	Gas chromatography

7. Combinations of 1 through 6
    Crop protected (system 4)
    Animal controlled (system 1)
    Systemic (system 6a)
	
	Potatoes
	Flea beetles (*Epitrix species*)
	Insecticides found effective:
	carbaryl, DDT, dieldrin, endosulfan,
	and endrin

and combinations with other pesticides. These products have trade names. The large number of names used for one chemical is a barrier to communication, making international committees on nomenclature to establish standards for adopting common names a necessity. It is essential that all interested groups participate in the naming and in the use of the names agreed upon. In particular, the cooperation of journal editors and authors is needed.

The rules for naming and indexing chemical compounds[1,2] help the reader to find references to the pure chemical in *Chemical Abstracts* and elsewhere. The rules are revised periodically to meet the demands of a changing scientific community. Nevertheless, TDE, DDD, Rhothane®, p,p'-DDD and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane, for example, all stand for essentially the same chemical, although one may be more specific than another. They are all used in the pesticide literature.[3] TDE is the approved name in the United States, although DDD and p,p'-DDD are often used. Rhothane® is the registered name for a commercial product, whereas the last name in the series above is the IUPAC* or *Chemical Abstracts* name; it refers to the main isomer in the mixture.

The names listed in the U. S. Department of Agriculture "Summary of Registered Agricultural Pesticide Chemical Uses" and those used in the pesticide regulations of the Food and Drug Administration are usually the best names selected from a number of possibilities. Commercial names are not usually published in government regulations. Other lists[3] may be consulted. If much greater accuracy in naming is desired, it may be necessary to turn to laboratory research because a great deal more work, for example, to establish spatial relationships and purity, is needed before naming can be unambiguous.

INORGANIC CHEMISTRY

Inorganic compounds constitute about 10 per cent of the dollar value of the total United States market.[4] One of the common inorganic chemicals is copper

* International Union of Pure and Applied Chemistry.

sulfate; it is used both as a pesticide and as a reagent for the analysis of other pesticides. In these uses some of the chemistry involved may be similar; for example, copper (II) probably forms bonds with sulfhydryl groups and perhaps with other sulfur groups.

This is a quantitative reaction,[5] as shown in REACTION 1.

$$X = Fe^{+3}, Zn^{+2}, H^+, Na^+, \text{ other} \qquad \lambda \text{ max} = 435\, m\mu$$
$$CCl_2H_2$$

(1)
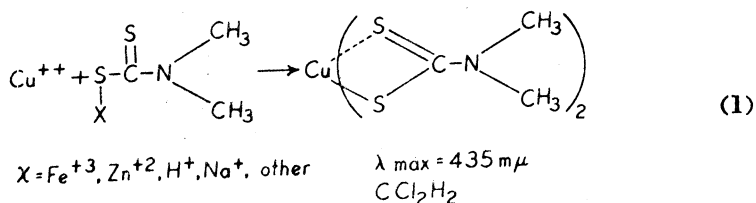
$CuSo_4 \cdot 5H_2O$ is thus incompatible with some of the dithiocarbamates, some dithiophosphates, and some other systems involving sulfur groupings.

As seen in TABLE 1, other heavy metals are used as salts or in conjunction with organic groups, as in phenylmercuric acetate. Daum[6] has recently reviewed the application of organometallics to agriculture.

Some nonheavy metal pesticides ($NaClO_3$) are used widely in the control of plants. Sulfur in its many oxidation states will be covered under the head, "Organic Chemistry," although sulfur has long been used as free sulfur and with lime.

ORGANIC CHEMISTRY

The chemistry of organic pesticide compounds is scattered throughout the literature,[3] depending on the discipline studied or the emphasis given. These organic pesticides are arranged in TABLE 1 by their action on living systems and later by their chemical functional groups. Even with these groupings, it is not easy to draw hard and fast rules about the chemical behavior of a particular substance from its position in TABLE 1.

One of the important groups of chlorinated hydrocarbon insecticides is the aldrin-Toxaphene group (TABLE 3a). The chemistry of part of this group—the diene group—was reviewed by Riemschneider.[7] He lists the chemical evidence for the structure of aldrin, dieldrin, chlordane, heptachlor, Telodrin[10], and several other related compounds; side products from the different manufacturing processes are also discussed. These compounds resulting from side reactions may be found as residues. This, of course, applies to all the approximately 800 chemicals registered for use in the United States and to other compounds not registered, but used abroad. Thus, it is important to know how a pesticide is manufactured and what its side products are. Some of the reactions of aldrin and dieldrin are given in FIGURE 1. Similar structures and reactions are given in FIGURE 2 for isodrin and endrin.

Photodieldrin is several times more toxic than dieldrin (see Crosby's paper in this monograph.) In considering pesticide toxicity, much more work is needed in the area of isolation and evaluation of photolytic products, since almost all applied pesticides are exposed to the sun's rays before harvest. The conversions in FIGURE 1 and FIGURE 2 illustrate the reactive portions of the molecules. The chlorine atoms in aldrin, dieldrin, isodrin, and endrin are relatively unreactive toward base because (1) by elimination reactions, they would form double bonds at bridge-head carbon atoms, in violation of Bredt's rule; (2) for low-energy elimination reactions, the hydrogen and chlorine atoms are not in the proper

transplanar positions; and (3) for displacement reactions it is difficult for base to attack the backside of the four chlorine atoms attached to aliphatic positions because they are protected by the bicyclic bridge system. The two chlorine atoms attached to olefins are known to be generally unreactive toward base. This general reaction with base has exceptions, however. Adamovic[8] reviews and extends the reaction of aromatic amines and light with chlorinated organic pesticides. Here the bases do react to give colored materials, but the chemistry is as yet unknown.

Toxaphene and Strobane® each contain many compounds, as shown by thin layer chromatography (TLC) and gas-liquid chromatography (GLC). When one examines the results of the chlorination of camphene, using 1:1 molar ratios of chlorine and camphene,[9] it is clear why so many compounds exist. The reaction involves rearrangement, elimination, and addition. In the case of Toxaphene, KOH reacts to dehydrochlorinate some or all of the compounds, in contrast to no reaction with the aldrin group.

With the chlordane family, the principles of elimination and displacement reactions still apply to the six Cl atoms located in positions related to aldrin. However, an allylic chlorine atom is available in pure heptachlor that can give the displacement reaction, and the elimination reaction can occur with some facility in chlordane and its isomers. Allylic halogens are generally displaced with greater ease than chlorine in saturated compounds (FIGURE 3). The reactions of aldrin and dieldrin apply equally well to the chlordane family of compounds, with the exception of the extra chlorine atoms.

At this point it should be made clear that pesticides are usually impure; for example, technical chlordane contains 25–40 percent of compounds that are not the substance shown in FIGURE 3 as chlordane. These other compounds arise from the manufacturing process. Raw agricultural products may contain pesticides from a previous spraying program. Thus, care must be exercised in attributing chemical or biological reactions to any one substance, unless the sample or chemical has been thoroughly identified.

The DDT group (TABLE 3a) generally can lose HCl to form an olefin (DDE) with base. It can also lose a chlorine atom through chemical reduction to form TDE (FIGURE 4). Castro reported[10] that, in a model system for biological dehalogenation, iron (II) deuteroporphyrin was found to convert DDT to TDE. In other studies,[11] chromium (II) sulfate also reduced trihalomethyl groups in varying degrees, depending on the concentration of chromium (II). The CCl_3 group is found in many pesticides, in addition to DDT, such as captan and trichloroacetic acid. Therefore, this reduction reaction might be expected in these compounds, as well.

When dicofol (Kelthane®) is heated in a gas chromatographic column, it often fragments into $CHCl_3$ and a dichlorobenzophenone. Since often only one peak is seen in addition to the solvent peak, this peak might be easily mistaken for dicofol; thus, it might be assumed to have chromatographed intact. This mistake is more likely to be made, since dicofol can be chromatographed intact under proper column conditions. Caution is therefore necessary in order not to attribute a peak in a gas chromatogram to a particular intact compound unless further data are available (FIGURE 5).

Dilan® has an acidic hydrogen. This chemical property is used in the analysis[12] for at least two compounds found in Dilan®. The aci-form is dominant on the basic side, and this form can react with ferric chloride to give a unique color for Dilan®. The question should always be raised: How many compounds might one encounter here that would react in a similar manner (FIGURE 5)? This must be

TABLE 3a

INSECTICIDES: HALOGENATED HYDROCARBONS (PRIMARILY CHLOROHALOGENS)

Alphabetical Listing	Grouped by Similarity of Structure
aldrin	1) Aldrin-Toxaphene group
benzene hexachloride (BHC)	aldrin
chlordane	chlordane
Chlorobenzilate	dieldrin
chloroform	endosulfan (Thiodan)
chloropicrin	endrin
dichloropropene	heptachlor
DDD (see TDE)	~~dichloropropene~~
DDT	Kepone
dicofol	mirex
dieldrin	Strobane®
Dilan®	Toxaphene
endosulfan (Thiodan)	
endrin	2) BHC group
ethylene dibromide	benzene hexachloride
ethylene dichloride	(also a fungicide)
heptachlor	lindane
Kelthane® (see dicofol)	
Kepone	3) DDT group
lindane (part of BHC)	Chlorobenzilate
methoxychlor	DDT
methyl bromide	dicofol (Kelthane®)
mirex	Dilan®
methyl chloride	methoxychlor
orthodichlorobenzene	orthodichlorobenzene
paradichlorobenzene	paradichlorobenzene
Perthane®	Perthane
Propylene dichloride	TDE (DDD) (saturated)
Rhothane® (see TDE)	
Strobane®	4) Aliphatic halides (low carbon chain)
TDE (DDD) (Rhothane®)	chloroform
Telone	chloropicrin
Tetrachloroethylene	Dichloropropene
Thiodan® (see endosulfan)	ethylene dibromide
Toxaphene	ethylene dichloride
Trichloroethylene (trichloroethene)	methyl bromide
	methyl chloride
	Propylene dichloride
	Telone
	Tetrachloroethylene
	Trichloroethylene

kept in mind for all of the pesticides and the naturally occurring compounds that remain after a preanalytical clean up procedure and that may be present in relatively high concentrations along with the pesticide.

Methoxychlor and Perthane® can lose HCl with base, as does DDT. However this ability to lose HCl is apparently not important in the toxicity to insects. It appears that the shape or size of the DDT group of compounds is an important factor, since model compounds containing no chlorine have biological activity.[13]

Cristol et al.[14] and Hine et al.[15] have studied the loss of HCl from benzene hexachloride (BHC) isomers in base. It appears that the β-isomer is about 10,000 times more stable in nature and toward base than the other isomers tested. With an electron capture detector in GLC, the β-isomer is also about half as sensitive in response as an equivalent amount of the other BHC isomers. Although no

TABLE 3b

PHOSPHATES AND PHOSPHONATES

Abate[a]
azinphosmethyl (Guthion[a])
Baytex[a] — (see Fenthion)
Bidrin[a]
Birlane[a]
carbophenothion (Trithion[a])
Ciodrin[a]
Co-Ral (see coumaphos)
coumaphos (Co-Ral)
DDVP (see dichlorvos)
demeton
diazinon
Dibrom (see naled)
dichlorvos (DDVP, Vapona)
dimethoate
dioxathion (Delnav[a])
Dipterex (see trichlorofon)
disulfoton (Di-Syston[a])
Di-Syston (see disulfoton)
Dylox (see trichlorfon)
EPN
ethion
fenthion (Baytex[a])
Guthion[a] (see azinphosmethyl)
malathion
methyl parathion
Methyl Trithion[a]
mevinphos (Phosdrin[a])
naled (Dibrom[a])
Nemacide[a] (V-C 13)
parathion
phorate (Thimet[a])
Phosdrin[a] (see mevinphos)
phosphamidon
ronnel
Ruelene[a]
TEPP
trichlorfon (Dylox, Dipterex)
Trithion[a] (see Carbophenothion)

1) Aliphatic phosphates (trialkyl)
  demeton
  dimethoate
  dioxathion
  Di-Syston
  ethion
  malathion
  phorate (Thimet)
  TEPP (Pyro Phosphate)

2) Vinyl phosphate or similar
  Bidrin[a]
  Birlane[a]
  Ciodrin[a]
  dichlorvos (DDVP)
  mevinphos
  naled (Dibrom)
  phosphamidon
  trichlorfon (phosphonate)

3) Aromatic phosphates
  Abate
  azinphosmethyl (Guthion)
  carbophenothion (Trithion)
  diazinon
  EPN (phosphonate)
  fenthion (Baytex)
  methyl parathion
  Methyl Trithion
  Nemacide[a] (V-C 13)
  parathion
  ronnel
  Ruelene[a]

connection has been shown between these two facts, the dehydrochlorination work has produced a fundamental truth: initial *trans* conformation of the H and Cl in the dehydrohalogenation reaction apparently does not occur readily in the β-isomer, and *trans* elimination is favored for this and other systems. Other configurations, such as *cis* that might lead to elimination require greater energies of activation. This *trans* dehydrochlorination is therefore fundamental to all chlorinated hydrocarbon systems (REACTION 2).

(2)
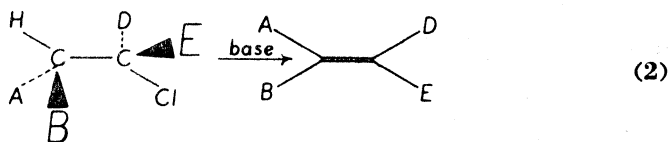
The main product of dehydrohalogenation of BHC is 1,2,4-trichlorobenzene.

TABLE 3c

INSECTICIDES: CARBAMATES AND CARBONATES

Alphabetically Listed	Similar Functional Groups
Banol	1) -N-methylcarbamates
carbaryl (Sevin®)	Banol
Bayer 37344	Bayer 37344
Bayer 39007	Bayer 39007
Bayer 44646	Bayer 44646
Dessin®	carbaryl
Isolan®	NIA 10242
Dimetan	Tranid
Dimetilan®	Temik
MCA – 600	MC-A-600
NIA 10242	RE-5353
Pyramat®	U. C. 10854 (H-8757)
Pyrolan®	Zectran
RE-5353 (Bux®)	
Sevin® (see carbaryl)	2) N,N-dimethylcarbamate
Temik®	Dimetan
Tranid®	Dimetilan
U. C. 10854 (H-8757)	Isolan
Zectran®	Pyramat
	Pyrolan
	3) Carbonate
	Dessin

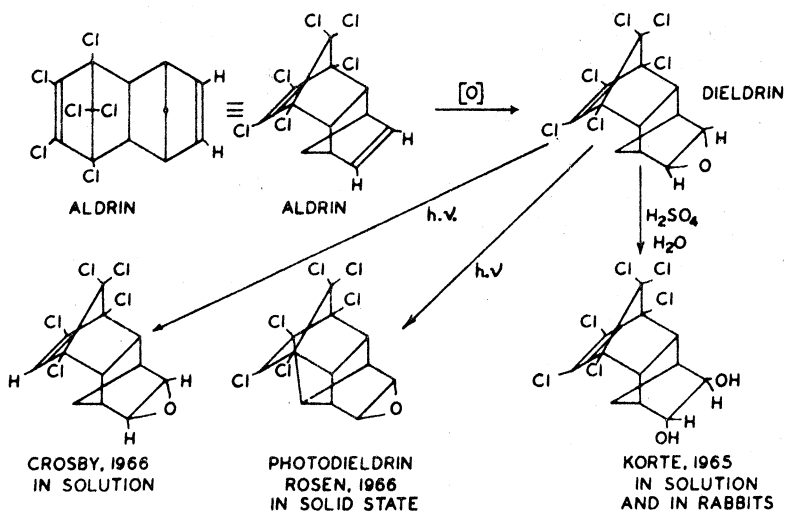| CROSBY, 1966 | PHOTODIELDRIN | KORTE, 1965 |
| IN SOLUTION | ROSEN, 1966 | IN SOLUTION |
| | IN SOLID STATE | AND IN RABBITS |

FIGURE 1. Aldrin-dieldrin reactions.

TABLE 3d

INSECTICIDES: OTHER CHEMICALS

Alphabetically Listed	By Similar Structure of Compounds
acrylonitrile	1) Sulfides, Sulfones, Sulfites, and Sulfonates
allethrin (aluminum phosphide)	Aramite®
Aramite®	chlorbenside
Binapacryl	fenson
calcium arsenate	Genite 923
calcium cyanide	ovex
carbon disulfide	Sulphenone
Chlorbenside	tetradifon (Tedion)
Cryolite	Thanite
dinitrobutylphenol	
dinitrocresol	2) Dinitrophenols
dinitrocyclohexylphenol	binapacryl
diphenylamine	dinitrobutylphenol
ethyl formate	dinitrocresol
ethylene oxide	dinitrocyclohexylphenol
fenson	
hydrogen cyanide	3) Inorganic
Genite 923®	aluminum phosphide
lead arsenate	calcium arsenate
Lethane 384®	calcium cyanide
lime sulfur	cryolite
Metaldehyde	hydrogen cyanide
methyl formate	lead arsenate
Morestan®	lime sulfur
naphthalene	Paris green (copper acetoarsenite)
nicotine sulfate	Sulfur
ovex	
paris green (copper	4) Other Synthetic Organic
acetoarsenite)	acrylonitrile Lethane 384
piperonyl butoxide	allethrin metaldehyde
propylene oxide	carbon disulfide methyl formate
pyrethrins (active cpd)	diphenylamine Morestan
pyrethrum (whole-dried	ethyl formate naphthalene
flower)	ethylene oxide piperonyl butoxide
rotenone	hydrogen cyanide propylene oxide
ryania	
Sabadilla	5) Natural Occurring
Sulfur	nicotine sulfate
Sulphenone®	pyrethrins (active compounds)
Tedion® (see tetradifon)	pyrethrum (whole-dried flower)
tetradifon (Tedion®)	rotenone
Thanite®	ryania
	sabadilla

Once the first HCl molecule is eliminated, the other two HCl molecules are lost so rapidly that the bracketed species have not been isolated (FIGURE 6).

Reports on phosphorus chemistry have greatly increased in recent years, due in part to the rapid growth in phosphate pesticides research. Some of the general reactions they can undergo are pyrolysis, hydrolysis and oxidation (FIGURE 7).

Nucleophiles, such as NH_2OH, oximate anions, hydrogen peroxide ions, and O-Cl, which show the common structural features of an electronegative atom with unshared electrons α to the attacking atom, all exhibit reactivity toward phosphoryl phosphorus much greater than would be predicted from their basicities[16] (REACTION 3).

$$(CH_3O)_2 \; P \overset{S}{\underset{X}{\Bigl\langle}} \; + H_2\ddot{N}-\ddot{O}\diagdown_H \; \longrightarrow (CH_3O)_2 \; P \overset{S}{\underset{\underset{H}{NOH}}{\Bigl\langle}} \; + HX \qquad (3)$$

X = leaving group
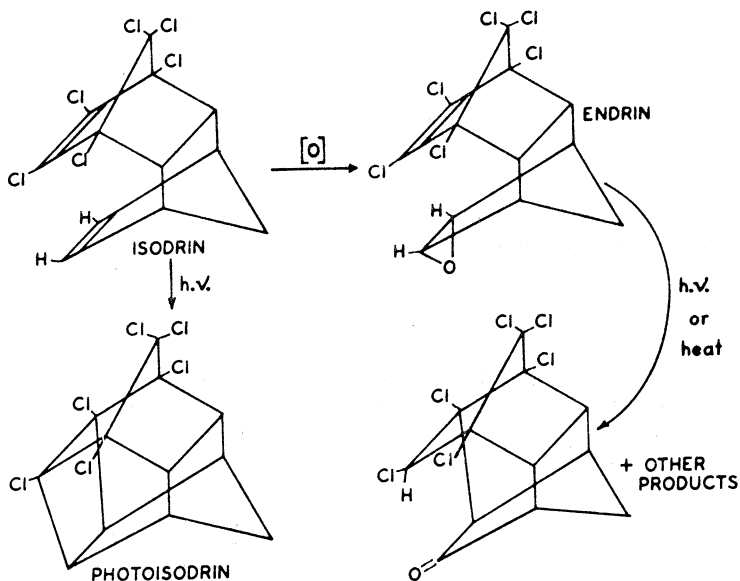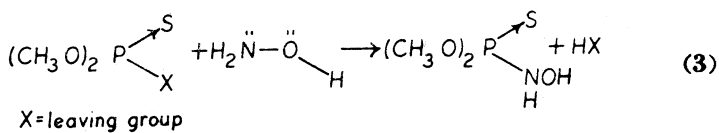
FIGURE 2. Isodrin-endrin reactions.
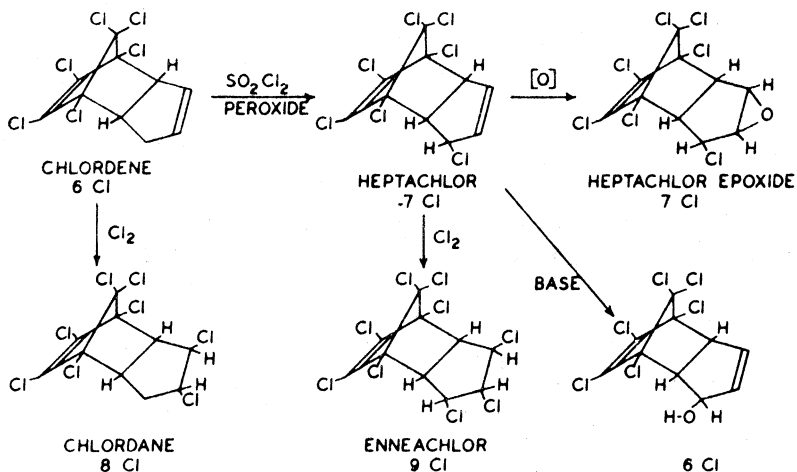
FIGURE 3. Chlordane family reactions.
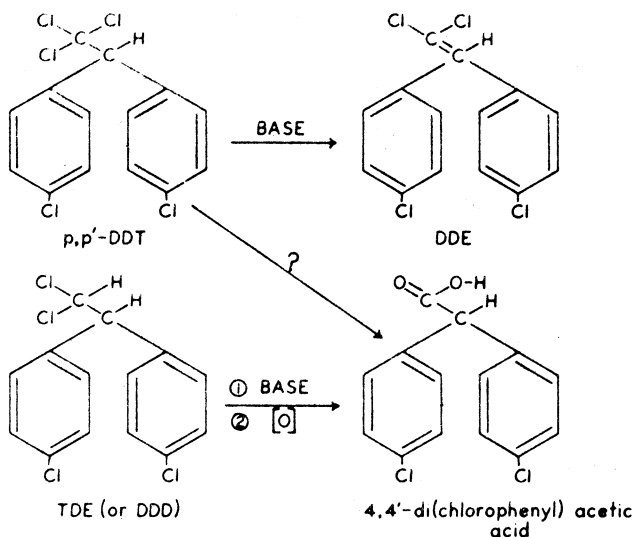
FIGURE 4. DDT family reactions.
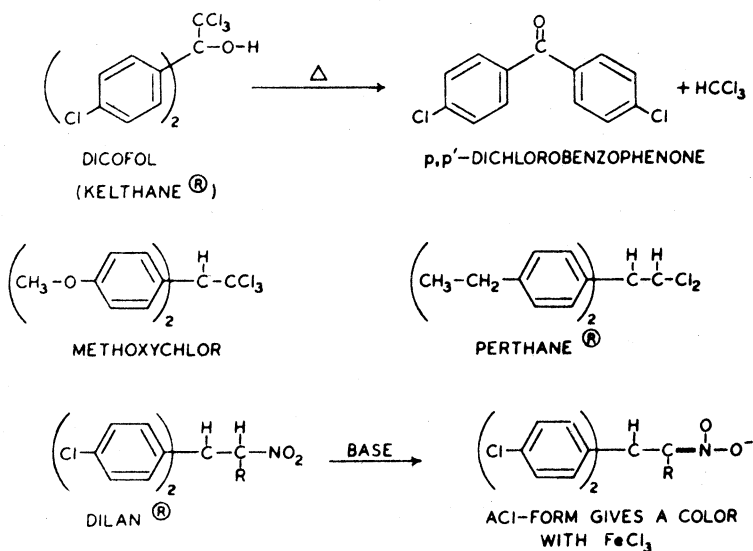
FIGURE 5. DDT analogues.

It is well documented that phosphate insecticides can phosphorylate enzymes and other parts of living systems because they have good leaving groups. However, the herbicidal aliphatic phosphates have poor leaving groups and, relatively speaking, do not inhibit cholinesterase. With heating under macro conditions, aliphatic phosphates can alkylate amines.[16] Aliphatic amines should be even easier to alkylate than aromatic amines, or anilines (FIGURE 8).

Phosphonates are true examples of organophosphorus compounds, that is, compounds containing a direct carbon-phosphorus bond. EPN and trichlorfon serve as examples of phosphonate pesticides presently in use (FIGURE 9).

Trichlorfon not only rearranges, but also loses, HCl to give DDVP. The driving force for the reaction may be the formation of a new phosphorus-oxygen bond. The relation between the two hydrolysis products is given for trichlorfon and DDVP. The rearrangement of trichlorfon in water can be followed by gas chromatography.[17] The products are extracted periodically into a solvent that can be injected directly into a gas chromatograph and followed as long as phosphorus is present in the molecule.
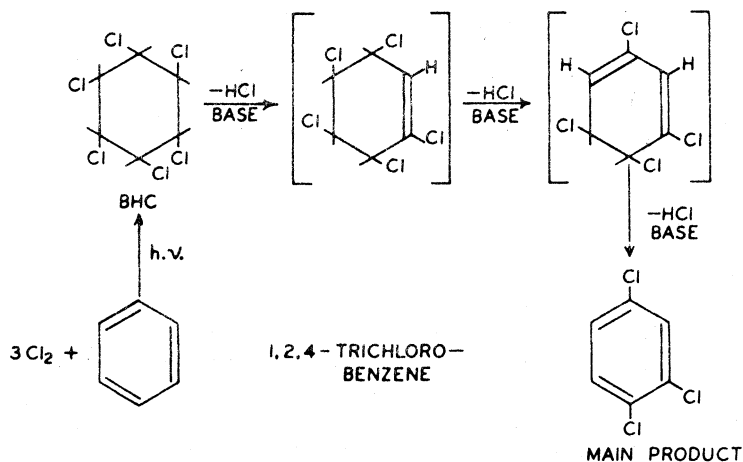
FIGURE 6.   BHC dehydrohalogenation.
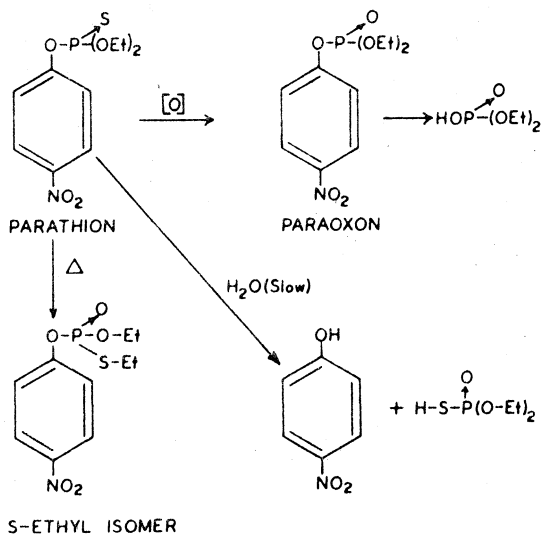
FIGURE 7.   Parathion reactions.

$$(RO)_2 P \diagup^{O}_{O} Ar + R'-O-H \longrightarrow (RO)_2 P \diagup^{O}_{O} R'$$

$$P \diagdown O$$

CLEAVAGE

$$+ ArOH$$

PHOSHORYLATION

$$R-X' \quad CH_3 \longrightarrow O-P \diagup^{O}_{O} R' \longrightarrow R-X-CH_3$$
$$\quad CH_3-O$$

C—O CLEAVAGE

$$H-O-P \diagup^{O}_{O} R'$$
$$CH_3-O$$

ALKYLATION
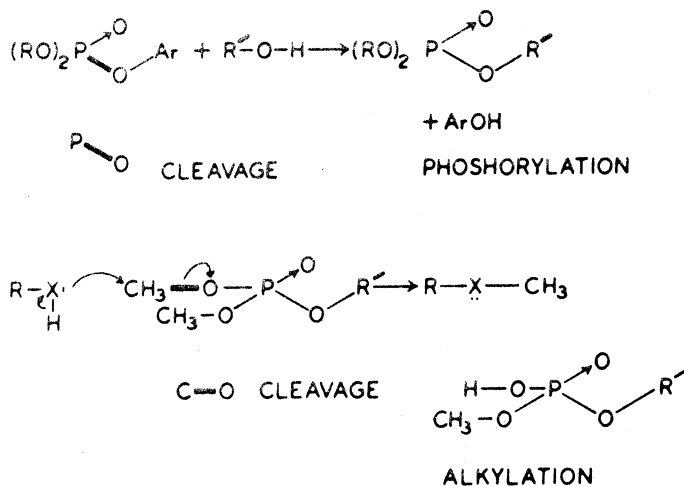
FIGURE 8. Phosphate reactions.

TRICHLORFON

DDVP

DIBROM

EPN
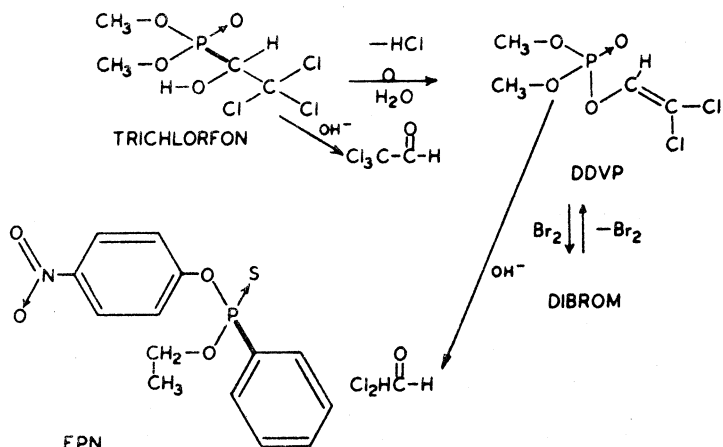
FIGURE 9. Phosphonate reactions.

Heterocyclic aromatic groups and aromatic carbocyclic groups behave similarly in phosphate pesticides. Guthion® is hydrolyzed to three products, all of which have been used to determine the amount of Guthion® present (FIGURE 10). Analytical methods based upon these hydrolysis products illustrate the interferences in a "valid" analysis. In an impure sample, low or high yields can be obtained for either the parent or the metabolites, depending upon which method is used—that is, which compound is being determined—unless the analytical method is specific for the intact compound.

Dimethoate can be hydrolyzed at the amide linkage as well as the P-O (phosphate) bond. This is true for other phosphate pesticides, as well. Malathion also can hydrolyze at the C-S linkage, leaving the two sulfur atoms with the phosphorus atom, as shown (FIGURE 11). Elimination appears to be the cause of

DIAZINON

AZINOPHOSMETHYL
(GUTHION®)

λ max ≈ 420 mμ

DYE $\xleftarrow{\text{(1) diazotize}}_{\text{(2) couple}}$ $+CH_2O$
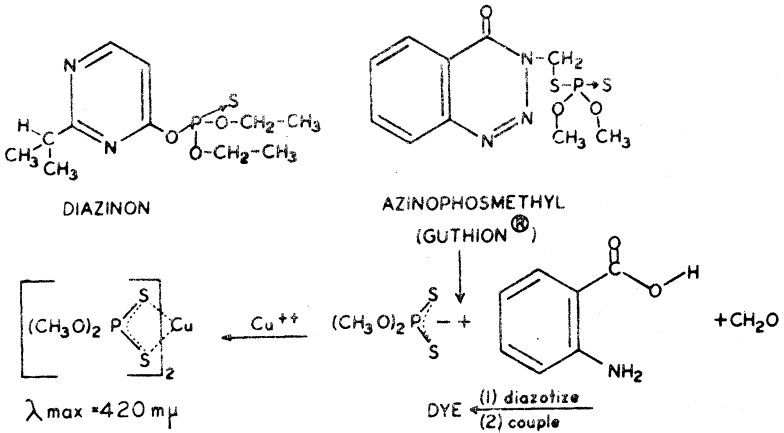
FIGURE 10.   Heterocyclic phosphate reactions.

MALATHION

DIMETHOATE   OTHER PRODUCTS

FIGURE 11.   Hydrolysis of phosphates.

A SULFOXIDE   A SULFONE

PHORATE (THIMET®) is similar

FIGURE 12.   Oxidation of disulfoton.

the formation of this dimethyl dithiophosphoric acid and fumaric acid. Other products can form, with the usual displacement reaction.

An isolated sulfide group can form sulfoxides and sulfones. These oxidation products, at least in the phosphate series, are usually better cholinesterase inhibitors than the parent compound (FIGURE 12).

In general, phosphate pesticides inhibit acetylcholinesterase irreversibly, whereas N-methyl- and N,N-dimethylcarbamate pesticides inhibit reversibly. This first reaction is said to be a transphosphorylation process and the second a transcarbamylation[18] process (see Wilson's paper and O'Brien's paper in this monograph). More work is needed on these reactions in plants and animals, since these two processes may form compounds that would lead to aliphatic phosphate and carbamate residues that may be neither extractable nor rapidly degraded. This type of reaction with natural products could apply to many pesticides other than carbamates and phosphates.

The carbamate group is found in a large variety of pesticides—insecticides, herbicides, and fungicides—and in drugs. Typical of the insecticidal carbamates (FIGURE 13) (aryl N-methylcarbamates) used in this country is carbaryl (Sevin®). These carbamate insecticides can be hydrolyzed with various bases[18] within minutes, whereas the herbicidal N-phenylcarbamates require much longer periods of hydrolysis under the same conditions. The N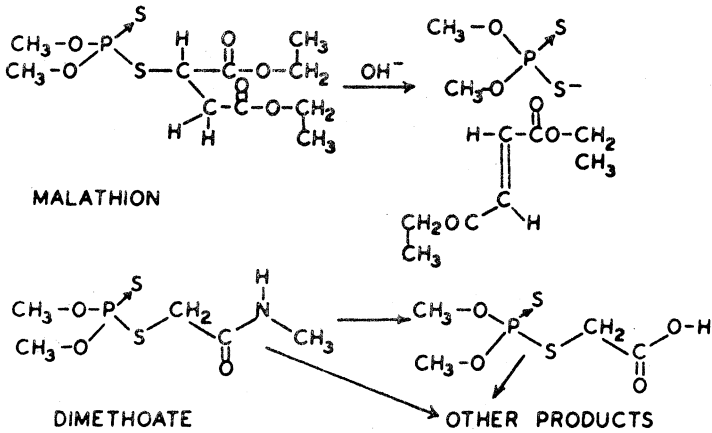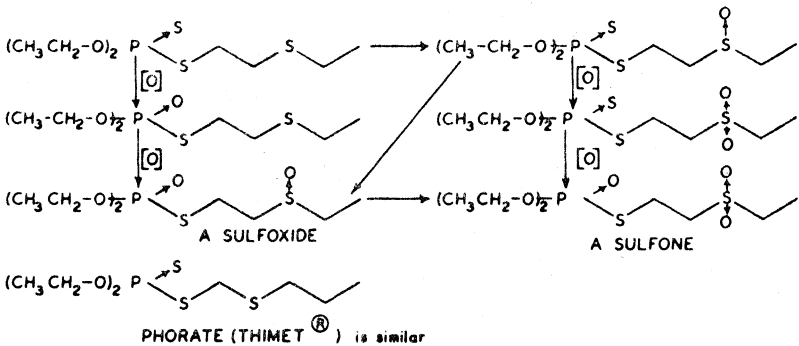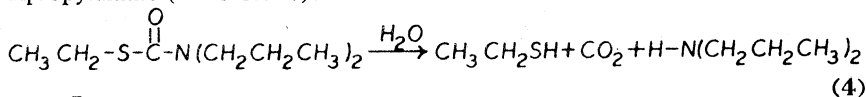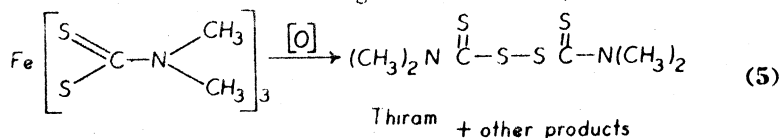-methylcarbamates can be nitrosated quantitatively, or nearly quantitatively, on the ring, with the nitrogen replacing the hydrogen.[19] When carbaryl and other N-methylcarbamate insecticides are heated[20] or bombarded with an electron beam[21] or when carbaryl is photolyzed,[22,23] 1-naphthol or the corresponding phenol and methyl isocyanate are formed. Some new cholinesterase-inhibiting compounds were also reported. Since methyl isocyanate appears to form easily, its chemistry was studied. Methyl isocyanate was found to be selective in reacting with various hydroxyl[24,25] and other groups after reaction. The N,N-dimethylcarbamates from NMR studies have a planar carbamate group.[26] These carbamate insecticides have a very narrow band in the infrared, attributed to the C=O absorption.[27]

Eptam (ethyl di-n-propylthiolcarbamate), a herbicide, is hydrolyzed by water in a first-order reaction at 20° C, yielding ethyl mercaptan, carbon dioxide and dipropylamine (REACTION 4).

$$CH_3CH_2-S-\overset{\overset{\displaystyle O}{\|}}{C}-N(CH_2CH_2CH_3)_2 \xrightarrow{H_2O} CH_3CH_2SH + CO_2 + H-N(CH_2CH_2CH_3)_2$$

(4)

Eptam

Ferbam is a dithiocarbamate and a fungicide (REACTION 5).

$$Fe\left[\overset{S}{\underset{S}{>}}C-N\overset{CH_3}{\underset{CH_3}{<}}\right]_3 \xrightarrow{[O]} (CH_3)_2N\overset{\overset{\displaystyle S}{\|}}{C}-S-S\overset{\overset{\displaystyle S}{\|}}{C}-N(CH_3)_2$$

(5)

Thiram + other products

It reacts with air and light to give decomposition products of unknown structures; however, thiram is probably one of them.[5] Vapam™, a soil fumigant, decomposes to a toxic, gaseous substance, methyl isothiocyanate (REACTION 6).

Clearly, the carbamates are a versatile group of pesticides.

$$CH_3-\overset{\overset{\displaystyle H}{|}}{N}-\overset{\overset{\displaystyle S}{\|}}{C}-S^-Na^+ \xrightarrow{Soil} CH_3-N=C=S$$

(6)
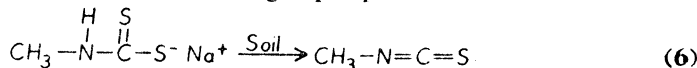
Methyl Isocyanate

2-Cyclohexyl-4,6-dinitrophenol (DNOCHP) is acidic and can also form molecular compounds (i.e., addition complexes) with aromatic and aliphatic hydrocarbons, amines, phenols, and other compounds similar to picric acid. Karathane®, an ester of a similar dinitrophenol, would be expected to behave in a manner similar to DNOCHP, since it is a mixed acid anhydride and thus is easily hydrolyzed to another dinitro alkylated phenol (FIGURE 14).

Sulfonates are generally difficult to hydrolyze; ovex is no exception. As with most sulfonates the C-O bond (not the S-O bond) is cleaved during hydrolysis. When an aliphatic alcohol is a part of the sulfonate, C-O bond cleavage would be expected to give alkylation.

FIGURE 13.   Aryl N-methycarbamate (carbaryl) reactions.

FIGURE 14.   Other insecticides.

AMINOTRIAZOLE   GLUCOSIDE

(TRIAZINE)
SIMAZINE

FIGURE 15. Heterocyclic herbicides.

There are many more miticides and insecticides (See list in TABLE 3). For further information, consult the work of scientists in this monograph, and that of scientists associated with the manufacturer of the particular product.

Piperonyl butoxide (FIGURE 14) is not in itself an insecticide, but it acts as a powerful synergist for many of the phosphate, carbamate, pyrethrin, and other types of insecticides. The methylenedioxy group is fairly stable, but this ring system can be opened with acid to form formaldehyde and the dihydroxy alkyl benzene.

Like other amines, aminotriazole, or amitrol forms derivatives with carbonyl compounds, which may account for the ease of formation of glucosides and other metabolites (FIGURE 15). Free amines, like amitrol and anilines, are in general easily oxidized. Coupling would be expected from such an oxidation, among other results (See the paper by Freed & Montgomery on herbicidal chemistry in this monograph).

One of the reactive sites of simazine is at the chlorine-carbon bond. This position appears to be generally reactive for all the triazine chemicals (FIGURE 15). Free radical intermolecular alkylation may be another type of reaction involving the methylthio- and methoxy triazine chemicals.

Captan is one of several phthalimide-type fungicides used in the United States. The reactive portion appears to be in the S-C-Cl₃ group (see REACTION 7) but,

as with aldrin, the double bond also forms epoxides (See the paper by Owens on fungicidal chemistry in this monograph).

There is a large group of fumigant chemicals that generally alkylate various

amines, mercaptans, and alcohols, both in and outside of the living system (REACTION 8).

$$CH_3-Br + \begin{cases} R-S-H & R-S-CH_3 \xrightarrow{CH_3Br} R-\overset{\displaystyle CH_3}{\underset{\displaystyle |}{\overset{\displaystyle |}{S}}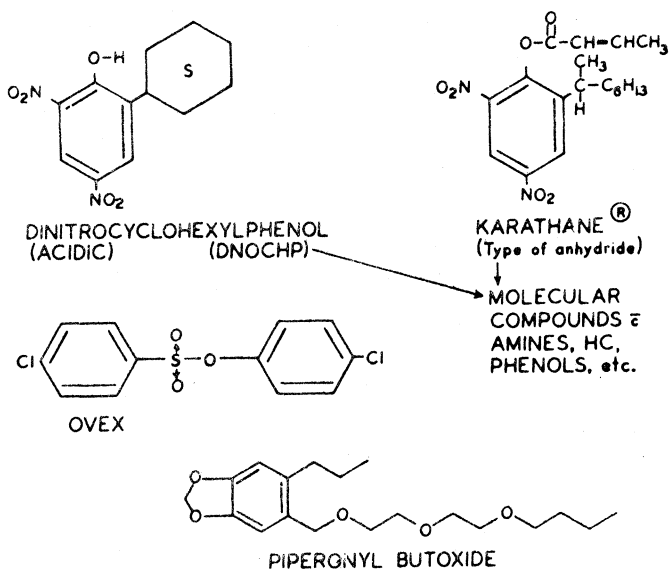}-CH_3 \\ R_2-N-H \xrightarrow{-HBr} R_2N-CH_3 \xrightarrow{HBr} R_2\overset{+}{N}-CH_3 \\ R-O-H & R-O-CH_3 \qquad\quad H \end{cases} \qquad (8)$$
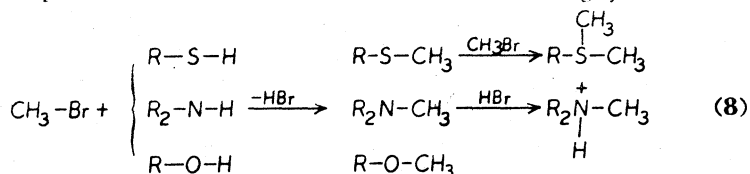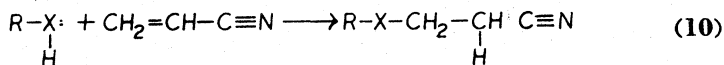
Methyl bromide is a primary example. Using radiolabeled ClH_3-Br under conditions simulating the fumigation of wheat. Winteringham *et al.*[28] and Bridges[29] reported that the histidine and lysine components in wheat were methylated on the basic amino groupings. Alkylation took place, as well, on the S-H and O-H groups in other naturally occurring compounds.

When used as a fumigant of spices, ethylene oxide has been reported[30] to give ethylene chlorohydrin, ethylene glycol, and hydroxyethyl ethers of carbohydrates (REACTION 9).

$$\begin{matrix} R \\ \diagdown \\ C\text{-----}CH_2 + Cl^- \text{ or } R'OH \longrightarrow \\ H \diagup O \end{matrix}$$

$$R-\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle H-O}{|}}{C}}-CH_2 \quad \text{and} \quad R-\overset{\overset{\displaystyle R'-O}{|}}{C}-CH_2 \qquad (9)$$
$$ Cl O-H$$

$$R-\underset{\underset{\displaystyle Cl}{|}}{C}\text{-----}\overset{\diagup O-H}{CH_2} \qquad R-\underset{\underset{\displaystyle O-R'}{|}}{\overset{\overset{\displaystyle H-O}{|}}{C}}-CH_2$$
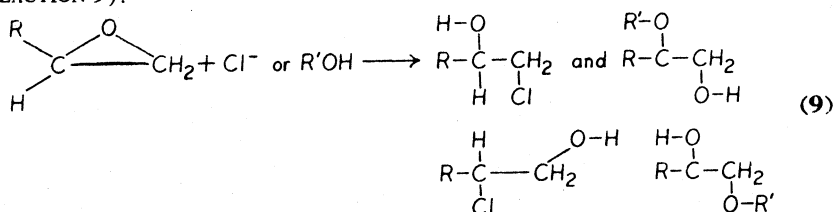
Propylene oxide[30] behaves similarly. If these relatively unstrained epoxides are opened by chloride ion, carbohydrates, and water, should other epoxides be expected to behave similarly?

Acrylonitrile, another fumigant, is known to add rapidly to mercaptans and certain amines[31], as seen in REACTION 10.

$$R-\underset{\underset{\displaystyle H}{|}}{X}{\cdot} + CH_2=CH-C\equiv N \longrightarrow R-X-CH_2-\underset{\underset{\displaystyle H}{|}}{C}H C\equiv N \qquad (10)$$

Crosby discusses some other aspects of the organic chemistry of pesticides in this monograph.

ANALYTICAL CHEMISTRY

Burchfield discusses instrumentation in pesticide analyses in this monograph. However, the chemical bases for some analytical procedures have been given as chemical reactions in previous sections of this paper. A recent survey (November, 1964–October, 1966) of the latest developments in pesticide residue analysis was reported by Williams and Cook.[32] Where possible, this report devoted attention to the chemistry involved in the analysis. These three sources, together with their references, will cover analytical chemistry adequately.

PHYSICAL CHEMISTRY

The physicochemical properties of pesticides are often utilized to obtain answers to questions about such factors as purity, volatility, thermal stability, polarity, and partition values. For example, phase changes are used to determine purity (cryoscopic measurements, m.p., etc.). Beroza and associates, among many investigators, have been particularly active with physicochemical parameters involving partition values for many pesticides, reaction-gas chromatography, etc. They also reported that DDT (m.p. 108.5, with a vapor pressure of 1.9×10^{-7} mm Hg at 20°C) is rapidly co-distilled with water at room and higher

temperatures.[33] This may be what is expected for highly divided DDT. From the data it appears that DDT is not soluble in water, even at parts per billion (ppb) levels, and is lost at a constant rate from the placid water's surface. Samples containing DDT, or DDT combined with other pesticides, and water must therefore be protected from this kind of loss if the analysis is to reflect the DDT content at the time the sample is collected.

Another use of physicochemical properties of pesticides is to be found in their chromatographic behavior. The Food and Drug Administration develops and uses methods of analysis that can separate and quantitatively determine a large number of pesticides on an individual basis in one analysis.[34-37] These are multiple detection systems; they must determine many pesticides with the same analysis. Several reports have appeared on TLC and GLC, but a great deal more work is needed on the general physicochemical properties of pesticides and their metabolites. Nuclear magnetic resonance,[26] infrared spectrometry[27] and mass spectrometry have already been mentioned as techniques that show how carbamates behave. Insight into the penetration, adsorption, translocation, and activation of pesticides has been obtained and can be further explored through the physicochemical approach.

BIOCHEMISTRY

A fairly complete review through December 31, 1965 was compiled by Menzie[38] on the metabolism of pesticides. Current reviews are available in reports by working committees of the Food and Agriculture Organization (FAO) and IUPAC. Much of the work on metabolism has been done or is being done by the companies that market or that are hoping to market a particular pesticide. These data gradually are reported in the literature. Some government and university scientists are studying metabolism; e.g. Baron and Doherty[39] at the Food and Drug Administration studied the metabolism of Banol® (3,4-dimethyl-6-chlorophenyl N-methylcarbamate), an experimental carbamate insecticide, and Korte and Arent[40] at the University of Bonn reported the metabolism of dieldrin in rabbits. Korte also synthesized the metabolic product (See diol in FIGURE 2). Refer to Fukuto and Metcalf's paper in this monograph for a summary of this rapidly expanding field.

PESTICIDE CHEMISTRY WITHIN OTHER DISCIPLINES

The foregoing are the acknowledged subdivisions of chemistry. How are pesticides being studied in other disciplines where chemistry plays a minor role? Benson and Jones[3] have cited some of the outstanding references and sources of information in the literature of pesticide chemistry. Any research program depends upon the information sciences. Shepard has prepared an economic review[41] of the pesticides (pounds produced, total sales, pounds sold, cost per unit, etc.) for many years. Some of his data come from the Tariff Commission Report on Pesticides. Plimmer, Rosen, Roburn, Crosby, Gunther, Slade, Casida, and others with their associates are gradually reporting on the photochemistry of pesticides. Soil biochemistry is a complex area discussed in compendia and several forthcoming books.[42] Jacobson[43] has reviewed the isolation, identification, and synthesis of insect sex attractants. Insect chemosterilants have been reviewed by Borkovec.[44] There is no single book on the chemical manufacture of pesticides; however, the patent literature for each individual pesticide would be the place to begin. The American Chemical Society has sponsored a symposium on the chemistry of organophosphate pesticides.[45]

CONCLUSIONS

Chemical studies on the behavior of pesticides have contributed greatly to our understanding of the biological behavior of pesticides. Some outstanding studies of the chemical reactions of pesticides have been presented. The chemical reactions, physical behavior, and ideas for one pesticide apply to many other compounds. Some precautions and several inherent problems have been raised. No one as yet, however, has a foolproof method for predicting the biological activity of a pesticide under the conditions found in the cornfield, for example. This may come eventually when we learn much more about the behavior of the chemicals and the biological systems to be controlled. In achieving this method of prediction, man will learn more about his own life and ways of protecting it from the inherent risk of using these reactive chemicals.

[NOTE ADDED IN PROOF: Between the time that this manuscript was prepared and the actual time of publication, a number of outstanding technical books and articles have appeared which would bring the reader closer to covering the literature of pesticide chemistry and its principles.

The National Academy of Sciences[46] is publishing a series of six volumes on the *Principles of Plant and Animal Pest Control,* most of which have already appeared in print. This set should prove invaluable as a supplement to this monograph. In the area of pesticide analysis, the *Pesticide Analytical Manual* of the Food and Drug Administration has been expanded to cover all pesticides that have been approved for use on raw agricultural products.[47] This manual was revised and corrected in 1968, and periodic updatings are distributed. In the area of metabolism, two books have appeared since Menzie's review:[38] the book by O'Brien[51] covers the insecticides well; Hodgson's book,[48] although using the word "pesticide," actually deals mainly with the enzymatic oxidation of insecticides together with metabolites, their synergists, model compounds, and some drugs. Herbicidal degradations are covered by the treatise by Kearney and Kaufman[42] and the fungicides by an advanced treatise in two volumes edited by Torgeson.[52]

A number of important specific references have also appeared, but only those which reflect in a major way on work presented here have been included. Although BHC does in general break down with base as shown in FIGURE 6, the bracketed pentachlorocyclohexene compound has recently been found in soil and has been synthesized independently.[49]

A recent review of the alkylating properties of alkyl thiophosphates[50] showed that this property could be a major mode of reaction of this type of pesticide with amines and mercaptans, (See FIGURE 8 where X is nitrogen, sulfur, or oxygen.)

A major examination of the NMR properties of pesticides is in progress for the organophosphorus pesticides,[53] chlorinated hydrocarbon pesticides[54] and carbamate pesticides,[55] and is expected to be continued for other classes of pesticides.

Summary reports of the Commission of the Pesticides Section, Applied Chemistry Division, International Union of Pure and Applied Chemistry have also been published.[56]]

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DISCUSSION OF THE PAPER

D. MACDOUGALL (*Chemagro Corp., Kansas City, Mo.*): I hope that in the total discussion of pesticides this week you will bear in mind that chlorinated hydrocarbon insecticides represent about 30 per cent of the total amount of the pesticides used in this country. Some people are very inclined to forget this and indict all pesticides on the basis of evidence based only on the chlorinated hydrocarbon insecticides.

DR. BENSON: Dr. MacDougall is absolutely correct. However, Dr. Kraybill wrote all of the speakers asking what compounds would be covered at this particular conference, and those people who replied had their particular compounds mentioned in my paper and the handouts, with the exception of chemicals not used commercially as pesticides.