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Development of Pesticide Technology and Environmental Chemistry in the United States

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INTRODUCTION

The history and development of pesticide technology in the United States has, in many respects, paralleled that of Western Europe and Japan. The diversity of agriculture in the United States, and consequently the diversity of pesticidal chemicals used in American agriculture, make it somewhat unique. The United States is also one of the leading pesticde manufacturers, with six companies (Dow Chemical, du Pont, Eli Lilly, Monsanto, Stauffer, and Union Carbide) accounting for about a third of the major global sales (Table 1). Sales of pesticides in North America, from all manufacturers, was about 39% of global sales.

Superimposed on the phenomenal growth of the U.S. pesticide industry over the last three decades has been an increasing regulatory role by various agencies in the Federal Government. This increased regulatory activity has been triggered by growing concern about the quality of the environment and a suspected link between exposure to industrial chemicals and human cancer. The regulatory measures have improved the safety of pesticides and fostered some new and unique advances in the field of environmental chemistry.

It is not the purpose of this paper to examine the health-related problems of pesticide usage, since this lies more in the domain of toxicology; rather it will examine some aspects of the American pesticide technology, regulations, and usage. With this background information, some environmental aspects of pesticides, including persistence, movement, and degradation will be examined.

GROWTH OF THE U.S. PESTICIDE INDUSTRY

Chemical pest control prior to World War II was extremely limited. Prior to World War I, the principal insecticides used in U.S. agriculture were the inorganic arsenicals, lime-sulfur, petroleum oils, and nicotine. In the interval between World Wars I and II, pyrethrum, rotenone, fluorine compounds, thiocyanates, and dinitro compounds appeared on the market. Since 1940, DDT, the cyclodienes, the organophosphates, and the carbamates came into large use.

Chemical weed control developed somewhat later than the insecticide industry in American agriculture. Prior to the mid or late 1940's, which is generally considered to be the beginning of the modern era of chemical weed control, certain inorganic salts--including arsenate, borate, and chlorate--were used as herbicides. The introduction of 2,4-D, the phenylureas, and the s-triazines marked the beginning of the growth of the American herbicide industry.

The production and use of pesticides have steadily increased over the past 30 years. Production for all pesticides in the United States in 1975 was 1.61 billion pounds, up 13.5% over 1974. Total annual sales are rapidly approaching $3 billion. The major area of growth in pesticide production has been in the herbicide industry. Herbicide production in 1975 totalled 788 million pounds, up 30.4% over 1974. Herbicide sales represented 62% of all pesticide dollar sales. Insecticide production in 1975 totalled 666 million pounds, down 21.1% from 1974. Fungicide production has never reached the production and use levels of insecticides and herbicides and amounted to 155 million pounds in 1975. The United States production of several leading insecticides and herbicides during 1974 is shown in Table 2.

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The rapid growth of the American pesticide industry has slowed down over the last two years. One of the reasons for this decline has been the increasing costs for producing new pesticides, one facet of which relates to the more stringent requirements for additional registration information on new compounds and a reassessment of information on the older compounds. Currently, many pesticides are undergoing a risk/benefit analysis to determine whether future registration will be granted or denied. At this point then, it would be worthwhile to review the history of pesticide regulation in the United States.

PESTICIDE REGULATION

The major laws since 1910 affecting pesticide regulations in the United States are shown as follows:

Year	Law	Responsible Agency*
1910	Federal Insecticide Act	USDA
1938	Federal Food, Drug & Cosmetic Act	FDA
1947	Federal Insecticide, Fungicide and Rodenticide Act	USDA
1954	Pesticide Chemical Amendment	HEW
1972	Federal Environmental Pesticide Act	EPA

Pesticides have been under government regulation since 1910, following enactment of the Federal Insecticide Act, which was administered by the United States Department of Agriculture (USDA). This law prevented the manufacture, sale, or transportation of impure or mislabeled insecticides and fungicides. With the revised Federal Food, Drug and Cosmetic Act of 1938, accountability was shifted to the Food and Drug Administration, and that agency was made responsible for testing materials to prove them "poisonous or deleterious" to the satisfaction of the court when action was desired to remove them from the market. The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), enacted in 1947, extended the scope of the 1910 act to include rodenticides and herbicides. Premarketing registration was required for products to be shipped interstate, and a system of label claims and registration was established. The act was enforced by USDA. In 1954, the Pesticide Chemicals Amendment to the Federal Food, Drug and Cosmetic Act (an amendment of the 1938 act) provided for a system of fees to support the procedures involved and established better procedures for obtaining tolerances to be used in determining possible exemptions for pesticides. Since it established tolerance limits for pesticide residues in foods, more information was required on safety, efficacy, and residues. It was administered by the Department of Health, Education and Welfare (HEW). The Food Additive Amendment of 1958 expressly excluded pesticide chemicals and pesticidal residues on crops and in processed foods when such residues had resulted from legal uses of pesticides on crops. This amendment included the "Delaney clause" on carcinogens, which stated that no additive shall be deemed safe if it is found to induce cancer when ingested by man or animals.

The Federal Environmental Pesticide Control Act of 1971 significantly amended the FIFRA of 1947. It established the U.S. Environmental Protection Agency (EPA) with broad authority to regulate pesticides in the United States. This act does the following:

1. Requires all U.S. pesticides to be registered or approved by the Federal Government.

2. Classifies pesticides for general or restricted use; those that are restricted may only be applied by or under the supervision of certified applicators, due to hazard to the individual or to the environment.

3. Establishes state applicator certification programs (in which farmers may be certified as private applicators) and cooperative enforcement programs.

4. Prohibits the misuse of pesticides (any use inconsistent with the label is a crime, whether or not personal or crop injury results or residue exceeding the tolerance

* USDA - United States Department of Agriculture, FDA - Food and Drug Administration, HEW - Department of Health, Education and Welfare, EPA - Environmental Protection Agency.

is found at harvest), adds civil to increased criminal penalties, and otherwise strengthens enforcement.

5. Requires pesticide-producing establishments to be registered and to submit information regularly on production and sales volume.

6. Authorizes indemnification of certain owners of pesticides that are suspended, then cancelled.

7. Authorizes the EPA Administrator to establish pesticide packaging standards, regulate pesticide and container disposal, issue experimental use permits, conduct research on pesticides and alternatives, and monitor pesticide use and persistence in the environment.

A new review process, Rebuttable Presumption Against Registration (RPAR), has been initiated by EPA to ensure a full gathering of scientific information on pesticide safety and a thorough assessment of the risks and benefits of pesticide products. Some of the pesticides currently under review are: the rodenticides 1080, 1081, and strychnine and the insecticides endrin, chlorobenzilate, chloroform, kepone, and BHC.

PESTICIDE USAGE

Because of the extensive development of the American pesticide industry, the user has a large number of compounds to combat the major pests affecting crop production. It is estimated that approximately 350 insecticides and 160 herbicides are registered in the United States on a large number of crops. Products in which these pesticides are sold number in the thousands.

It is beyond the scope of this paper to consider all of the possible uses of pesticides in various cropping systems. It is appropriate, however, to consider a major crop of mutual interest in Egypt and the United States: cotton. The major insecticide market in the United States is on cotton for the control of cotton boll weevil (Anthonomus grandis), lygus bug (Lygus lineolaris and hesperus), pink boll worm (Pectinophora gossypiella), cotton boll worm (Heliothis zea), and tobacco budworm (Heliothis virescens). The herbicide market in cotton is also substantial, used primarily for the control of crabgrass (Digitaria sanguinalis), Johnson grass (Sorghum Halepense), Barnyard grass (Echinochloa crus-galli), crowfoot grass (Dactyloctenium aegyptium), prickley sida (Sida spinosa), spurred anoda (Anoda Cristata), cockelbur (Xanthium strumarium), pigweed (Amaranthus retroflexus) and morning glory (Ipomoea spp.) The major insecticides and herbicides used in cotton, along with expenditures and acreage treated are shown in Tables 3 and 4.

The preceding sections provide a brief insight into the scope of pesticide technology in the United States. As this technology has evolved, techniques for studying the environmental parameters of pesticides has steadily increased and improved. The following sections will examine some of the important environmental processes affecting pesticides.

ENVIRONMENTAL CHEMISTRY OF PESTICIDES

Three of the most important properties of a pesticide in the environment are persistence, movement, and degradation. These parameters can be measured in both laboratory and field studies.

Laboratory studies devoted to investigating the environmental fate of pesticides have usually examined individual processes such as microbial metabolism, soil leaching, surface and vapor phase photodecomposition, volatilization from plant or soil surfaces, and plant uptake. In the environment, however, all of these processes may be operative on the molecule, so that in each stage of the pesticide dissipation process, one or more processes may play a major role. It has been extremely difficult to study two or more of these processes under controlled conditions which will enable a clear understanding of the contribution of each. Simplified model laboratory systems are now being developed which enable

simultaneous measurement of numerous factors affecting pesticide dissipation in the environment.

The following sections will review some general aspects of pesticide persistence, movement, and degradation. When appropriate, laboratory techniques designed to study specific processes will be discussed.

Persistence

A large number of factors affect the persistence or life history of a pesticide molecule in the environment. Soil, climatic, and pesticide structural properties are three factors primarily responsible for governing the persistence of pesticides in soils. There are a large number of secondary factors that also influence persistence. It is difficult, therefore, to arrive at any realistic figures either on half-life or on the time required for complete destruction of a pesticide molecule. An extensive review of the literature has yielded some general guidelines on the persistence of various classes of molecules (Figure 1).

Each bar represents a family of closely related pesticides. The open spaces in each bar represent individual biocides in the larger pesticide family. The length of each bar in Figure 1 represents the time required for 75 to 100% loss of the compound in the soil environment. It is assumed that the rates of application are those normally used in agriculture and represent averages of all soil and climatic conditions. The data used in preparing Figure 1 do not take into consideration local geographic conditions, differences in soil type, formulation, depth of placement, method of application, soil organic matter content, soil moisture holding capacity, topography, cover, soil temperature, rainfall, and a host of other variables that are responsible for differences observed under actual field conditions with the same compound. Nevertheless, they do indicate what might be anticipated on a general basis for the persistence of these various classes of compounds in soils.

A more detailed analysis of the persistence of individual pesticides is found in Figure 2. It is important to note that the time indicated on each graph in Figure 2 changes from months to weeks in some cases.

It comes as no surprise that the chlorinated hydrocarbon insecticides, including compounds such as DDT, dieldrin, aldrin, chlordane, and others, are some of the most persistent compounds encountered in the environment. Under normal rates of applications, these compounds may persist for two to five years. One of the virtues of the chlorinated hydrocarbon insecticides was the full season control afforded by these pesticides. At the other end of the spectrum are found the organic phosphorus insecticides, such as parathion, malathion, phorate, and others which are not considered persistent materials. They usually dissipate within one to two weeks. It is extremely fortunate that these materials do break down rapidly in soils, since they represent some of the more toxic members of the pesticide family. Between the extremes in persistence represented by the chlorinated hydrocarbon insecticides, we have the vast array of compounds represented by the organic herbicides. Some of the herbicides may persist for a few days, some a few weeks, some a few months, and a few for longer than one growing season. As a general rule, the herbicides are considered less persistent than the organochlorine insecticides.

Persistence is one of the most important factors to take into consideration in assessing pesticide significance in the environment. The longer a pesticide persists in soils, the greater the opportunity for it to move from its original site of application and appear in other environmental components.

Soil persistence studies can be conducted under laboratory conditions that are comparable to field conditions if a number of precautions are taken. The two most important parameters are soil quality and pesticide rate of application. Dry soils stored for long periods of time in closed containers do not give good comparisons to fresh soil, since the microbial ecology is adversely altered by storage. Consequently, only fresh soil recently obtained from the field is usable in persistence and metabolism studies. Excessively high application rates under laboratory conditions usually prolong the persistence of a pesticide.

A reasonable soil persistence study can be conducted with soil moisture at about 70% field capacity and a pesticide concentration in the range of 1 to 10 p.p.m.

Soil biometer flasks represent one of the simplest methods of measuring pesticide metabolism and persistence under laboratory conditions. The flask (Figure 3) consists of a main vessel containing soil (about 50 g.) and the ^{14}C labeled pesticide, while the side arm contains a base (0.1N NaOH) to trap any metabolically evolved $^{14}CO_2$. The biometer flask method allows a number of variables to be studied with comparative ease.

Movement

A second important factor in assessing the significance of pesticides in the environment is their ability to move from the original site of application. There are several routes by which a pesticide may move in the environment, i.e., by vertical leaching down into the soil profile, by erosion and movement of absorbed pesticides in soil particles, and by the vapor movement of a pesticide off of the soil surface into the atmosphere.

The vertical mobility of various classes of pesticides down into the soil profile is shown in Table 5. Those pesticides in mobility class "1" are generally considered immobile in soils and would not leach readily into soils. In contrast, pesticides in mobility class "5" are relatively mobile and could be found at greater depths in soils. The remaining classes, i.e., 2,3,4, represent intermediate, but increasing, degrees of mobility.

The insoluble chlorinated hydrocarbon insecticides are in mobility class "1" and generally tend to remain on or near the soil surface. Consequently, they pose little or no threat to groundwater purity but are subject to surface erosion and movement along with soil particles. It is now abundantly clear that soil surface movement is partly responsible for the appearance of pesticides in the aquatic environment.

The acid herbicides such as TCA, dalapon, and 2,3,6-TBA are leached readily in soils and may move to great depths during a normal growing season. With few exceptions, the more mobile pesticides found in classes "4" and "5" are the acid herbicides. Fortunately, these pesticides are usually degraded fairly rapidly in the environment, and consequently one does not detect them in ground water supplies.

There are several methods of studying leaching under laboratory conditions. The soil column and soil thin layer chromatography (TLC) are two fairly widely used methods. Soil TLC is a relatively simple and rapid technique. We have used soil TLC to measure the relative mobility of a large number of pesticides, as shown in Table 5. Various soil parameters have been examined to determine their effect on leaching. We find, in general, that higher soil organic matter is associated with greater adsorption and less movement of pesticides.

Volatility can be measured by the use of polyurethane foam plugs. A simple flask method allows for measurement of both volatility and microbial metabolism (Figure 4). Any volatile pesticides leaving the soil surface are trapped on the foam plugs, while metabolic $^{14}CO_2$ passes through the plugs and is trapped in alkali. The volatile pesticide is removed in a soxhlet extractor. We find that most of the pesticide loss occurs during the first one to three weeks after application.

Degradation

Photodecomposition, microbial metabolism, and chemical conversion are natural processes in the environment which are responsible for pesticide degradation. The persistence of a pesticide in the environment is a function of the rate at which these various processes operate singly or in combination. As a general rule, the products of these degradative processes are less toxic than the parent materials. There are a few examples, however, of pesticides which are degraded to more toxic insecticides or more persistent metabolites than the parent material. It is only in recent years that we have had the equipment and knowledge to study the fate of a pesticide in the environment using laboratory techniques. The following sections of the paper will deal with our knowledge concerning the photode-

composition, microbial metabolism, and chemical conversion of pesticides.

Photodecomposition

There is sufficient ultraviolet irradiation in sunlight to cause the alteration of many synthetic organic pesticides. Photolytic reactions in sunlight essentially are bounded by the UV cutoff of the ozone absorption spectra (about 290 mu.) on one end and the low energy limit for activation of bond breaking at the other. Under laboratory conditions there are three principal types of UV light sources that have become commercially available for studying pesticide composition. These include (1) incandescent, (2) arc, and (3) fluorescent light sources. These photochemical reactions usually are carried out in organic solvents or aqueous solutions and more recently there have been attempts to study the vapor phase photolysis of pesticides in air.

One example of a photochemical reaction that is important in the environment involves the chlorinated benzoic acids. In the presence of a UV light source, the herbicide 2,3,6-trichlorobenzoic acid gives rise to a number of dichloro and monochlorobenzoic acids. Ultimately, benzoic acid is produced. This is typical of many photolytic reactions, and one observes a cleavage of the carbon-chlorine bond and the replacement of the chlorine atom with a hydrogen. Another example is the photooxidation of DDT. In air and in the presence of a UV light source, DDT is converted to the 4,4'-dichlorylbenzophenone.

These represent two simple reactions that are observed under laboratory conditions. In reality, when one irradiates a chlorinated pesticide in an organic solvent or in an aqueous solution, a large number of complex products are observed. Only recently have we been able to isolate and characterize these complex products by the aid of mass spectrometry. The photochemical decomposition products of DDT are exceedingly complex molecules and the environmental significance of these molecules is uncertain at the present time. Nevertheless, we feel that with new instrumentation and the great sensitivity and selectivity afforded by gas chromatography combined with mass spectrometry, we will be able to isolate and characterize a large number of these hitherto unknown photodecomposition products.

Microbial Metabolism

The natural community of microorganisms in soils is responsible for metabolizing a vast array of complex organic pesticides. Soil fungi, bacteria, and actinomycetes have all been implicated. These organisms possess enzymes which cleave the chemical bonds found in many pesticides. As a general rule, the resultant products of metabolism are usually less toxic than the parent material and generally tend to be more polar or water soluble. There are several comprehensive textbooks which now cover our vast amount of knowledge on the microbial metabolism of pesticides.

Some metabolites are more persistent and more toxic than their parent compounds. This is true in the case of the insecticides aldrin and heptachlor. Soil microorganisms are responsible for the conversion of aldrin to dieldrin and the conversion of heptachlor to heptachlor epoxide. The products of the reaction, dieldrin and heptachlor epoxide, are also quite potent insecticides and may persist longer in the environment than their parent compounds, aldrin and heptachlor.

These are two simple examples of metabolic reactions which are known to occur in soils. In reality, the overall picture is far more complex, since one pesticide may yield 10 to 15 major metabolites prior to being completely fragmented into CO_2, H_2O, and chloride ion. These metabolic reactions also take place in plants and animal systems. The reactions encountered in plants and animals are somewhat different from those in soils and may be more complex since some metabolites from conjugates with a number of naturally occurring sugars and amino acids. We are making satisfactory progress in the isolation and identification of these metabolites from biological systems. However, the purification of these materials to remove naturally interfering substances is one of our major obstacles.

Chemical Conversion

An important class of reactions involved in soils and other biological systems are purely chemical reactions which are not associated with any living system. These reactions are less well understood than the microbial reactions of pesticides, but in a few cases they might be extremely important. For example, the chloro-s-triazines represented by the compounds atrazine, simazine, and propazine are converted to their two hydroxy analogs by purely chemical reactions in the environment. There have been detailed examinations of various biological systems to determine whether the hydroxylation of the chloro-s-triazines is a biological reaction; to this point, all have met with failure. It is now clear that the conversion of atrazine to hydroxy atrazine is a chemical reaction which is mediated and facilitated by the electronic properties of certain soil components. In plants, a natural plant constituent is responsible for carrying out this reaction.

Desulfuration reactions are also chemical reactions in some systems. Some of the best known examples of desulfuration reactions occur among the organophosphorous (OP) insecticides which contain a phosphorothioic moiety. Two important desulfuration reactions involve the conversion of parathion to paraoxon and malathion to malaoxon. In both cases, desulfuration results in an activation step with the formation of a more potent cholinesterase inhibitor.

Ecosystems

One of the most sophisticated laboratory systems for measuring the environmental fate of pesticides is the microagroecosystem. These model systems (Figure 5) permit simultaneous monitoring of pesticides in four environmental phases: soil, plant, water, and air. Nash, et al (1976) have reported on the distribution of toxaphene and DDT sprayed on cotton in one agroecosystem chamber. Volatilization of toxaphene was consistently more than twice that for DDT even though the application rate was only double. Both insecticides were concentrated in the surface 0-1 cm. depth of soil 90 days after application; plants lost about 80% of the applied insecticides during the same time period.

SUMMARY

The American pesticide industry has rapidly expanded over the last three decades. With this expansion, the usage of pesticides has also substantially increased. Parallel with the growth in production and usage has been the enactment of pesticide regulatory laws that have fostered new environmental guidelines for registration. Three important environmental parameters of a pesticide are persistence, movement, and degradation. The persistence of a pesticide depends on soil, climate, and structural features of the molecule. Pesticide movement from its original site of application represents one of the major sources of environmental contamination. Factors responsible for pesticide degradation in the environment are photodecomposition, microbial metabolism, and chemical reactions.

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Table 1.

Twelve Major Pesticide Manufacturing Companies and Their Global Sales of Pesticides

Company	1976 Sales 1976 Sales	Percent of Company Sales
Bayer	$1,125,000,000	12.8
Ciba-Geigy	933,000,000	24.0
Shell	568,000,000	15.3
Monsanto	460,000,000	10.8
Rhone-Poulenc	348,000,000	8.0
Dow Chemical	320,000,000	5.7
BASF	317,000,000	3.6
Stauffer Chemical	278,000,000	25.3
DuPont	265,000,000	3.2
Union Carbide	240,000,000	3.6
ICI	230,000,000	3.3
Eli Lilly	212,000,000	15.8
Total	5,296,000,000	12.1 (Average)

Data taken from Chemical and Engineering News, August 1, 1977.
Source--Wood Mackenzie & Co., Edinburgh, Scotland.

Table 2.

The Production and Use of Selected Pesticides in the United States
(Millions of Pounds)

Insecticides	Production	Use
Aldrin	13	12.7
Carbaryl	53	25
Carbofuran	6	5
Chlordane	20	15
Diazaninon	12	7
Disulfoton	5	5
Malathion	24	8
Methyl Parathion	51	40
Parathion	14	10
Toxaphene	76	58
Herbicides		
Alachlor	24	11
Atrazine	95	75
Bromacil	4	3
Diuron	6.5	6.7
MSMA	24	19
Trifluralin	21	17
2,4,-D	55	48

Data taken from R. von Rumker et al, EPA Contract 540/1-74-001 (1974).

Table 3.

Expenditures and Use of Insecticides for U.S. Cotton Production 1973-1974

Insecticide	Expenditures Dollars	Expenditures %	Use Acres	Use %
Dicrotophos	1,481,000	1.4	1,380,000	2.7
Disulfoton	1,640,000	1.6	746,000	1.5
Chlorphenamidine	5,180,000	5.0	4,020,000	7.9
Aldicarb	2,433,000	2.4	462,000	0.9
Monocrotophos	3,133,000	3.0	1,435,000	2.8
Azinphos Methyl	1,683,000	1.6	1,178,000	2.3
Toxaphene	1,907,000	1.9	1,631,000	3.2
Parathion	22,640,000	22.0	14,035,000	27.5
Endrin/Parathion	3,667,000	3.6	1,587,000	3.1
Toxaphene/Parathion	19,916,000	19.4	10,369,000	20.3
Other Misc. Chemicals	12,106,000	11.8	4,460,000	8.7
Other Misc. Combinations	26,923,000	26.2	9,710,000	19.0
Unidentified	121,000	0.1	57,000	0.1
Totals	102,828,000	100	51,058,000	100

Data taken from A. Aspelin, EPA Contract 68-01-1928 (1975).

Table 4.

Expenditures and Use of Herbicides for U.S. Cotton Production 1973-1974

Herbicide	Expenditures Dollars	Expenditures %	Use Acres	Use %
Trifluralin	29,092,000	40.5	7,255,000	31.4
Fluometuron	15,470,000	21.5	4,249,000	18.3
MSMA	4,472,000	6.2	3,021,000	13.1
Prometryne	3,062,000	4.3	1,384,000	6.0
Dinitramine	2,683,000	4.0	507,000	2.2
Diuron	2,536,000	3.5	1,139,000	4.9
DSMA	1,412,000	2.0	900,000	3.9
Fluorometuron/MSMA	2,633,000	3.7	963,000	4.2
Other Misc. Chemicals	4,155,000	5.8	1,506,000	6.5
Other Misc. Combinations	6,166,000	8.6	2,192,000	9.5
Unidentified	2,000		1,000	
Totals	71,863,000	100	22,917,000	100

Data taken from A. Aspelin, EPA Contract 68-01-1928, (1975).

Table 5

Relative Mobility of Pesticides in Soils

Mobility Class

5	4	3	2	1
TCA	Picloram	Propachlor	Siduron	Neburon
Dalapon	Fenac	Fenuron	Bensulide	Chloroxuron
2,3,6-TBA	Pyrichlor	Prometone	Prometryne	DCPA
Tricamba	MCPA	Naptalam	Terbutryn	Lindane
Dicamba	Amitrole	2,4,5-T	Propanil	Phorate
Chloramben	2,4-D	Terbacil	Diuron	Parathion
	Dinoseb	Propham	Linuron	Disulfoton
	Bromacil	Fluometuron	Pyrazon	Diquat
		Norea	Molinate	Chlorphenamidine
		Diphenamid	EPTC	Dichlormate
		Thionazin	Chlorthiamid	Ethion
		Endothall	Dichlobenil	Zineb
		Monuron	Vernolate	Nitralin
		Atratone	Pebulate	C-6989
		WL 19805	Chlorpropham	ACNQ
		Atrazine	Azinphosmethyl	Morestan
		Simazine	Diazinon	Isodrin
		Ipazine		Benomyl
		Alachlor		Dieldrin
		Ametryne		Chloroneb
		Propazine		Paraquat
		Trietazine		Trifluralin
				Benefin
				Heptachlor
				Endrin
				Aldrin
				Chlordane
				Toxaphene
				DDT

From Helling, Kearney, and Alexander (Advances in Agronomy 23, 147-240, 1971).

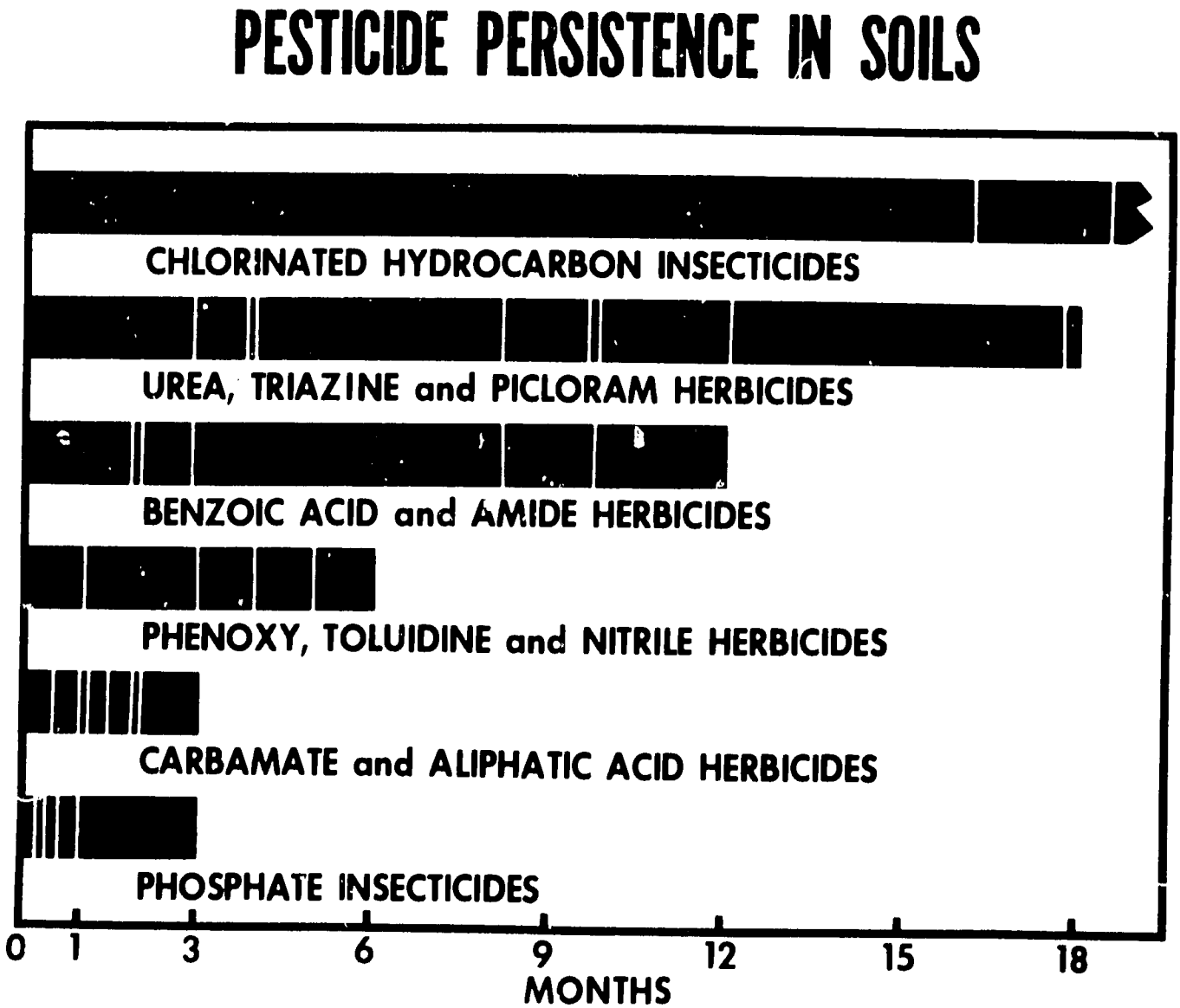

Figure 1

Soil persistence of major classes of organic pesticides. From Kearney, Nash, and Isensee, "Current Research on Persistent Pesticides," edited by Miller and Berg, C. C. Thomas, Springfield, Ill., p. 54-67 (1969).

PESTICIDE PERSISTENCE IN SOILS

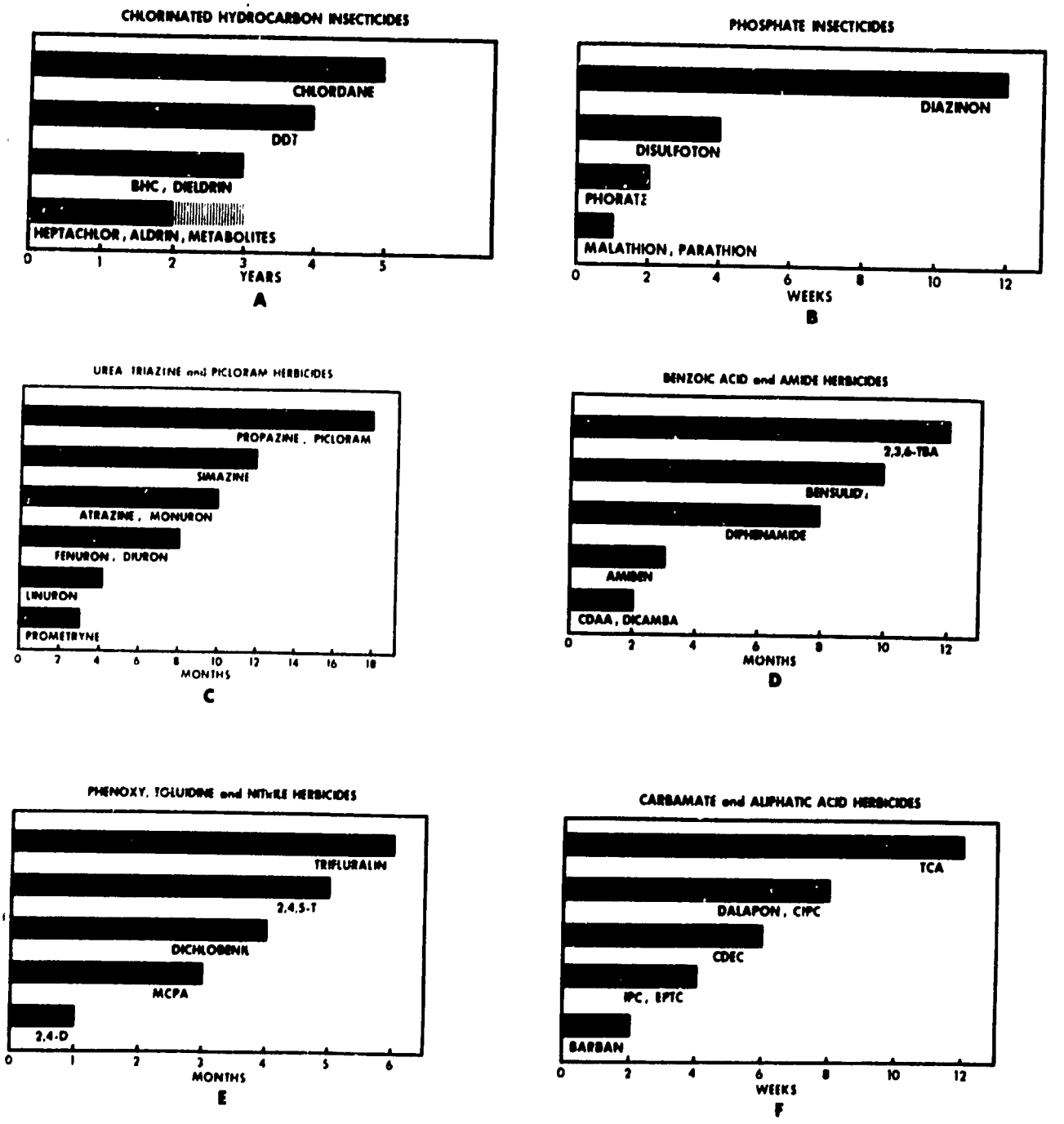

Figure 2

Soil persistence of selected organic pesticides. From Kearney, Nash, and Isensee, "Current Research on Persistent Pesticides," Edited by Miller and Berg, C. C. Thomas, Springfield, Ill, p. 54-67 (1969).

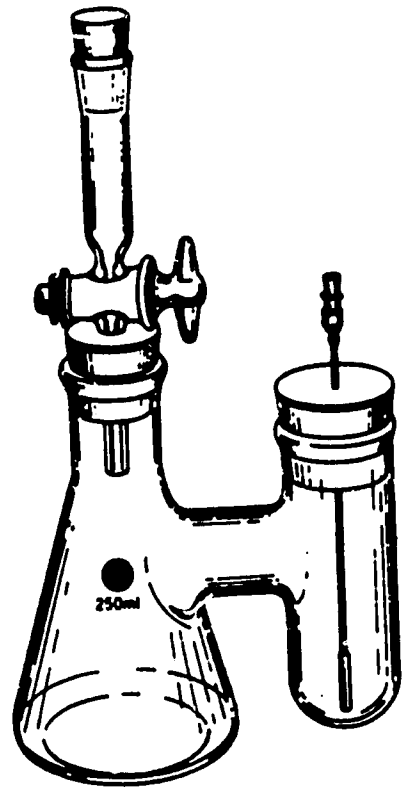

Figure 3. Soil biometer flask for studying pesticide metabolism. From Bartha and Pramer, Soil. Sci., 100, 68-70 (1965).

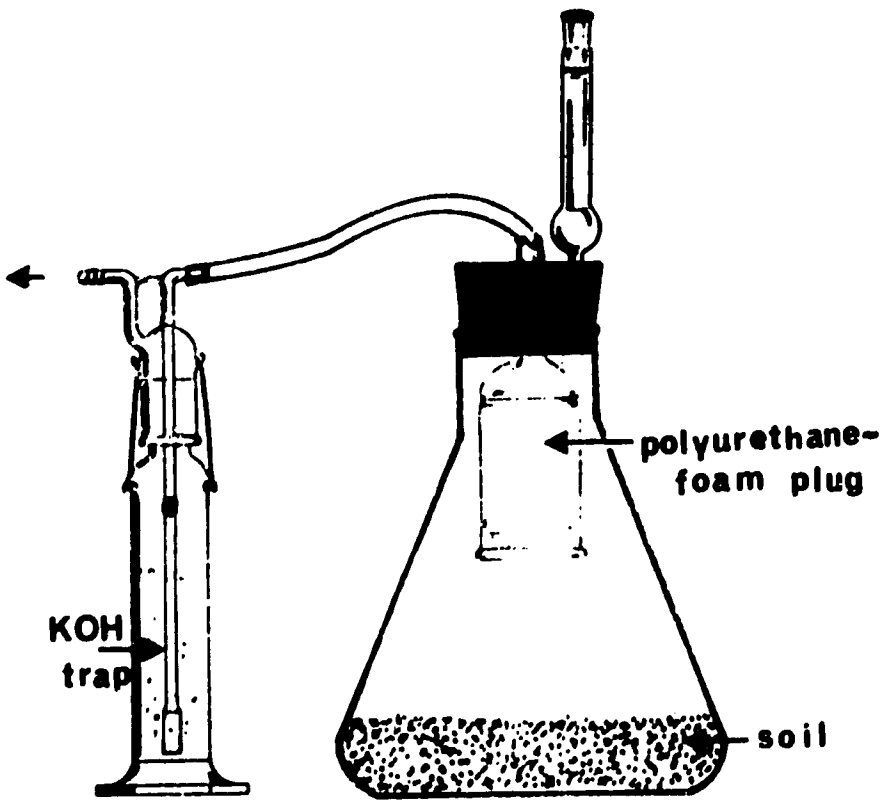

Figure 4. A simple system to measure volatility and metabolism of pesticides in soils. From Kearney and Kontson, J. Agr. Food Chem., 24, 424-26 (1976).

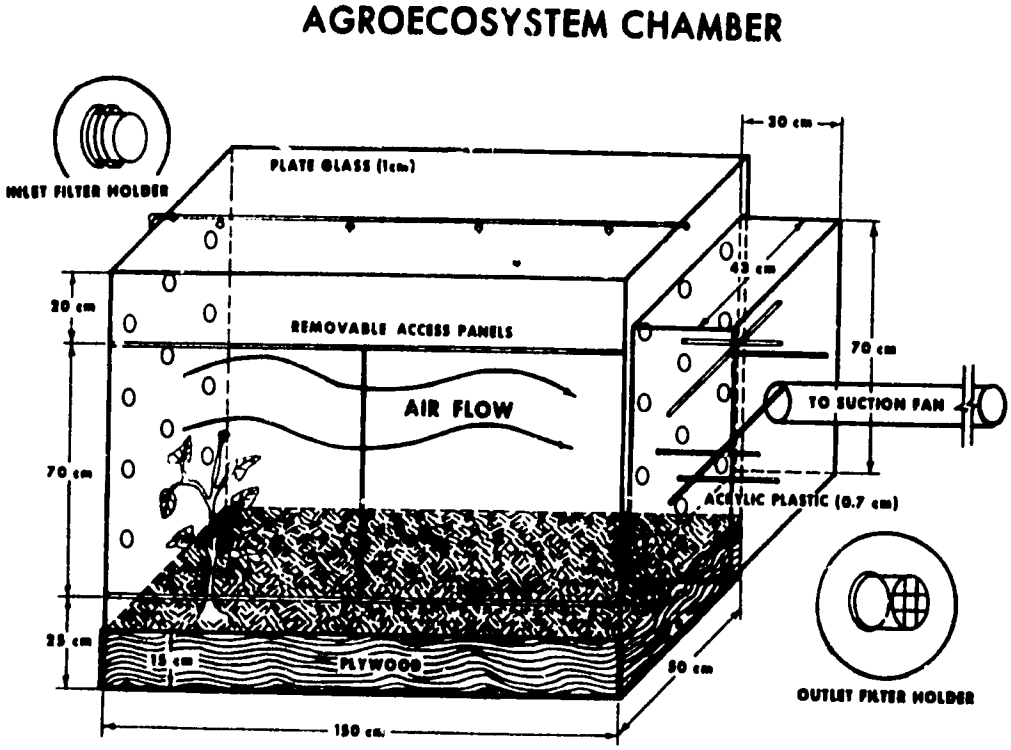

Figure 5

Design of the agroecosystem chamber for measuring pesticide dynamics in soil, air, plants, and water. From Nash, Beall, and Harris, J. Agr. Food Chem., 25, 336-41 (1977).

Halogenated Heterocycles and Heterocyclic Carbamates for Pesticides Research

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Carbamates are well known for their broad-spectrum biological activity. A huge number of aliphatic, aromatic, and heterocyclic carbamates have been tested for their toxicity to insects and microorganisms of agricultural and medicinal importance as well as for their phytotoxicity agains plants. A wide variety of these compounds proved to have well defined biological activities in these directions.

Several carbamates are now used in the field as insecticides, fungicides, and herbicides, e.g., carbaryl, lannate, temik, etc. Carbamate insecticides in general proved to be far less toxic to animals and human beings than organophosphorus compounds and consequently these received preference for use in the field.

Usually, insects develop resistance to known pesticides, and one of the methods used to overcome this resistance is the use of synergists with the applied insecticide.

In this article, a brief summary of our recent work on the chemistry of some halogenated heterocycles and heterocyclic carbamates related to this area of research is outlined.

POLYHALO-1,3-BENZODIOXOLES, 1,4-BENZODIOXENS AND RELATED SUBSTANCES

It has been shown that certain oxygen heterocycles show synergistic activity with pyrethrin as well as with carbamate insecticides and that methylenedioxy compounds are the most active members of this class. Gertler, et al (1), have reported on the activity of the methylenedioxyphenyl structures (1 and 2 in Figure 1). Meanwhile, piperonyl butoxide [3] proved to have remarkable activating properties when used as synergist with N-methyl and N,N-dimethyl carbamates (e.g., carbaryl), and it has been included in several insecticide formulations. In this connection, it has been also claimed that in some cases adulteration of carbaryl with methylenedioxy compounds enhanced its activity to insects resistant to DDT.

This prompted us to synthesize newer carbamates incorporating the 1,3-benzodioxole ring structure for evaluation as insecticides which may act as their own synergists, especially in connection with the problem of resistance of cotton worms.

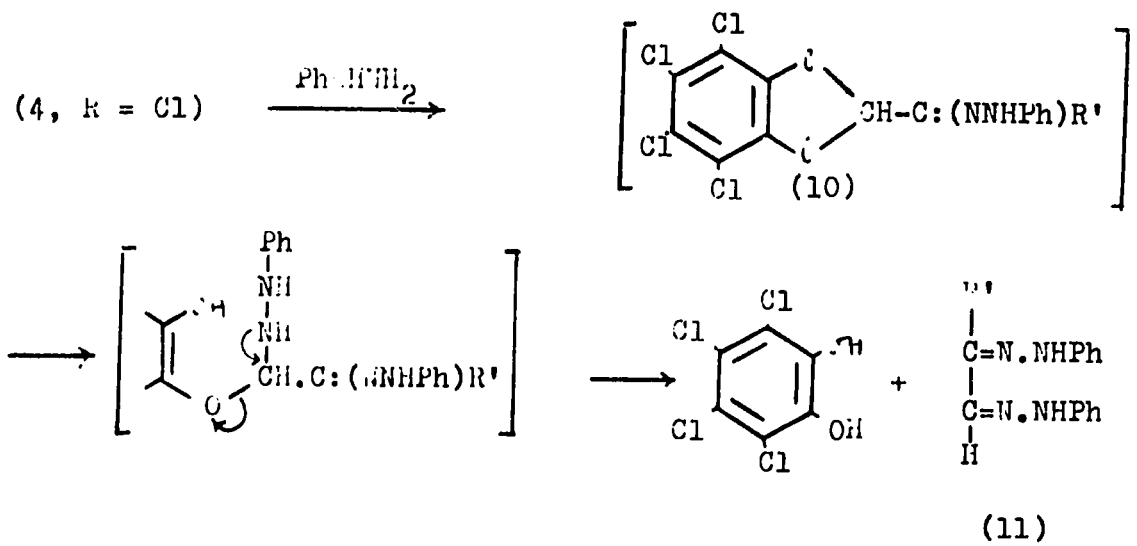
We have found (2, 3) that the high potential quinones, tetrahalo-o-benzoquinones, in contrast to other o-quinones, react readily with diazoketones to give the hitherto unknown series of the ketonic tetrahalo-1,3-benzodioxoles. Thus, 2-benzoyl- [4a], 2-p-anisoyl- [4b], 2-p-toluoyl- [4c], 2-p-chlorobenzoyl- [4d], 2-β-naphthoyl [4e], 2-(2-thienoyl)- [4f] and 2-(2-furoyl)- [4g] -4,5,6,7-tetrachloro-1,3-benzodioxoles, could be readily obtained by reacting tetrachloro-o-benzoquinone [5a] with the corresponding diazoketones [6] in boiling benzene. The bromo-analogues [4, 4 = Br] were obtained in a similar manner from tetrabromo-o-benzoquinone [5b].

The ketonic benzodioxoles [4, R = Cl] react with benzoylhydrazine to give the corresponding benzoylhydrazones without cleaving the dioxole ring. Meanwhile, with hydroxylamine hydrochloride in pyridine, the corresponding oximes [7, R'' = H] were obtained which reacted smoothly with methyl isocyanate affording the oxime carbamates [7, R'' = $CONH.CH_3$]. The latter provide a hitherto unknown series of oxime carbamates

incorporating the polyhalomethylenedioxyphenyl structure and thus favorable to be tested as insecticides which may act as their own synergists. Members of this series are actually acetophenone oxime carbamates analogues linked to the polyhalo-1,3-benzodioxole ring. Acetophenone oxime N-methyl carbamate itself proved to have pronounced insecticidal properties (4).

The carbonyl function of the ketonic benzodioxoles [4, R = Cl] was smoothly reduced with complex metal hydrides, affording the hydrols [8, R"=H] which reacted with methyl isocyanate affording the corresponding carbamates of the type [9] which provided another unknown series of polyhaloheterocyclic carbamates incorporating the methylenedioxyphenyl structure.

In contrast to the action of benzoylhydrazine and hydroxylamine, we have found (2) that 4 [R = Cl] is readily cleaved by the highly nucleophilic phenylhydrazine to give substituted arylglyoxal osazones [11] according to the following scheme through the initial intermediate formation of a phenylhydrazone of Type 10:



In support of the proposed mechanism is the fact that 4f and g, when reacted with phenylhydrazine in equimolecular ratios under mild conditions, the phenylhydrazones [10, R' = 2-thienyl and 2-furyl, respectively] were obtained which afforded the corresponding osazones upon interaction with phenylhydrazine under more drastic conditions.

In contrast to the action of phenylhydrazine, we found that hydrazine hydrate reacts with 4 to give aldazines of Type 12 which are favorable to be tested for their phytotoxicity against plants and for their antimicrobial activities. These are presumably formed through the intermediate formation of a substituted glyoxal dihydrazone of the Type 13 due to the instability of the latter (Figure 1).

The glyoxal osazones [11] were readily cyclized to the corresponding biologically important vic-triazoles [14] by copper sulfate in dioxane (2). Although several 4-aryl-2-phenyl-1,2,3-triazoles have been previously described, very little has been reported on the preparation of 2-aryl-1,2,3-triazoles with heterocyclic substituents at the 4-position. As far as we are aware, 4-(2-thienyl)- and 4-(2-furyl)-2-phenyl-1,2,3-triazoles are the first two examples.

In connection with the synergistic activity of the methylenedioxyphenyl structure, it has been reported (5) that enlarging the five-membered methylenedioxy ring to a six-membered ring (e.g., 1,4-dioxane) led to a decrease in activity but did not, however, quench it.

We investigated the possibility of synthesizing carbamates incorporating the 1,4-benzodioxan ring system which have structural analogy to the 1,3-benzodioxoles mentioned above in order to compare their insecticidal activity and to establish a chemical biological relationship.

We have found (6, 7) the tetrachloro-o-benzoquinone, in contrast to other o-quinones previously investigated, add to the acrylophenones [15] to give the ketonic dihydrobenzodioxins [16] in absence of light and thus present the hitherto unknown thermal cycloaddition of open chain α,β-unsaturated ketones to the heterodiene system of the α-dicarbonyl moiety of the quinone.

The ketonic 1,4-benzodioxins [16] reacted with hydroxylamine to give the corresponding oximes which reacted with methyl isocyanate to give the N-methyl carbamates [17] and thus provide another new series of heterocyclic oxime carbamates for evaluation as pesticides and which are analogous to the 1,3-benzodioxoles [7, R''' = $CONH.CH_3$].

The benzodioxens [16] were reduced with sodium borohydride to give the corresponding secondary alcohols [17, R'' = H, R''' = H], whereas they reacted with organomagnesium halides to give the tertiary alcohols [18, R'' = alkyl or aryl; R''' = H]. The secondary alcohols reacted with methyl isocyanate to afford the corresponding N-methyl carbamates [18, R'' = H; R''' = $CONH.CH_3$].

Tetrachloro-o-benzoquinone reacted with 2-furylacrylophenones [15, R = 2-furyl; R' = phenyl, p-anisyl, or p-chlorophenyl] in equimolecular ratios in boiling benzene in a manner different from the other acrylophenones mentioned above including the 2-thienyl analogues (7). It added to the furyl ring affording [19], leaving the vinyl side chain intact and thus presenting the enhanced dienophilic character of the furyl ring. IR, UV, and nmr spectra of 19 are in agreement with the proposed structure. The nmr spectrum of 19 [R = OCH_3] included a pair of doublets at δ 7 and 7.45 p.p.m. (J = 15 Hz) for the coupled vinyl protons of the side chain. The high J value supports the trans configuration, which has also been suggested by infrared spectrum of the compound. The n.m.r. spectrum shows also signals for the adjacent protons a and b as a doublet and quartet at 5.45 and 5.75 p.p.m., respectively. The 3 Hz coupling constant suggested the cis relationship between these protons. Signals for the c proton at the dihydrofuryl ring appeared as a doublet at δ 6.4 p.p.m.

The monoadducts [19] reacted further with tetrachloro-o-benzoquinone under more drastic conditions to give the diadducts [20] which were also obtained by reacting 15 [R = 2-furyl] with the high potential quinone in a 1:2 ratio in boiling xylene. Bromine added to the monoadducts [19] to give the biologically interesting stable dibromides [21].

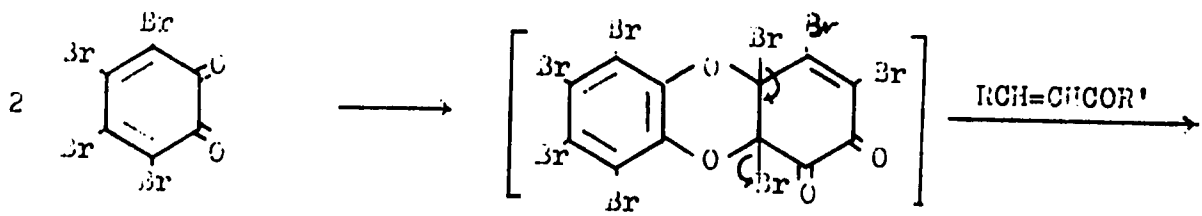
The monoadducts [19] were reduced with sodium borohydride to give the unsaturated alcohols [22].

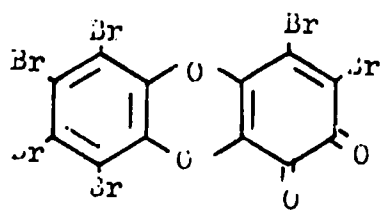
Benzylmagnesium chloride reacted with 19 to give the butyrophenones [23] through 1,4-addition to the vinyl side chain, leaving the dioxene and the dihydrofuryl rings intact. IR, UV, and nmr spectra are in accordance with the assigned structure.

In contrast to all other 1,4-benzodioxens previously investigated, we found (7) that the dioxen ring of 19 is readily cleaved by phenylmagnesium bromide under very mild conditions affording the propiophenones [24] along with tetrachlorocatechol, and the reaction mechanism has been suggested. The electronic, infrared, and nmr spectra of 24 are quite in agreement with the assigned structure. The aliphatic protons of the $CH-CH_2$ group produced a splitting pattern between 3 and 5 p.p.m. for an ABX system in the nmr spectrum.

In an attempt to prepare the bromoanalogues of the benzodioxens of 16 [R = α and β-naphthyl] by the action of tetrabromo-o-benzoquinone on the corresponding acrylophenones, the tetrabromo-2,3-dihydrobenzodioxens [25, R = 1- or 2-naphthyl] and/or the acrylophenone dibromides [26] were obtained along with the cyclic ether [27] (8).

Formation of the dihalide by the action of tetrahalo-o-benzoquinones on olefinic compounds has not been previously reported. Formation of acrylophenone dibromides apparently proceeds as follows, and the isolation of 27 from the reaction supported the proposed mechanism:





(27)

RCHBr - CHBr - COR'

(26)

R - CH = C - COR'
|
Br

(28)

With 2-thienyl acrylophenones, the corresponding α-bromo-acrylophenones [28, R = 2-thienyl] were exclusively obtained along with 27 presumably through elimination of HBr from a first formed dibromide of type 26 (9).

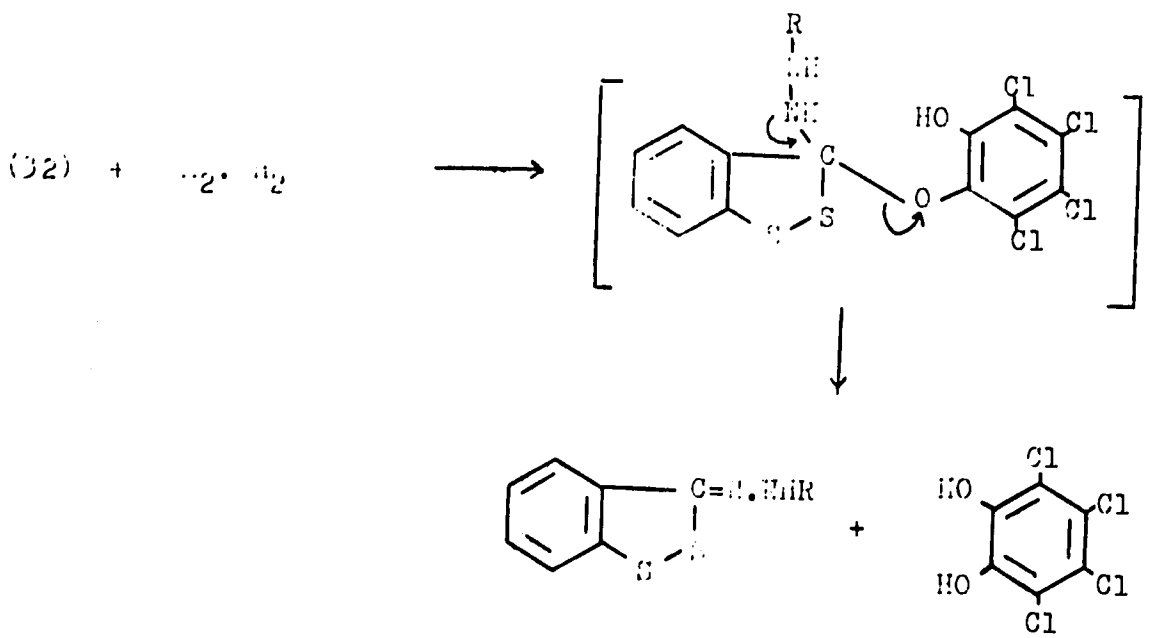
POLYHALO-1,3-BENZODIOXOLE-BENZOTHIAZINES AND -BENZODITHIOLES

It is known that some 3,1-benzoxazones and benzothiazinones as well as trithiones show phytotoxicity against plants of agricultural interest. For example, 2-phenyl-3,1-

benzoxazinone "Bentranil" [29, R = phenyl, X = O] has well-defined herbicidal properties and was usually formulated with other herbicides. 3H-1,2-benzodithiole-3-thione [30] showed postemergence phytotoxicity against plants of agricultural interest, such as Artemisia vulgaris and Chenopodium album.

In an attempt to obtain newer compounds which incorporate the polyhalo-1,3-benzodioxole with the dithiole or the benzothiazine rings for testing their phytotoxicity, we found that tetrachloro- and tetrabromo-o-benzoquinones react with 2-aryl-3,1-benzothiazine 4-thiones [29, X = S] in boiling benzene to give the hitherto unknown series of spiranes, the polyhalo spiro-1,3-benzodioxole benzothiazines [31] (12). In a similar manner, tetrachloro-o-benzoquinone reacted with 3H-1,2-benzodithiole-3-thione [33, X = S] to give the analogous polyhalo-spiro-1,3-benzodioxole - benzodithiole [32] (10). The spiranes [31 and 32] are not accessible by any other means except by applying this new reaction.

The spirane [32] reacted with hydrazines to give the corresponding hydrazones [33, X = N.NH_2 or N.NH.Ph] with tetrachlorocatechol according to the following scheme:



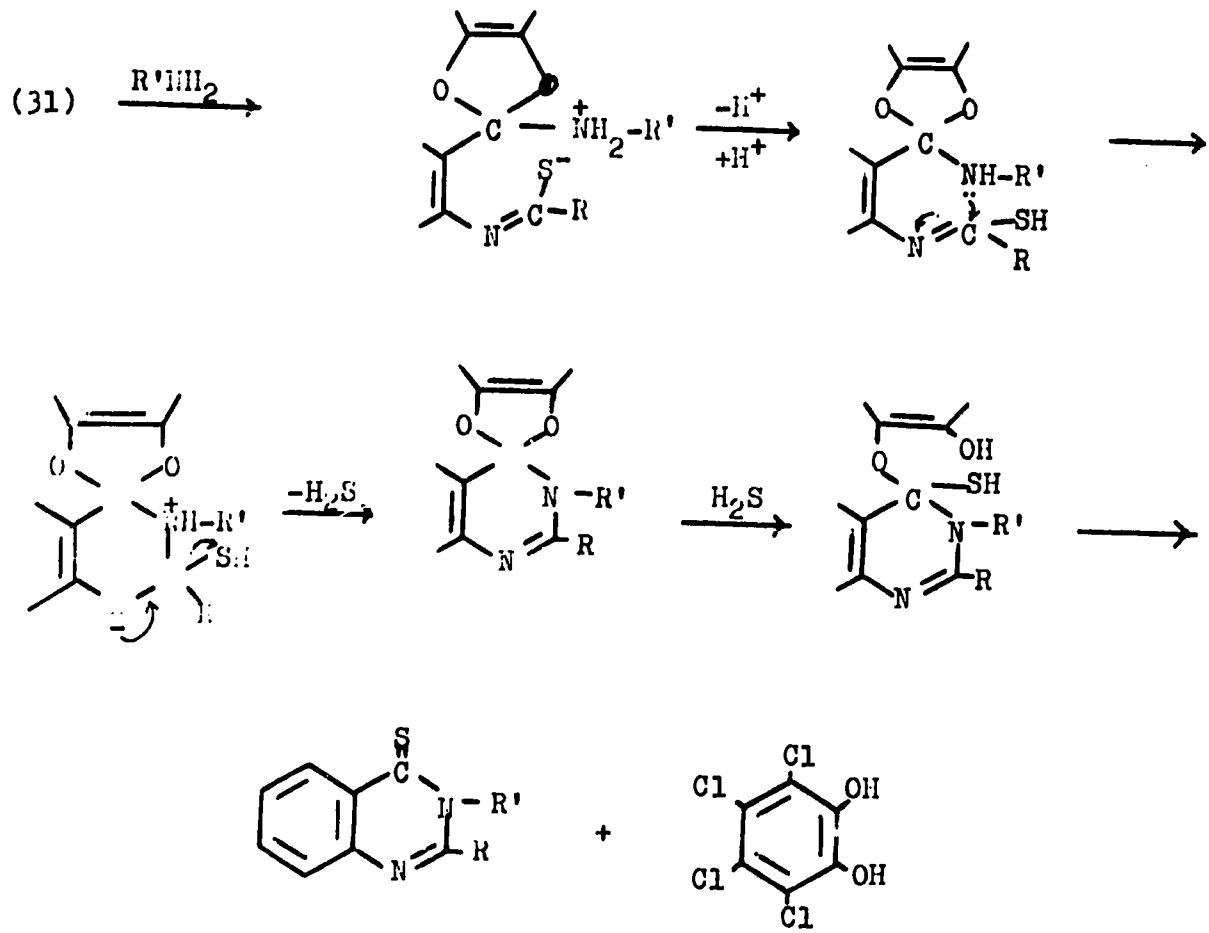
With hydroxylamine, 32 afforded the oxime [33, X = N.OH] which reacted with methyl and phenyl isocyanate affording the oxime carbamates [33, X = NOCONH.CH_3 and NOCONH.C_6H_5, respectively]. The carbamates of the cyclic disulphide structure are of value for pesticide research. They bear analogy to Lannate [34] and Temik [35] pesticides which are oxime carbamates incorporating the open chain sulphide moiety.

On the other hand, the spirane [32] reacted with amines to give the biologically important isothiazoline thiones [36] with tetrachlorocatechol (10).

In contrast to 32, we found that the spirane [31] reacts with amines and hydrazines in the same manner, affording the corresponding 2,3-diaryl-, 2-aryl-3-amino- and 2-aryl-3-phenylamino-quinazolines [37] along with tetrachlorocatechol according to the scheme on the next page (12).

A similar mechanism we have also proposed for the formation of isothiazoline thiones from 32 by the action of amines (11).

In connection with the polyhalobenzodioxoles and -benzodioxens, we have found that their spectra are characterized by exhibiting strong absorption in the 220 nm region, which we assigned to band I of benzene being red shifted to the near region because of full substitution of the benzene ring by auxochromes. This absorption is also found in the spectra of polyhalophenols and tetrahalocatechols. This characteristic absorption would help in the spectrophotometric identification of these and analogous compounds.



The IR spectra of the carbamates exhibit absorption that is due to carbonyl stretch vibrations of the carbamoyl moiety at higher frequency in the 1715 cm^{-1} region, since the ester aspect of the carbamate predominates over its amide aspect. This absorption can be utilized in the spectral determination of the carbamates.

The chemistry of the products is being further studied. Newer analogues as well as newer derivatives of the N-methyl carbamates are being prepared and the photochemistry of the carbamates will be studied.

ACKNOWLEDGEMENT

I would like to thank Dr. Nabih Saddik Girgis for the kind efforts he made while preparing and writing this article.

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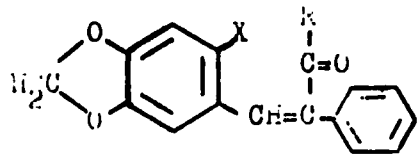
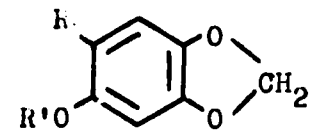
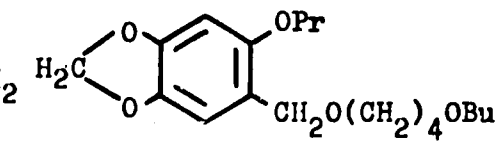


(1)



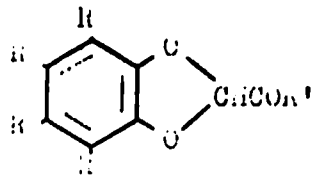
(2)



(3)

Pr = n-propyl

Bu = n-butyl



(4)

a, R = Cl ; R' = C_6H_5

b, R = Cl ; R' = $C_6H_4.OCH_3$-p

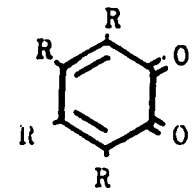
c, R = Cl ; R' = $C_6H_4.CH_3$-p

d, R = Cl ; R' = $C_6H_4.Cl$-p

e, R = Cl ; R' = $C_{10}H_7$-β

f, R = Cl ; R' = 2-thienyl

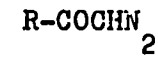
g, R = Cl ; R' = 2-furyl



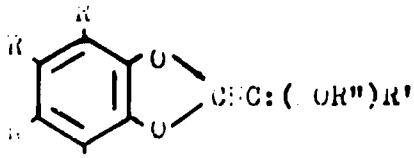
(5)

a, R = Cl

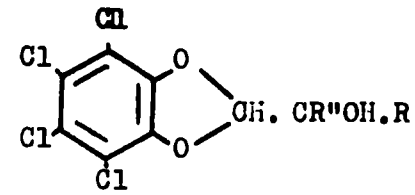
b, R = Br



(6)



(7)



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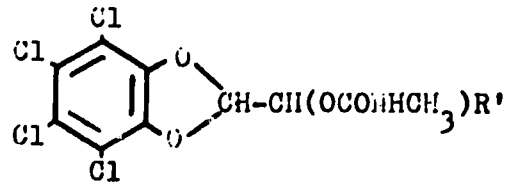

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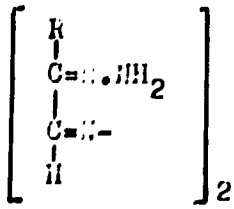

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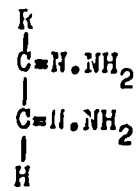

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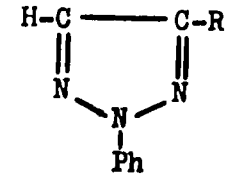


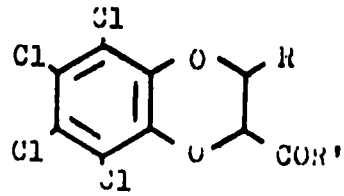
(14)

Figure 1

(Continued)

R-CH = CH-CO-R'

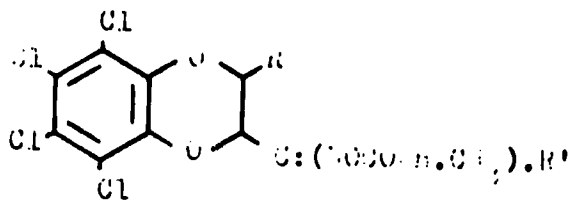
(15)



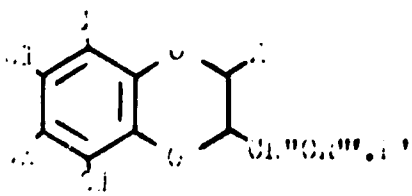
(16)

R = phenyl, α-naphthyl, 2-naphthyl or 2-thienyl

R'=phenyl, p-anisyl, p-tolyl, p-chlorophenyl, p-bromophenyl or 2,5-dimethylphenyl.



(17)



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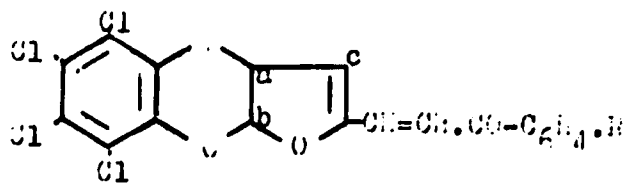
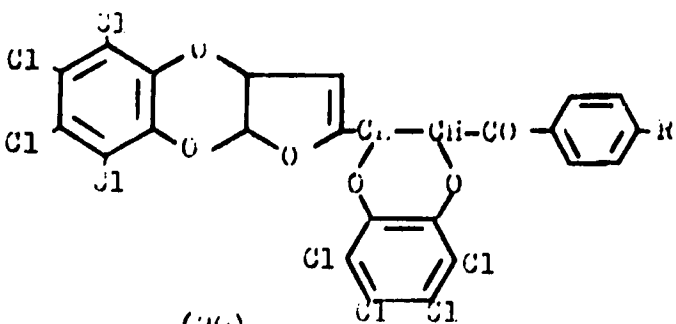


(19)

R = H, OCH_3 or Cl



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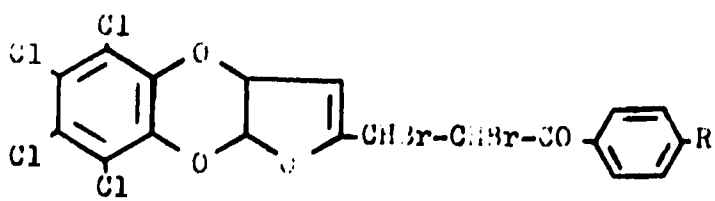

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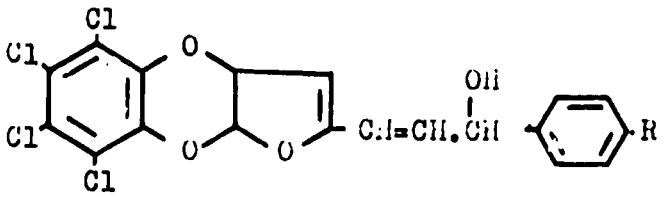

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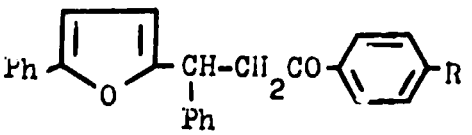

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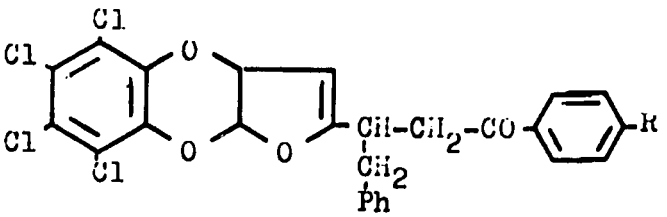

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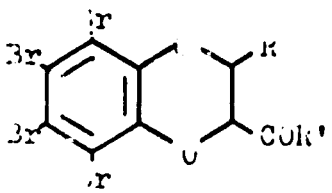
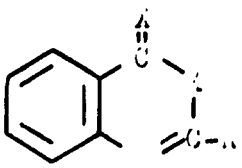


(25) = α- or β-naphthyl

R-CHBr-CHBr-CO-R'

(26)



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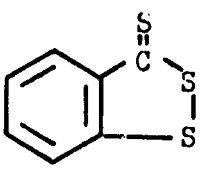

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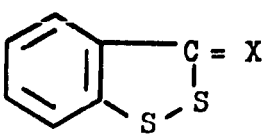

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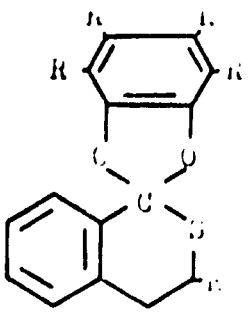

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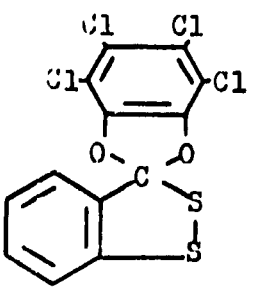
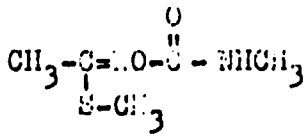


(32)

X = Cl or Br

R' = phenyl or substituted phenyl

Figure 1 (Continued)



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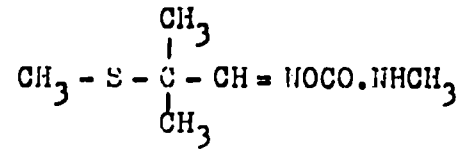

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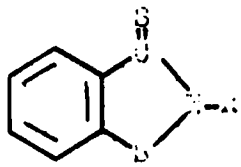

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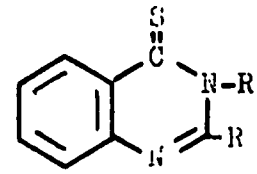

(37)

R = phenyl or substituted phenyl

R'=phenyl, substituted phenyl, NH_2 or NHC_6H_5

Figure 1 (End)

Chemistry and Environmental Impact of Pesticides in Development

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Midland, Michigan

INTRODUCTION

The greatest benefit of pesticides is their ability to help assure a varied and nutritious diet for an ever-increasing number of people, to control vector diseases such as yellow fever and malaria, and to protect livestock and nonfood crops such as cotton and forests against a variety of insects.

The insecticidal action of the earliest phosphorus compounds, such as parathion and diazinon, set a standard for pest control which even today is difficult to surpass. Toxicologically, the phosphates have in one respect an advantage over the chlorinated hydrocarbons because of the ability of living organisms to metabolize the ester functions to inorganic phosphates.

A disadvantage, in many instances, is the relatively high acute toxicity inherent in the mechanism of action. Low toxicity to animals and high toxicity to insects cannot easily be achieved. Acute toxicity is not, however, an insurmountable limitation in practice, since effective antidotes are now available. Also, the toxicologists can deal with acute poisoning with its symptomatic treatment much more easily than they can deal with chronic toxicity and its ensuing irreversible damage. Meanwhile, relatively nontoxic insecticides, including some phosphorus compounds, have been developed, and this trend is likely to continue for some time.

In spite of the many insecticides developed over the past 30 years, there remains a need for new economical insecticides with specific insecticidal activity, low toxicity to mammals, fish, birds, etc., and other properties which make them environmentally safe.

The development of an insecticide requires much more than the expensive task of synthesis and discovery of insecticidal activity. The originating organization must find a way to make it competitive with other insecticides. Success involves the interactions of many complicated and interrelated disciplines and requires that the product fit a number of economically important uses. Patent protection and good manufacturing know-how (such as engineering and packaging of raw materials, etc.) must be achieved. Toxicological, analytical, human, and environmental safety evaluation data must be generated along with development, marketing, registration, and sales expertise. A supplier must be found that is willing to provide capital and take the long-term risks necessary to recover the expenditures and losses suffered in early years of sales and development.

The chemistry discussed in this paper is restricted to the newer insecticides in use and under development in Egypt for the control of insects on cotton. Where appropriate, attempts are made to relate chemical processes under discussion to the more established and better-known insecticides that are commonly used.

The past decade has seen rapid realization of the need to weigh carefully the benefits of technology and the risks in its application. No event has driven this home so forcefully as the discovery that some of the chlorinated hydrocarbons degrade slowly and tend to be concentrated in organisms other than the target organisms. Brief discussions concerning effects on man and nontarget organisms follow the chemistry section.

CHEMISTRY

Chlorpyrifos

Chlorpyrifos and its analog, chlorpyrifos-methyl (Figure 1), are the only pyridinyl phosphate insecticides that have attained commercial significance. Their discovery and successful development are, to a great extent, attributable to an extensive investigation of chloropyridine technology that has been an integral part of the research program of the Dow Chemical Company since the late 1950's. The chemical similarities of pyridinols and phenols were an important factor in the invention of chlorpyrifos, but it is the differences that give the compound its unique chemistry and biological properties. Chlorpyrifos is a member of the 0,0-dialkyl phosphorothioate class of insecticides, a class that includes many large-volume commercial insecticides, such as parathion, diazinon, and fenitrothion.

Chlorpyrifos is prepared by the phosphorylation of sodium 3,5,6-trichloro-2-pyridinate with 0,0-diethyl phosphoro-chloridothioate (DEPCT) (Figure 2).

The phosphorylation reaction (Figure 3) is analogous to that used to produce most other 0,0-dialkyl phosphorothioate insecticides but it is especially interesting in that it involves the reaction of an ambident anion with a multifunctional substrate. Thus, the 3,5,6-trichloro-2-pyridinate anion can, theoretically, react either through its nitrogen or its oxygen atom and can attack DEPCT at either its phosphorus or one of its CH_2 carbon atoms. Fortunately, phosphorylation turns out to be by far the predominant reaction, and displacement takes place exclusively on oxygen. None of the N-phosphorylated or "pyridone" isomer has ever been detected. A very small amount of ethylation does take place and, in this case, the two isomers are formed in roughly equivalent amounts.

DEPCT, the organophosphorus intermediate used in the manufacture of chlorpyrifos, is made from phosphorus pentasulfide in a simple, two-step process (Figure 4). Treatment of phosphorus pentasulfide with ethanol gives 0,0-diethyl phosphorodithioic acid in high yield. The reaction goes equally well with methanol and other alcohols. These 0,0-dialkyl phosphorodithioic acid intermediates are valuable, not only for further conversion to phosphorochloridothioates such as DEPCT but also for direct conversion to another class of organophosphorus insecticides, the 0,0-dialkyl phosphorodithioates. This class includes many commercially important insecticides such as malathion and azinphos-methyl. Chlorination of the 0,0-diethyl phosphorodithioic acid gives DEPCT. It is noteable that the acid is best used without purification in this reaction, since many of the impurities present also give DEPCT on chlorination. DEPCT is purified by distallation, but this must be done under carefully controlled conditions as it can decompose explosively. Distillation of 0,0-dimethyl phosphorochloridothioate is even more treacherous. This process involves inexpensive raw materials and gives the desired product in high yield. It is, however, fraught with odor and waste disposal problems relating to the by-products hydrogen sulfide, sulfur monochloride, and hydrogen chloride. It has been said that there are three pounds of waste for every pound of product.

The phosphorus pentasulfide (Figure 5) required for this process is a large-volume phosphorus intermediate, only a fraction of which is used in the production of pesticides. It is manufactured by adding molten elemental phosphorus to molten elemental sulfur. The product, which is obtained in about 95% yield, is usually distilled and ground before use in the production of pesticides.

More than 30 commercial insecticides are based on phosphorus pentasulfide as the basic building block. A partial listing is given in Figure 6. The products are divided in the figure according to which of four key intermediates, 0,0-dimethyl and 0,0-diethyl phosphorodithioic acids and 0,0-dimethyl and 0,0-diethyl phosphorochloridothioates, is used in their production.

Chlorpyrifos is a reasonably stable molecule but reacts readily under some conditions, most notably with nucleophilic reagents (Figure 7). As with DEPCT, it can react with nucleophilic reagents in two ways -- by displacement on phosphorus, resulting in phosphorylation

of the nucleophile, and by displacement on carbon, resulting in alkylation of the nucleophile. Phosphorylation is the more common of these two alternatives and is favored by small, nonpolarizeable or charged nucleophiles such as hydroxide and alkoxide ions. Alkylation is favored by bulky, polarizeable, or neutral nucleophiles such as thiourea, mercaptide ions, and tertiary amines.

Hydrolysis is a good example of a reaction with a nucleophilic reagent (Figure 8). Chlorpyrifos hydrolizes slowly at pH 7, but more rapidly in basic or strongly acidic media. At 25° C. the half-life at pH 8 is about 23 days. The ratio of phosphorylation to alkylation under these conditions is about 85:15. The reaction is catalyzed by copper II ion, a phenomenon that has been attributed to copper chelate formation involving the pyridine nitrogen and phosphorothioate sulfur atom. In the field, chlorpyrifos appears to be even more stable to hydrolysis because of its low water solubility and high sorption on soil organic matter.

The isomerization of chlorpyrifos (Figure 9) to O,S-diethyl isomer can occur whenever a proper catalyst is present, because the isomerized product is of lower energy than chlorpyrifos. The reaction can be catalyzed or, actually, intitiated by nucleophilic reagents which are ethylated by chlorpyrifos, resulting in the formation of the O-ethyl O-3,5,6-trichloro-2-pyridinyl phosphorothioic acid anion. A wide variety of nucleophiles including amines and chloride ion are capable of acting as the initiator, and at high temperatures chlorpyrifos, itself, can become the initiator by virtue of the nucleophilicity of its sulfur atom. Once this anion is formed, it reacts with chlorpyrifos to form isomerized chlorpyrifos and regenerates itself. The reaction repeats itself until the anion is removed from the system by a side reaction or other means. Other mechanisms of isomerization are also likely, and further degradation of the isomerized chlorpyrifos is known to take place at elevated temperatures. Diethyl sulfide is a major product of such decompositions.

Chlorpyrifos is readily oxidized to chlorpyrifos-oxon (Figure 10) by common oxidizing agents such as nitric acid, hydrogen peroxide, and bromine water. The mechanism of this reaction is not well understood, but it is mentioned because of its profound influence on the biological and environmental properties of chlorpyrifos and, indeed, all organophosphorus insecticides containing the P=S moiety.

Diflubenzuron

Diflubenzuron (Figure 11) is an exciting recent development in insecticide chemistry, as it involves a new type of insecticidal compound as well as a new mode of action for insecticides. Philips-Duphar discovered this compound around 1970 as a result of an in-depth screening program in which the effect of compounds on insects over a long period was observed, coupled with a continuing synthesis program on compounds related to dichlobenil, the active ingredient of Casoron* herbicide. The combination of this compound with chlorpyrifos appears to take excellent advantage of the strengths of each and is sold as DC 702 insecticide for use in Mideast cotton.

Diflubenzuron can be manufactured from dichlobenil in a three-step process (Figure 12). Treatment of this herbicide product with potassium fluoride results in an exchange of the chlorine atoms for fluorine. The intermediate obtained, 2,6-difluorobenzonitrile, is hydrolyzed to its amide, and this is coupled with p-chlorophenyl isocyanate to obtain the acylurea. The final reaction in this sequence is a very clean one, but the first two present considerable waste problems in dealing with the by-product potassium chloride containing fluoride ion and in recovery of the sulfuric acid reaction medium. The production of dichlobenil, itself, is no easy matter and, thus, the commercial production of diflubenzuron is a significant accomplishment.

There is little published about the *in vitro* chemistry of diflubenzuron. It can be inferred from other investigations that the compound is a fairly stable one under most

* Trademark of Philips-Duphar

circumstances. Hydrolysis (Figure 13) appears to take place primarily by displacement at the benzoyl carbon atom, resulting in the formation of 2,6-difluorobenzoic acid and p-chlorophenylurea. The reaction is probably acid catalyzed. Diflubenzuron is a fairly strong acid and easily forms an anion with bases. This anion can be alkylated or acylated to obtain derivatives.

Phosfolan and Mephosfolan

Phosfolan and mephosfolan (Figure 14), are two closely-related heterocyclic phosphoramidates that were discovered by American Cyanamid in the early 1960's and developed primarily for use on Mideast cotton. They contain the dialkyl phosphoryl moiety in common with a large number of dialkyl phosphate insecticides, such as dichlovos and dicrotophos, and can be considered as members of the same class. They are, however, very remarkable organophosphorus insecticides in that they contain no obvious leaving group and thus would not be expected to inhibit acetylcholinesterase or kill insects.

It is tempting to speculate that the compounds undergo a rearrangement *in vivo* to form a transient systox-like metabolite (Figure 15) which may be the actual toxicant. There is no known evidence, however, that this is the case.

Phosfolan and mephosfolan can be manufactured from 1,2-ethane and 1,2-propanedithiol, respectively (Figure 16). Treatment of these dithriols with cyanogen chloride in a medium consisting of ethanol, hydrogen chloride and an aromatic hydrocarbon gives the required 2-imino-1,3-dithiolanes. These intermediates are phosphorylated with diethyl phosphorochloridate and a tertiary amine acid acceptor to obtain the subject insecticides.

The diethyl phosphorochloridate (Figure 17) used in the manufacture of phosfolan and and mephosfolan can be obtained by treating phosphorus trichloride with ethanol and then sulfuryl chloride. The yield of distilled product obtained is over 90%. This process involves several chemical reactions, and at least two alternate pathways are probably operative. Phosphorus trichloride reacts with ethanol to produce either triethyl phosphite or diethyl phosphorus acid, depending on the conditions, and especially whether or not the by-product hydrogen chloride is removed. Each of these intermediates is known to react with sulfuryl chloride--or just plain chlorine--to produce diethyl phosphorochloridate in good yield. This situation, of course, gives potential manufacturers of diethyl phosphorochloridate two additional possible starting materials that are commercially available.

Back-integrating still further (Figure 18), phosphorus trichloride, the basic building block for these compounds, is produced by chlorination of elemental phosphorus. Phosphorus trichloride itself is used as the reaction medium and must be present to moderate the highly exothermic reaction. Continuous processes are normally used. Like phosphorus pentasulfide, phosphorus trichloride is a very large-volume phosphorus intermediate, only a small fraction of which is used for the production of pesticides.

Phosphorus trichloride is, nevertheless, the basic building block for over 20 commercial insecticides, including profenofos, which will be discussed later. A number of these are noted (Figure 19). They are are divided according to the organophosphorus intermediate involved in their production. As can be seen, trimethyl phosphite is the most important intermediate from the point of view of the number of pesticides utilizing it.

Little is known about the reactivity of phosfolan and mephosfolan. It can be predicted that despite the fact that they are phosphates and phosphates normally hydrolyze faster than phosphorothioates, the compounds are fairly stable to base hydrolysis because of the lack of a good leaving group. Dealkylation or ring cleavage is likely uder these conditions.

As with other phosphoramidates, hydrolysis under acidic conditions is likely with cleavage of the P-N bond (Figure 20). This is due to protonation of the nitrogen atom.

Profenos (Figure 21) is a member of a very recently discovered and developed class of

phosphorothioate insecticides, the O-ethyl S-propyl phosphorothioates and dithioates. Other members of the class include Tokuthion* and Bolstar** insecticides. The remarkable aspect of this class of insecticides is the fact that in spite of all the O,S-dialkyl phosphorothioates investigated over the years, those with the O-ethyl S-propyl combination have only recently been found to possess uniquely strong insecticidal properties. CIBA-Geigy is the originator and developer of this compound.

As indicated earlier, the manufacture of profenofos is based on phosphorus trichloride (Figure 22). This can be converted to profenofos in several ways; the chemistry we consider to be most likely used will be presented. A portion of the phosphorus trichloride is converted to triethyl phosphite with ethanol and triethylamine. This is equilibrated with more phosphorus trichloride to obtain diethyl phosphorochloridite. Every possible combination of ethoxy and chloro substituents on phosphorus is formed in this exchange reaction, but the desired product is the predominant one and can be isolated by distillation. This organophosphorus intermediate reacts with propylsulfenyl chloride, which is the product of dipropyl disulfide and chlorine, to form O-ethyl S-propyl phosphorochloridothioate and ethyl chloride in an Arbuzov-type reaction. Profenofos is obtained by phosphorylation of 4-bromo-2-chlorophenyl with this phosphorochloridate and an acid acceptor.

Very little has been published about the reactivity of this new insecticide as yet. By comparison with other O,S-dialkyl phosphorothioate esters, however, one can predict that profenofos will be a relatively reactive compound and that it will react in a number of different ways (Figure 23). Hydrolysis, for example, should proceed readily, and three separate reactions should be observed: displacement at phosphorus with elimination of 4-bromo-2-chlorophenol, displacement at phosphorus with elimination of propanethiol, and displacement at carbon with elimination of the ethyl group.

Fenvalerate

The recent discovery and development of analogs of the ancient, naturally occurring pyrethroid insecticides that are spectacularly active in agronomic crops is a tremendous tribute to the tenacious research programs of Sumitomo Chemical and Michael Eliott and his co-workers at the Rothamstead Experiment Station in Great Britain. The dramatically increased photochemical stability of these compounds as compared to the natural pyrethroids is the principal property responsible for their activity in the field as well as indoors. Fenvalerate appears to be one of the most promising of this class of insecticides (Figure 24). Looking at the structure of this compound, one is hard-pressed to see much chemical resemblance to the natural pyrethrins. The ester linkage is just about the only common feature. Examination of three-dimensional models, however, reveals that they are related in a spacial sense. This plus its known roots in pyrethroid chemistry and similar effect on insects is enough to place it in the synthetic pyrethroid group. The compound contains two asymmetric centers and, therefore, two diasteriomeric and four optical isomers. The commercial product is a mixture of all of these.

The manufacture of fenvalerate (Figure 25) involves a long and complex set of chemical processes which makes the compound rather expensive on a per-pound basis. In order to simplify this somewhat for discussion, the preparation of two key intermediates, m-phenoxybenzaldehyde and p-chlorophenylacetonitrile, will not be presented. The process can be considered in three portions: preparation of the alcohol, preparation of the acid chloride, and the condensation of these units. The required alcohol is made by the addition of hydrocyanic acid to m-phenoxybenzaldehyde. This is classical chemistry and it goes readily. The production of the acid can be achieved by isopropylation of p-chlorophenylacetonitrile, using a phase transfer catalyst. The discovery that these catalysts are effective in this system is an important factor in making the production of fenvalerate possible. Hydrolysis of the resulting α-isopropyl-p-chlorophenylacetonitrile to the acid and conversion of this acid to its acid chloride using standard techniques gives the other required intermediate.

* Trademark of Nihon Tokushu
** Trademark of Bayer Leverkusen.

Finally, the alcohol and acid chloride can be condensed in the presence of an acid acceptor to obtain fenvalerate.

Fenvalerate, as has been mentioned previously, was chosen for development, partially because of its resistance to photodegradation. It does, however, react slowly in u.v. light with elimination of carbon dioxide (Figure 26). The compound hydrolyzes fairly readily with cleavage of the ester linkage and elimination of hydrocyanic acid. This ease of hydrolysis is a very important factor in its environmental and toxicological behavior.

ENVIRONMENTAL ASPECTS

Insecticides are obviously designed to be biologically active against target pests. However, we must also define the potential activity on nontarget organisms including birds, fish, wild and domestic animals, and man himself. A few countries require the definition of this total impact on the environment before the product can be registered for use.

The toxicity of a chemical is of primary concern in defining its potential environmental impact. The studies required for this definition are numerous and take over three years to complete. The potential for environmental impact of a chemical depends on its toxicity, the concentration present, duration of its presence, and opportunity for exposure.

Acute or single exposure studies are required to gather information primarily applicable to the users of the pesticide. In the acute studies conducted in laboratory animals, we define the potential for hazard that may occur to individuals which may be producing, formulating, mixing, or applying the pesticide. These tests include exposure as may be encountered by ingestion, skin contact, inhalation, or eye contact during the various functions required to be performed in the production and then actual application of the pesticide.

The data from the acute studies enable preparation of the precautionary statemements that appear on the pesticide label to minimize problems in use. For example, the acute toxicity of the insecticides of importance in Egypt are as follows:

Product	Acute Oral LD_{50} In Male Rats, mg./kg.	Dermal LD_{50} In Rabbits mg./kg.
Chlorpyrifos	163	~2000
Diflubenzuron	>2000	>2000
Mephosfolan	8	9
Phosfolan	8	240 (Formulated)
Profenofos	358	~3000

In addition to the acute toxicological studies, it is necessary to define the potential response to long-term exposure of the product. This is usually determined by conducting lifetime dietary feeding studies in rats and mice. In these studies, the investigator is determining the dose level which causes an effect, which target organ is affected, and what is the effect. With most organophosphate insecticides, the effect first observed is cholinesterase inhibition. One then must determine whether the amount of the pesticide or its metabolite which produced an effect in laboratory studies may be present in the food of man or his animals. This requires definition of the quantity of the pesticide residue which may exist in the food crop at the time of consumption.

Considerable time, effort, and expertise are required to obtain residue information. As analytical knowledge progresses, we are now able to identify residue levels in the parts per billion range.

The definition of the quantity or level of pesticide residue in the consumed crop is correlated with the toxicological data derived from numerous studies to define a safety factor. This indicates the possible response by nontarget organisms to ingestion of the food crop containing a detectable residue. By varying the time between last application of the pesticide and harvest, the potential residue level can be reduced significantly as well as the toxicological significance of the residue (Hoerger and Kenaga, 1972).

Despite the limitations of biological test methods, it is possible to increase one's confidence in estimating potential hazards, usually to an acceptable risk level. Evaluation of hazards are made through the use of data representing maximum and minimum values from each environmental parameter, such as concentration and fate of pesticide residues, toxicity of residues to various broad categories of organisms, stability and duration of residues, and exposure to these chemicals by various indicator organisms based upon laboratory and field data. The most developed approach is accomplished by measuring residues of pesticides in various environmental segments using accurate analytical methods and matching these residues with their corresponding toxicity to environmental indicator species of organisms over various periods of time, both acute and chronically.

The principal mode of measurement of toxicity of pesticides to wild mammals and to birds is through oral intake of measured concentrations in the diet (p.p.m.). These concentrations can be factored to mg./kg. of body weight/day when the dietary intake of the organism is known. The pesticide can be inserted into the animal in a single dose once a day for a direct mg./kg./day measurement.

The principal mode of measurement of toxicity to aquatic organisms is via the concentration (p.p.m.) of the pesticide in the water surrounding the organism. While it is not easily done with small organisms, or under field conditions, a single oral dose (especially for fish) can also be given under laboratory conditions.

Interpretation of simplified laboratory biological tests, while useful, rarely accounts for all of the significant variables in field tests, since constant changes in organisms and in pesticide residue levels occur in field tests. It is easy to oversimplify the evaluation of pesticides by the use of measurements from biological test methods which are misleading or wrongly interpreted. Government regulations and test method protocols promulgated by government regulatory agencies must be developed which can be used to evaluate accurately the unique biological, physical, and chemical properties and the use pattern of each candidate pesticide.

Considerable effort is spent in determining what is the fate of the pesticide once it has been introduced into the environment. As previously mentioned, the environmental impact of any pesticide is dependent on the concentration and duration of its presence. To define the duration of its presence, numerous tests are conducted (Figure 27).

Soil metabolism, soil persistence, degradation, and translocation in water are determined as well as the fate of the pesticide in air. We also need to know the quantity of the pesticide or its metabolite which may be available as a residue in food (Figure 28).

To assist in the evaluation of the duration of a pesticide in the environment, it is necessary to know the physical and chemical properties of the pesticide. Vapor pressure, water solubility, and particularly the octanol-water partition coefficient are useful values in the determination of environmental fate and potential residues in various compartments of the environment.

Another factor in defining the duration a pesticide resides in the environment is the determination of its metabolic pattern.

The metabolic pattern for a specific pesticide is often similar in various plants and animals, although differences can and do occur, thus necessitating studies in a number of species. Some pesticides are easily metabolized in animals and not in plants. The most omnipresent and versatile metabolizers are microorganisms, whether in animals, water, or soil. Some compounds which do not hydrolyze or photolyze easily in water are readily degraded by microorganisms. Some compounds hydrolyze with difficulty but photolyze easily.

Variations of pH in water solutions, water buffering, water sediments, temperature, and other physical and chemical factors are needed to isolate important degradative forces for pesticide molecules. Although one can argue with the test methods and reasons for running certain environmental chemistry residue and metabolism tests, the proposed "Guidelines for Registering Pesticides in the United States" (EPA 1975a), and "Registration, Reregistration, and Classification Procedures" (EPA 1975b) represent an organized approach to the resolution of the quantitative and qualitative evaluation of the metabolites and altered products of applied pesticides.

The next step in the evaluation of the impact on the environment is to determine the rate of dissipation of various residues of the pesticide. Much residue dissipation data are obtained through laboratory tests such as half-life determinations in soil, water plants, and animals. Determination of physical, chemical, and biological properties such as volatility, photolysis, microbial degradation and hydrolysis are useful preliminary tools for estimating residues in field tests. Consideration of data from a number of pesticides makes it obvious that their individual dissipation rates in air, soil, water, plant, and animal media vary greatly. Some pesticides are most stable in plants, others in water, animals, or soil -- often being entirely different in relative value -- depending on the stability of the compounds in the specific media. However, there is no scientific reason for not being able to calculate the approximate dissipation rates in various media after performing the basic pesticide stability and movement tests previously mentioned.

Given the modern analytical equipment and know-how, chemists need the guidance of biologists and biochemists as to the critical sites of biochemical action, toxicity, storage, and excretion in animals and plans for which the more sensitive analytical techniques can be used to match residues with toxicity.

Man and the Environment

We have just discussed the various considerations which are applied to determine the impact of the pesticide on the environment. A rather important component in the environment is man himself. We must be concerned with the possible effects of any pesticide on man at the research, production, application, and consumption levels. We accomplish this through the use of good industrial hygiene practices.

The occupational arena is a significant part of the total ecological system. Since exposure levels of chemicals can be measured, we can exert some control over the exposure levels and make contributions to the health and well-being of the people in the work area. These conditions can favorably affect the impact of the total system on our population, since a worker may spend one fourth of his time in an occupational area.

In controlling the occupational environment in the interest of health and well-being, establishing acceptable exposure limits for a healthful environment are necessary. In the United States these acceptable exposures are expressed as "acceptable concentrations" by the American National Standards Institute and as "threshold limit values" by the American Conference of Industrial and Governmental Hygienists. These limits are not exacting scientific thresholds of response. They are the judgments of people with knowledge and experience. The intelligent use of these limits depends on the understanding and judgment of the people who must control the occupational environment.

Industrial hygiene is the science of protecting man's health through the control of the work environment. Industrial hygiene is both a science and an art. It encompasses the total realm of control, including recognition and evaluation of those factors of environment emanating from the place of work which may cause illness, lack of well-being, or discomfort among workers or among the community as a whole.

Today, we see a blending of the functions of the industrial hygienist with those of occupational medicine. A tenet of our modern society is that every worker has the right to the fulfillment of his spiritual and material needs, while at the same time enjoying freedom from fear, trauma, and disease. Emphasis must shift from correction to preventative medicine and industrial hygiene. Occupational medicine is now an integral part of the

change. The rapid advancement in automation of analysis provides a tremendous challenge in the field of environmental control.

The industrial hygienist must be a competent, qualified individual educated in engineering, chemistry, physics, medicine, or a related biological science. His abilities may encompass three major areas (Figure 30): (1) recognition of the interrelation of environment and industry, (2) evaluation of the impairment of health and well-being by work and the work operations, and (3) the formation of recommendations for alleviation of such problems.

The scope of industrial hygiene is threefold. It begins with the recognition of health problems created within the industrial atmosphere. Some of the more frequently encountered causes of these problems are: chemical (liquid, dust, fume, mist, vapor, or gas); physical energy (electromagnetic and ionization radiation); noise, vibration, and exceedingly great temperature and pressure extremes; biological (in the form of insects, mites, molds, yeast, fungi, bacteria, and viruses), and ergonomic (monotony, competitive motion, anxiety, fatigue, etc.). These stresses must all be evaluated in terms of their danger to life and health as well as their influence on the natural body functions.

The second heading encompassed within the scope of industrial hygiene is that of evaluation. The work atmosphere must be evaluated in terms of long-range as well as short-range effects on health. This can be accomplished by a compilation of knowledge, experience, laboratory experimentation, and quantitative analytical data in the workplace.

A unique field, industrial hygiene, employs the chemist, physicist, engineer, mathematician, and physician in order to fulfill adequately the responsiblity inherent in the profession, which include the following (Figure 31):

1. Examination of the industrial environment, including the estabishment of baselines.

2. Interpretation of the gathered data from studies made in the industrial environment.

3. Preparation of control measures and proper implementation of these control measures.

4. Creation of regulatory standards for work conditions.

5. Presentation of competent, meaningful testimony when called upon to do so by boards, commissions, agencies, courts, or investigative bodies.

6. Preparation of adequate warnings and precautions where dangers exist.

7. Education of the work community in the field of industrial hygiene.

8. Conduct an epidemiologic study to uncover the presence of occupational-related illnesses.

Those people responsible for suggesting acceptable limits or for using acceptable limits are part of the ecological system -- the industrial hygienist, the physician, the toxicologist, and all the other environmental control people. The effectiveness of their operation can have a very significant effect on the occupational environment .

In conclusion, it may be stated that the successful development and production of pesticides in an effective and environmentally safe manner is clearly more than process chemistry and more than simple biology. It requires the marshalling of a complex of technologies and capital resources sufficient to cope with a multitude of concerns and finance a variety of production and backup hardware.

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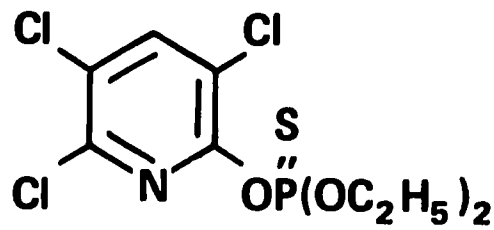
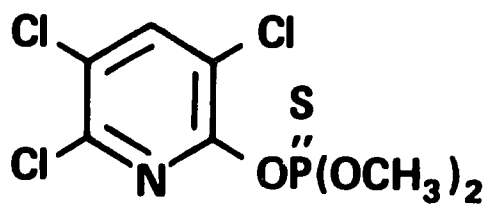


CHLORPYRIFOS

0,0,Diethyl 0-3,5,6-Trichloro-2-Pyridinyl Phosphorothioate
Dursban® Insecticide
Lorsban® Insecticide
DOWCO® 179



CHLORPYRIFOS-METHYL

0,0-Dimethyl 0-3,5,6-Trichloro-2-Pyridinyl Phosphorothioate
Reldan® Insecticide
DOWCO® 214

Figure 1

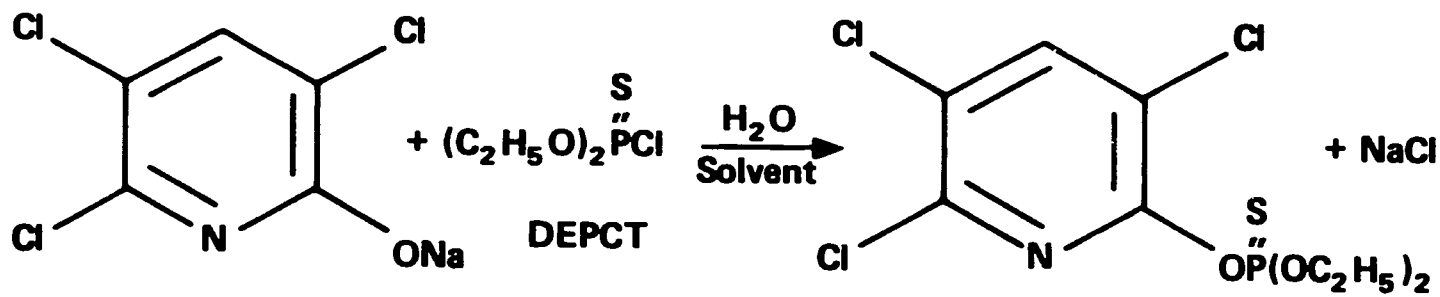

Cl
Cl
Cl
N
ONa
+ (C2H5O)2PCl
S
DEPCT
H2O
Solvent
Cl
Cl
Cl
N
S
OP(OC2H5)2
+ NaCl

Figure 2

Slide 3

POSSIBLE REACTIONS IN "PHOSPHORYLATION"

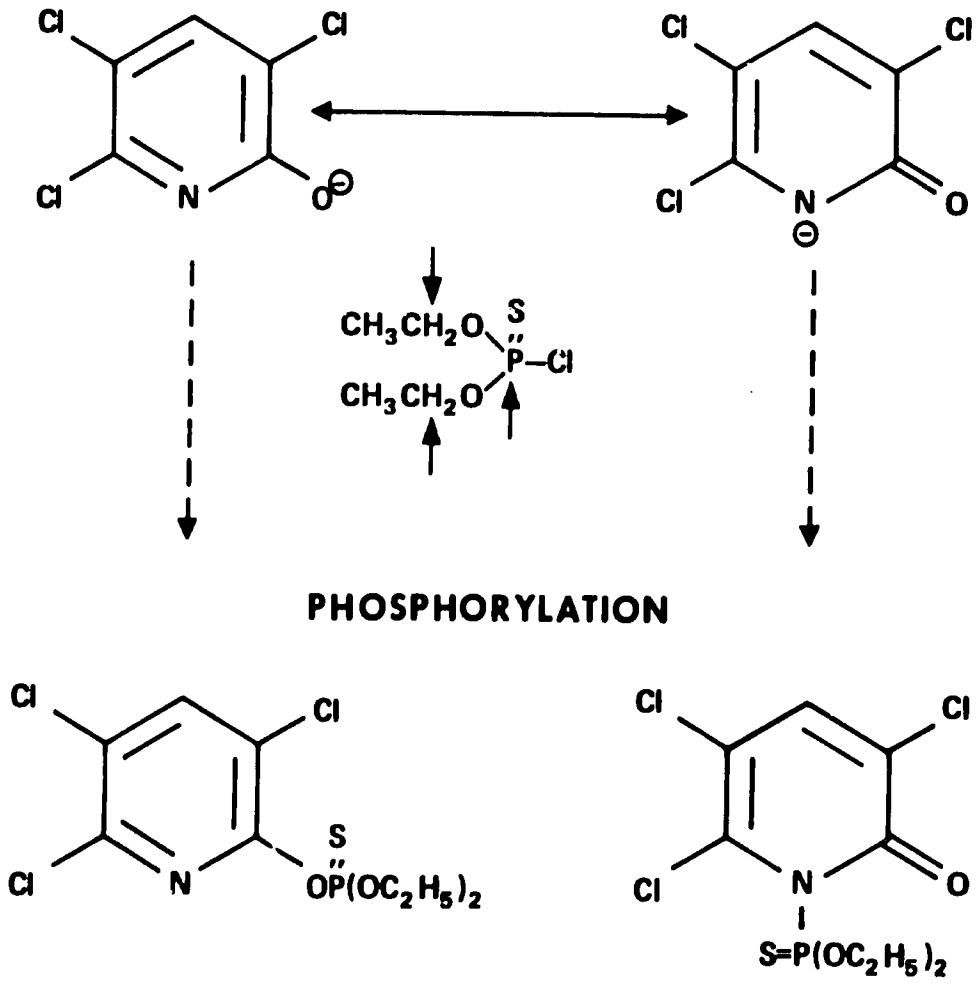


Figure 3

POSSIBLE REACTIONS IN "PHOSPHORYLATION"

ETHYLATION

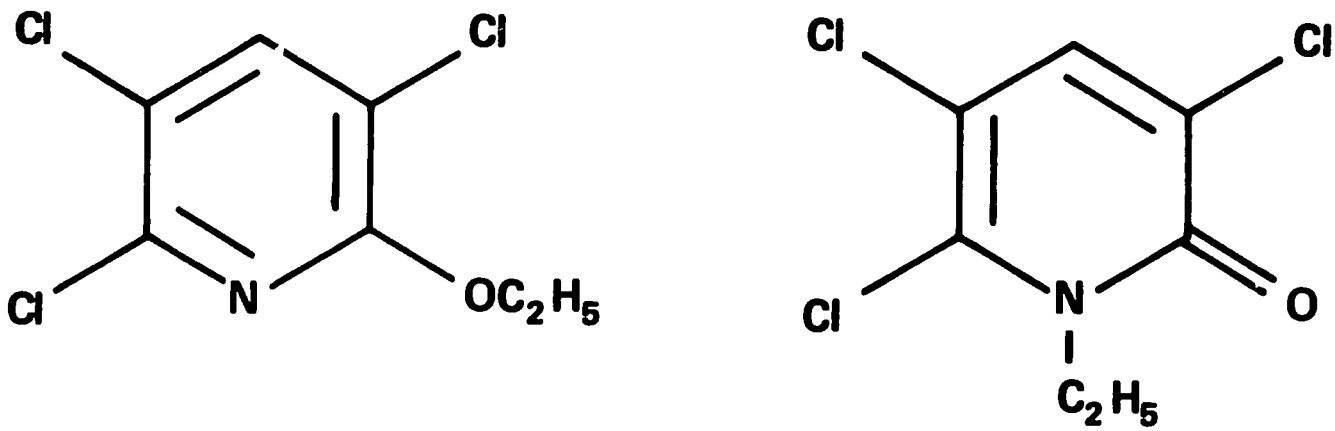


Figure 3A

DIETHYL PHOSPHOROCHLORIDOTHIOATE PROCESS CHEMISTRY

$$P_2S_5 + 4C_2H_5OH \longrightarrow 2\ (C_2H_5O)_2\overset{S}{\overset{\|}{P}}\text{–}SH + H_2S$$

$$2\ (C_2H_5O)_2\overset{S}{\overset{\|}{P}}SH + 3Cl_2 \longrightarrow 2(C_2H_5O)_2\overset{S}{\overset{\|}{P}}Cl + S_2Cl_2 + 2HCl$$

Figure 4

PHOSPHORUS PENTASULFIDE

$$P_4 + 10S \xrightarrow[\text{Melt}]{} P_4S_{10} \quad (P_2S_5)$$

Figure 5

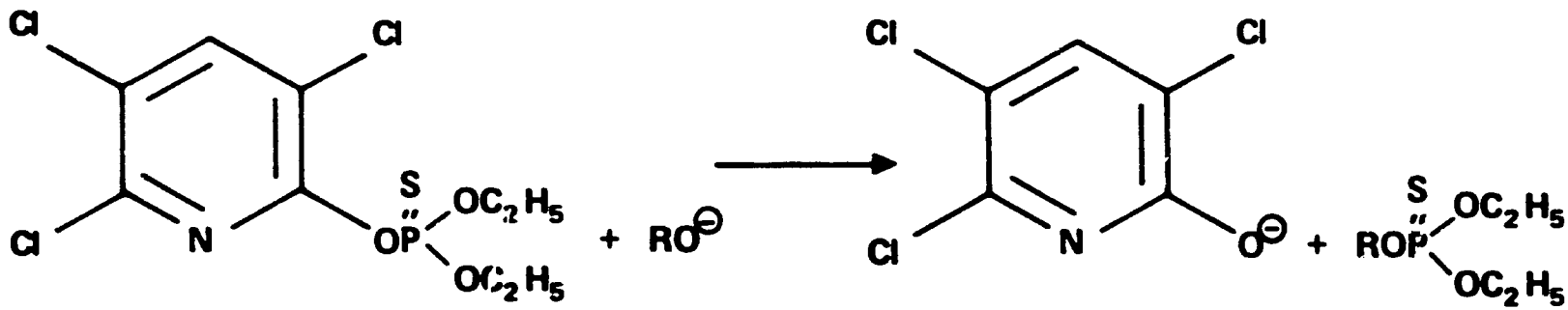
SOME ORGANOPHOSPHORUS INSECTICIDES BASED ON P_2S_5

$(CH_3O)_2\overset{\overset{S}{\|}}{P}SH$	Malathion Azinphos-Methyl (Gusathion® M) Methidathion (Supracide®) Phosmet (Imidan®) Oxydemeton-Methyl (Metasystox®)
$(C_2H_5O)_2\overset{\overset{S}{\|}}{P}SH$	Azinphos-Ethyl (Gusathion® A) Dialifos (Torak®) Disulfoton (Disyston®) Phorate (Thimet®) Phosalone (Zolone®)
$(CH_3O)_2\overset{\overset{S}{\|}}{P}Cl$	Methyl Parathion Fenitrothion (Sumithion®, Folithion®) Chlorpyrifos-Methyl (Reldan®) Temephos (Abate®) Methamidophos (Monitor®, Tamaron®) Acephate (Orthene®)
$(C_2H_5O)_2\overset{\overset{S}{\|}}{P}Cl$	Parathion Diazinon Triazophos (Hostathion®) Phoxim (Volaton®) Pirimiphos-Ethyl (Primicid®) Chlorpyrifos (Dursban®, Lorsban®)

Figure 6

NUCLEOPHILIC REAGENTS

PHOSPHORYLATION



ALKYLATION

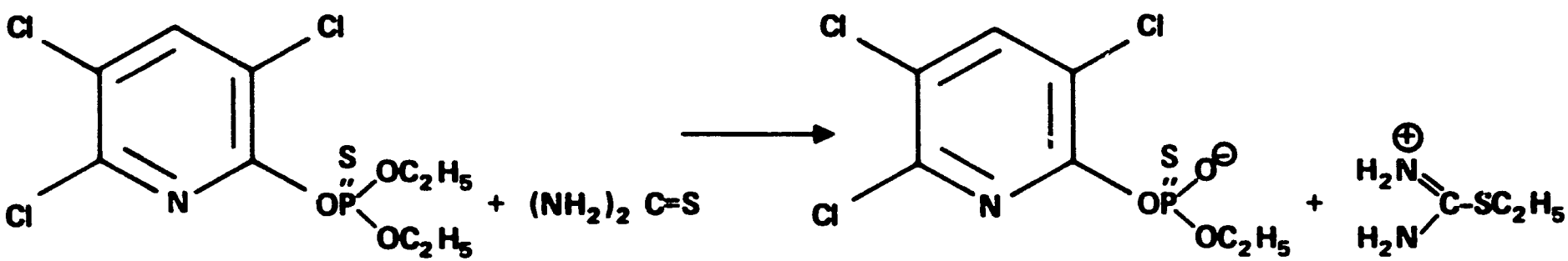


Figure 7

HYDROLYSIS

pH	Half-Life
4.7	62.7 Days
6.9	35.3 Days
8.1	22.8 Days

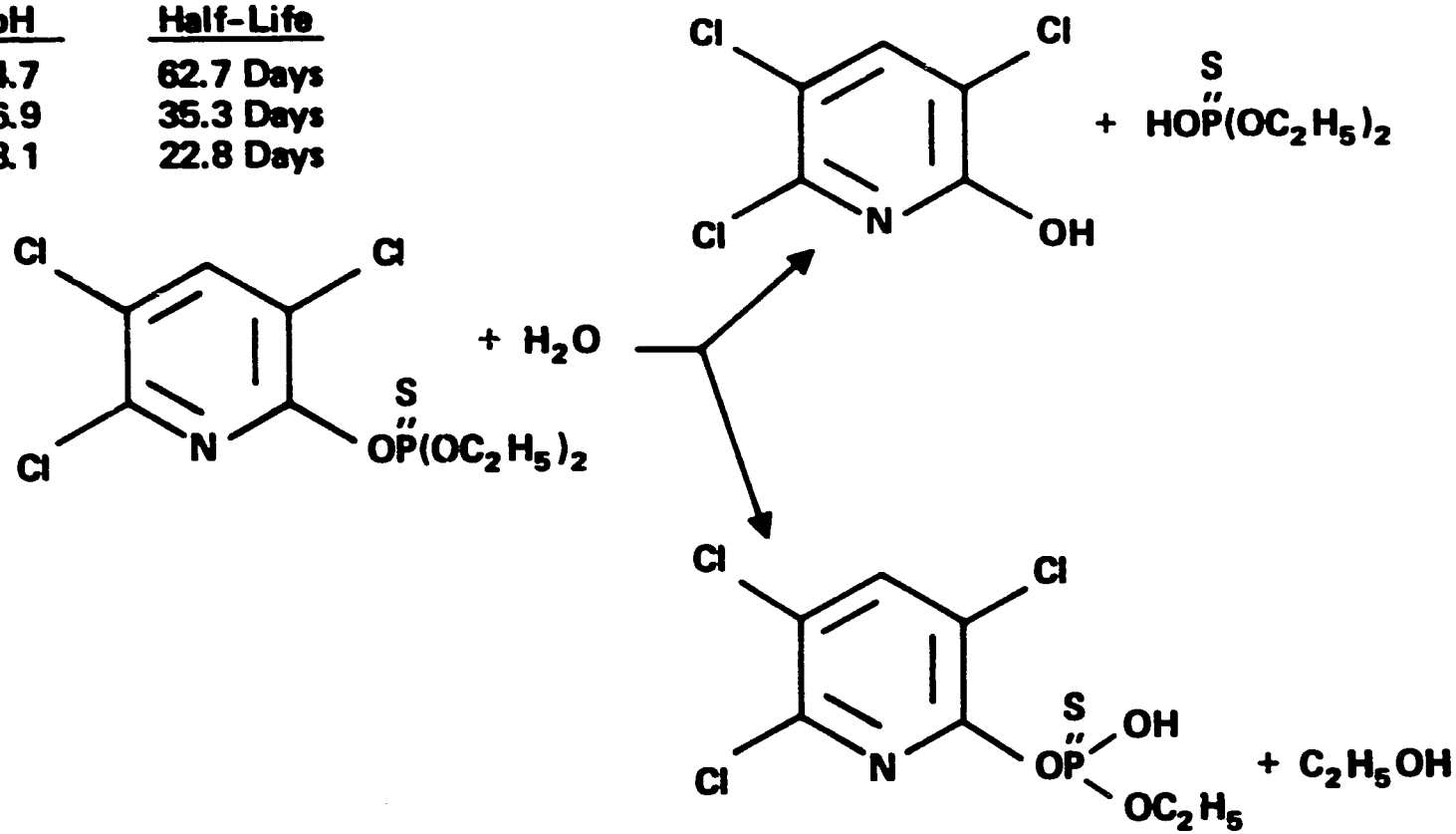


Figure 8

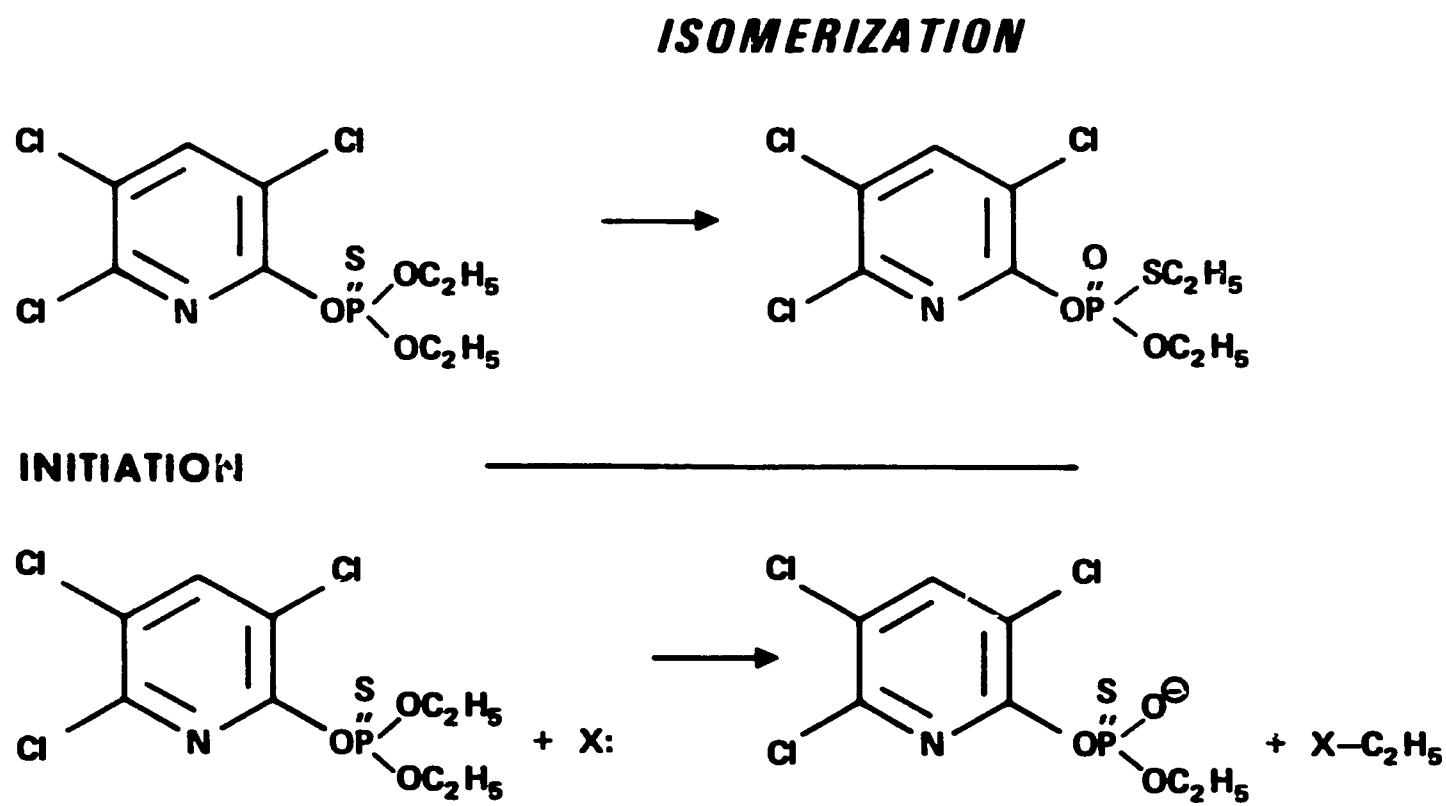

ISOMERIZATION
Cl
Cl
Cl
N
S
OP
OC2H5
OC2H5
O
SC2H5
INITIATION
+ X:
+ X–C2H5

Figure 9

ISOMERIZATION

PROPAGATION

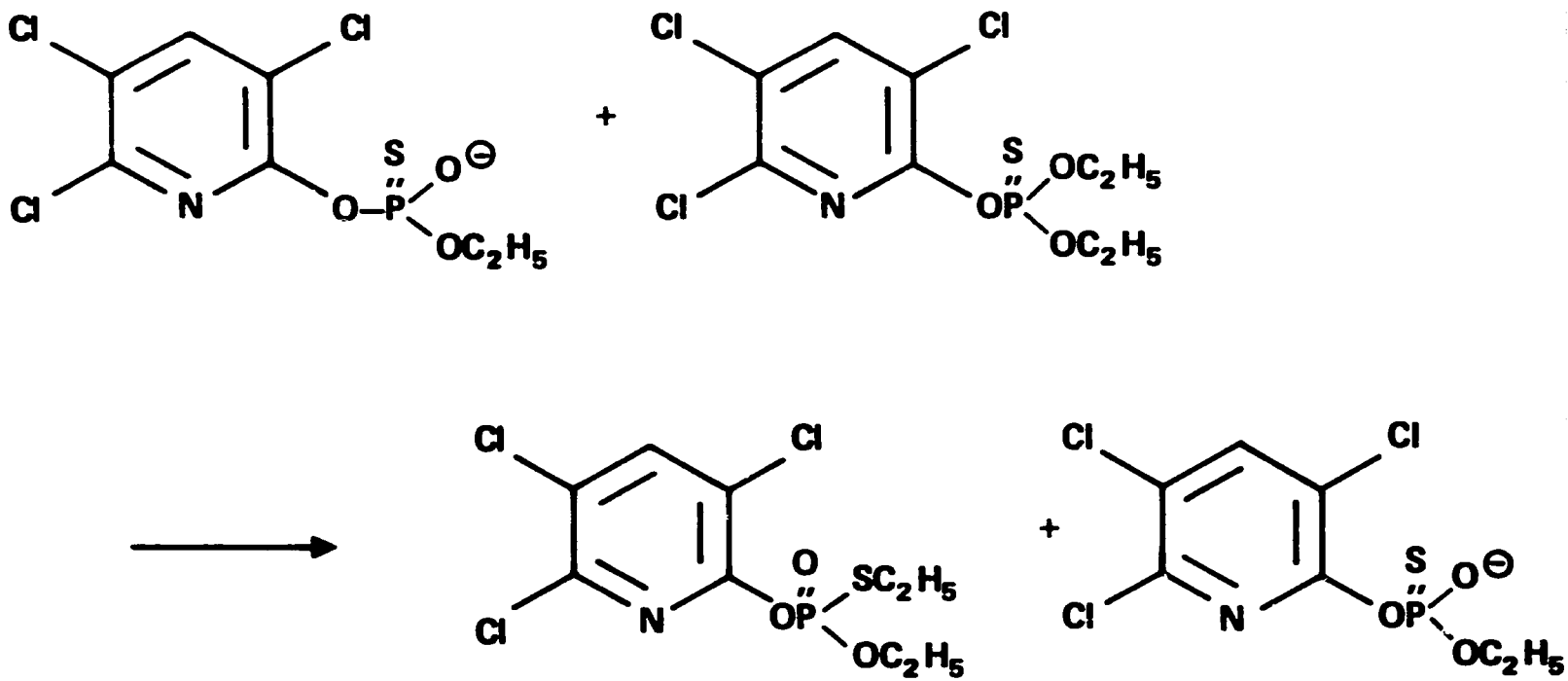


Figure 9A

OXIDATION

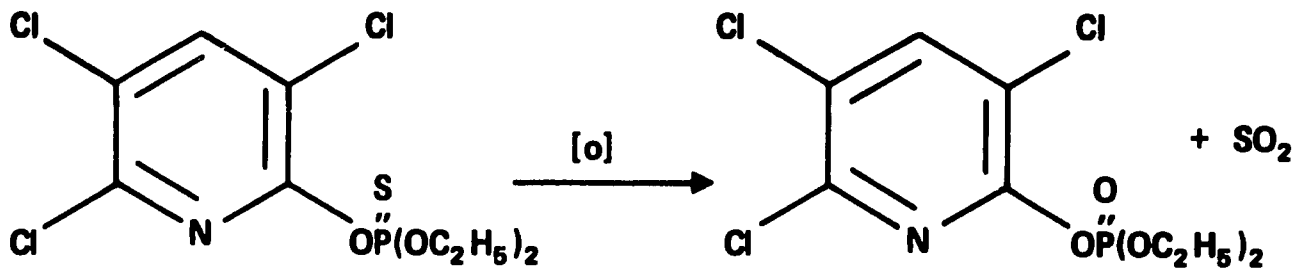
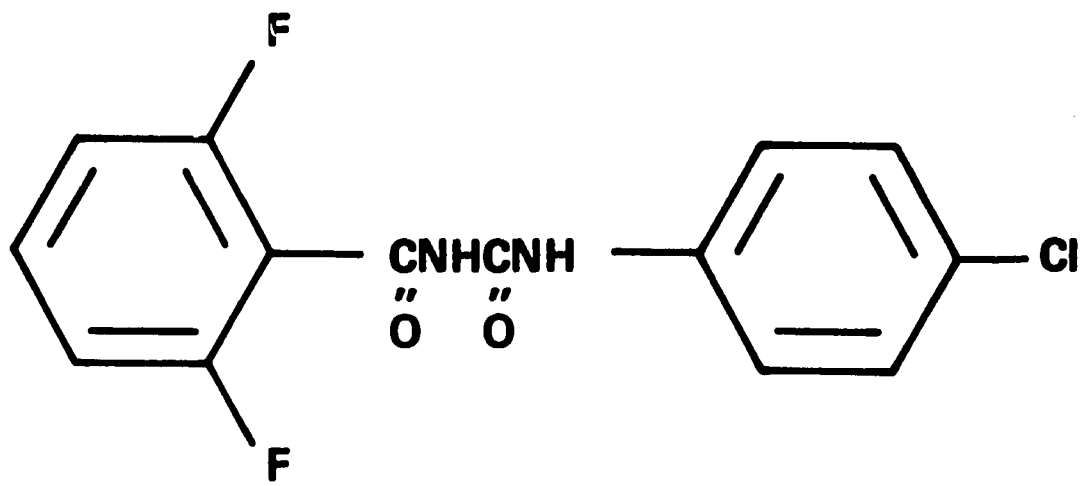


Figure 10



DIFLUBENZURON

N–(((4-Chlorophenyl)Amino)Carbonyl)-2,6-Difluorobenzamide

Dimilin® Insecticide
DC 702® Insecticide (With Chlorpyrifos)
PH 60-40

Figure 11

SUGGESTED DIFLUBENZURON PROCESS CHEMISTRY

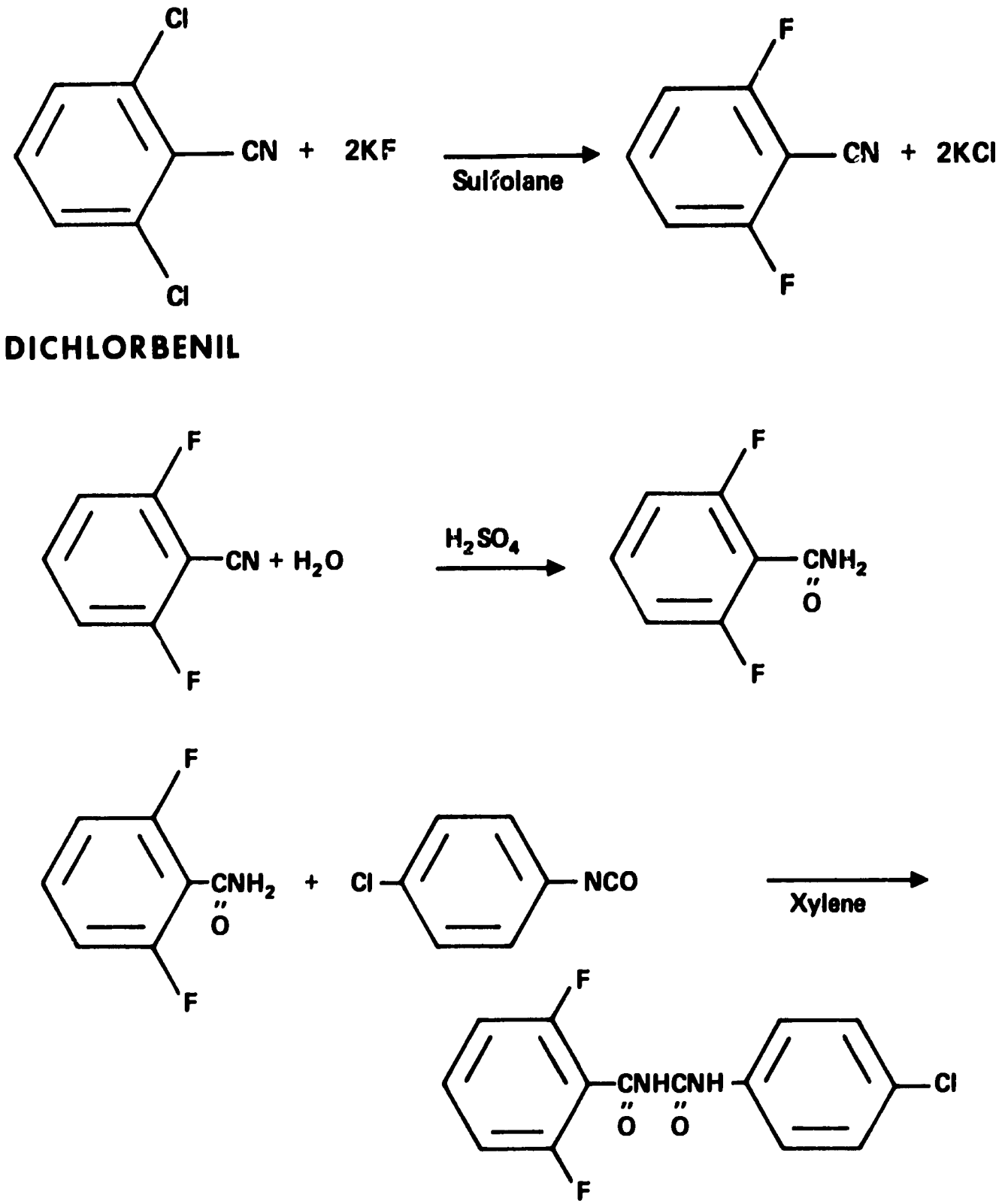
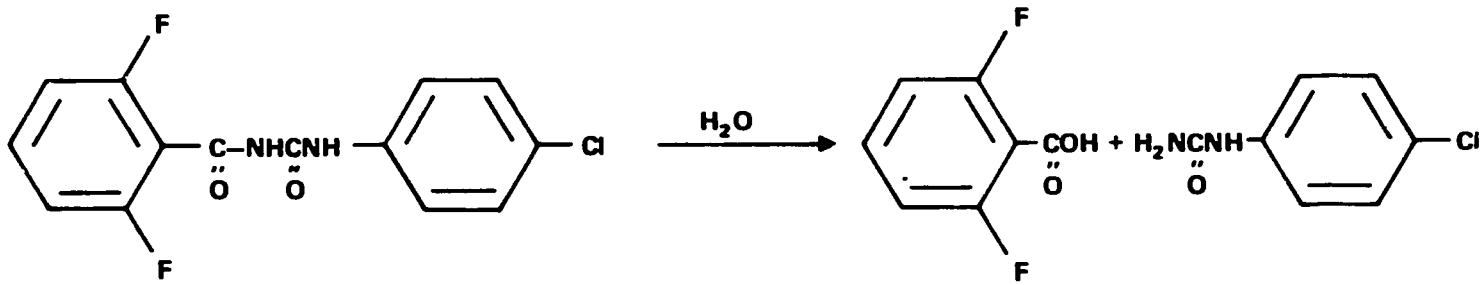


Figure 12

REACTIVITY OF DIFLUBENZURON

HYDROLYSIS



ANION FORMATION

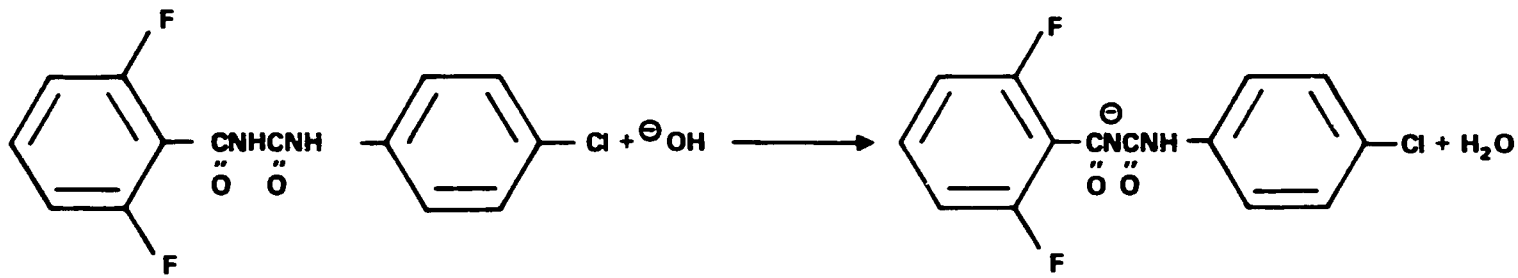
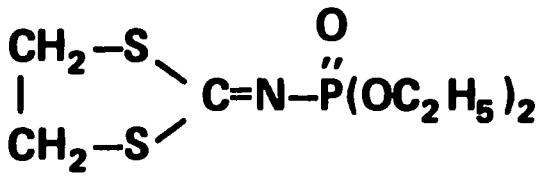


Figure 13

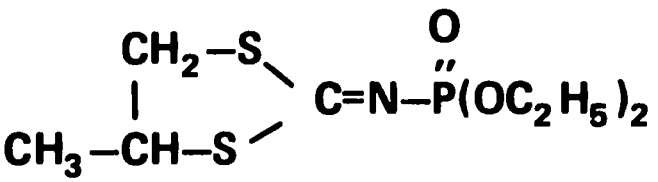


PHOSFOLAN

Diethyl 1,3-dithiolan-2-ylidenephosphoramidate

CYLOANE® INSECTICIDE

AC 47031



MEPHOSFOLAN

Diethyl 4-methyl-1, 3-dithiolan-2-ylidenephosphoramidate

CYTROLANE® INSECTICIDE

AC 47470

Figure 14

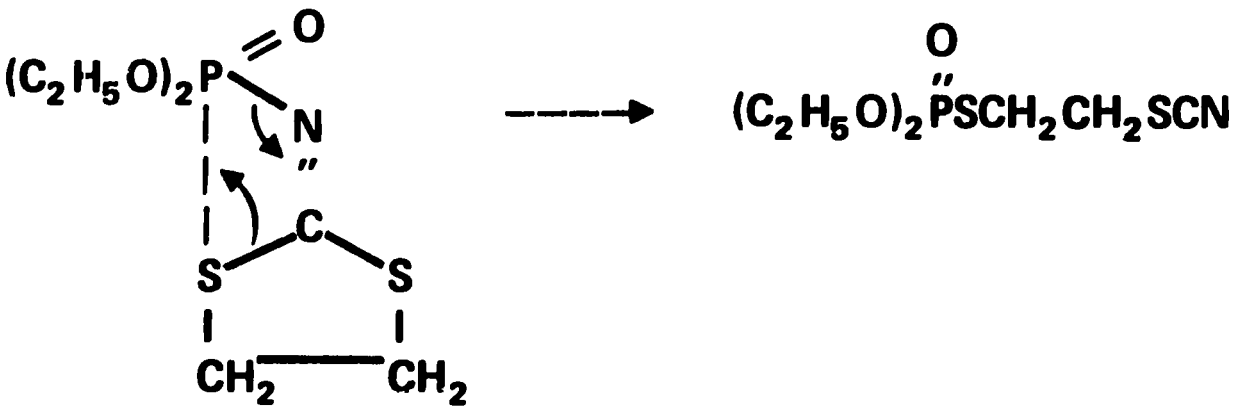


Figure 15

SUGGESTED PROCESS CHEMISTRY

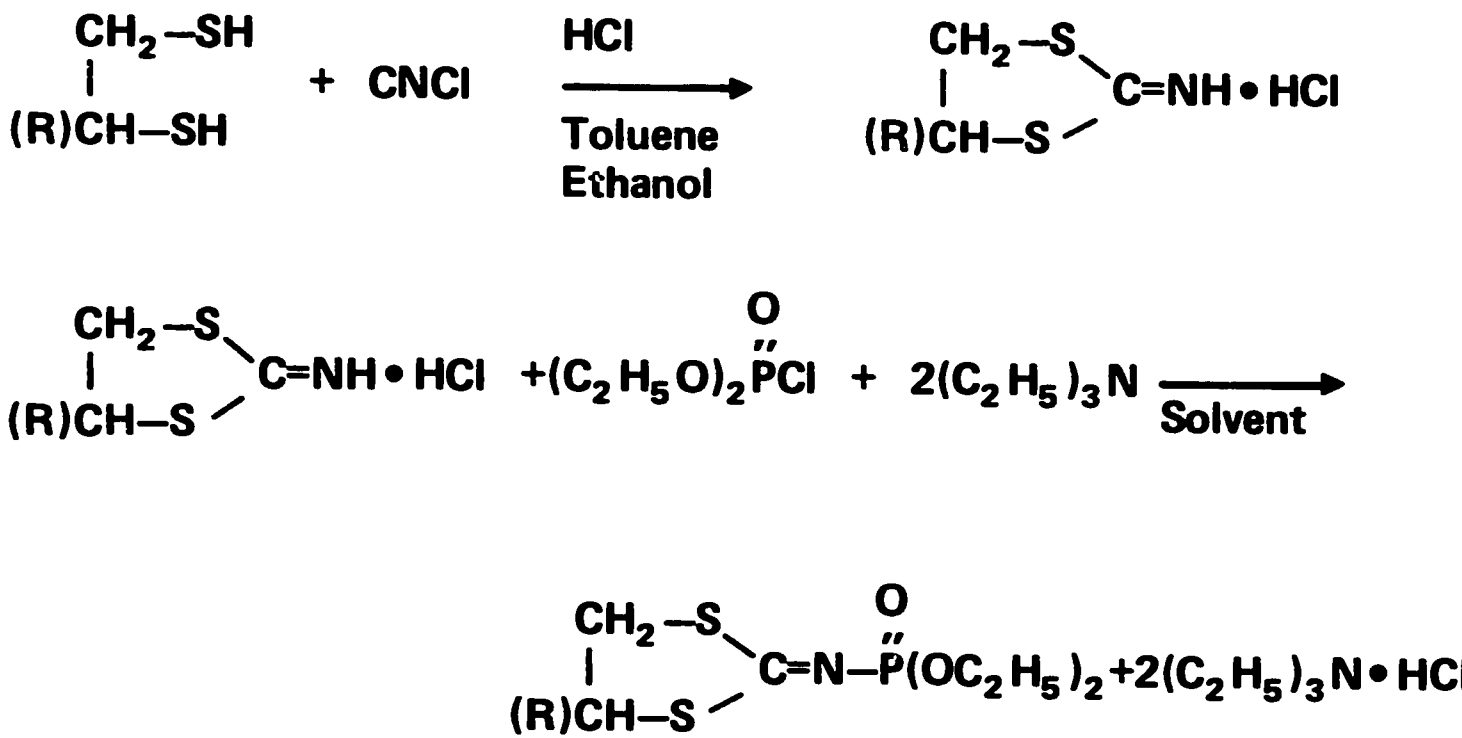


Figure 16

DIETHYL PHOSPHOROCHLORIDATE PROCESS CHEMISTRY

$$PCl_3 + 3C_2H_5OH + SO_2Cl_2 \longrightarrow (C_2H_5O)_2\overset{O}{\overset{\|}{P}}Cl + C_2H_5Cl + 3HCl + SO_2$$

$$PCl_3 + 3C_2H_5OH \xrightarrow{\text{(HCl removed)}} (C_2H_5O)_3P + 3HCl \xrightarrow{SO_2Cl_2} (C_2H_5O)_2\overset{O}{\overset{\|}{P}}Cl + C_2H_5Cl + SO_2$$

$$PCl_3 + 3C_2H_5OH \longrightarrow (C_2H_5O)_2\overset{O}{\overset{\|}{P}}H + 2HCl + C_2H_5Cl \xrightarrow{SO_2Cl_2} (C_2H_5O)\overset{O}{\overset{\|}{P}}Cl + HCl + SO_2$$

Figure 17

PHOSPHORUS TRICHLORIDE

$$P_4 + 6Cl_2 \xrightarrow[\text{Reflux}]{PCl_3} 4PCl_3$$

Figure 18

SOME ORGANOPHOSPHORUS INSECTICIDES BASED ON PCl_3

$(C_2H_5O)_3P$

Chlorfenvinfos (Supona®)

$(C_2H_5O)_2PCl$

Profenofos (Curacron®)

$(C_2H_5O)_2\overset{O}{\overset{\|}{P}}Cl$

Tetraethyl Pyrophosphate
Phosfolan (Cyolane®)
Mephosfolan (Cytrolane®)

$(CH_3O)_3P$

Dichlorvos (DDVP)
Naled (Dibrom®)
Monocrotophos (Azodrin®)
Dicrotophos (Bidrin®)
Stirofos (Gardona®)
Heptenophos (Hostaquick®)

$(CH_3O)_2\overset{O}{\overset{\|}{P}}H$

Trichlorfon (Dylox®)

Figure 19

HYDROLYSIS

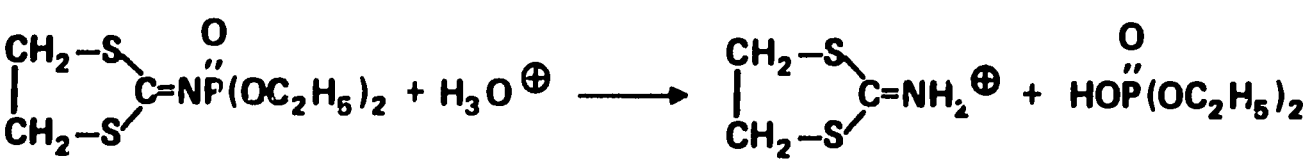
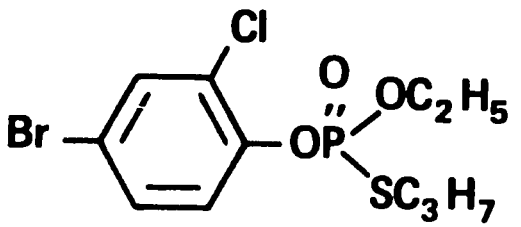


Figure 20



PROFENOFOS

0-4-Bromo-2-Chlorophenyl 0-Ethyl
S-Propyl Phosphorothioate
CURACRON® Insecticide
CGA 15324

Figure 21

SUGGESTED PROFENOFOS PROCESS CHEMISTRY

$$PCl_3 + 3C_2H_5OH + 3(C_2H_5)_3N \longrightarrow (C_2H_5O)_3P + 3(C_2H_5)_3N{\bullet}HCl$$

$$2(C_2H_5O)_3P + PCl_3 \longrightarrow 3(C_2H_5O)_2PCl$$

$$(C_2H_5O)_2PCl + C_3H_7SCl \longrightarrow (C_3H_7S)(C_2H_5O)P(=O)-Cl + C_2H_5Cl$$

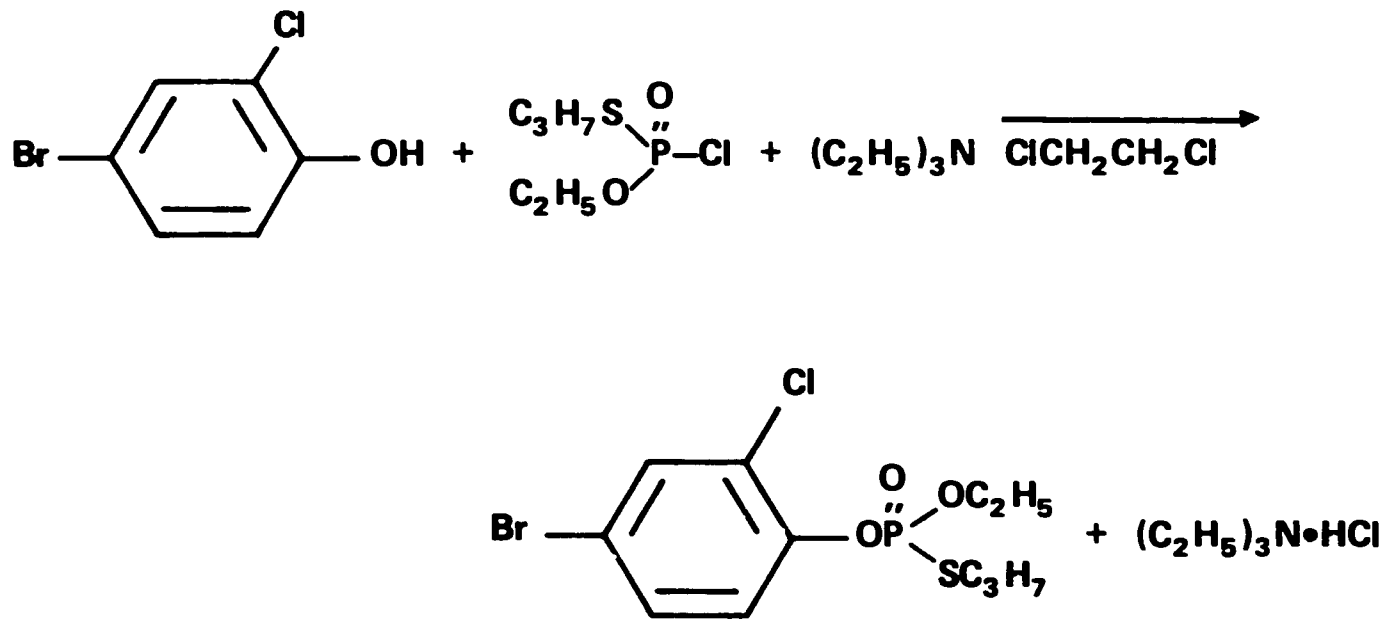


Figure 22

EXPECTED HYDROLYSIS REACTIONS

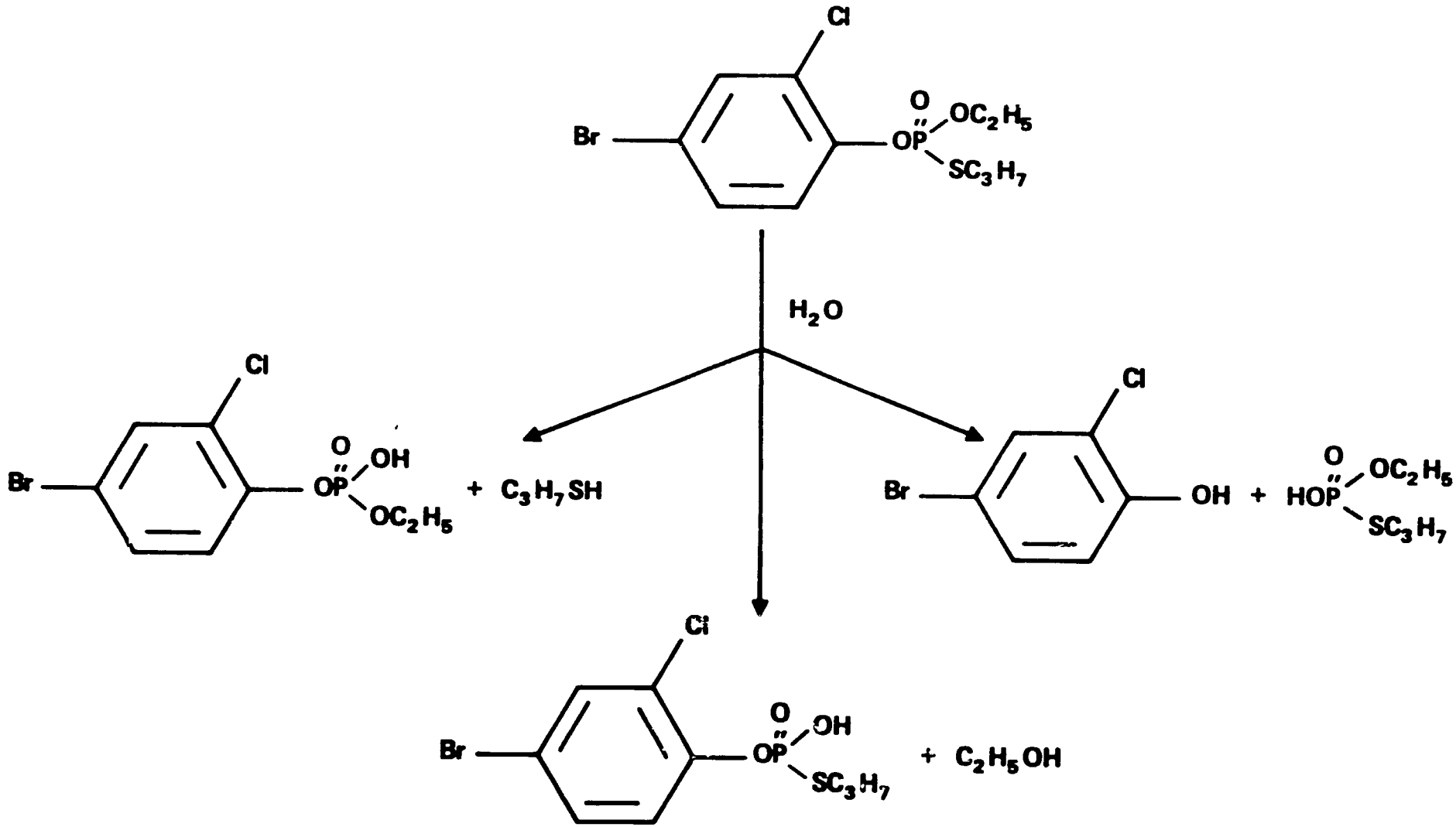
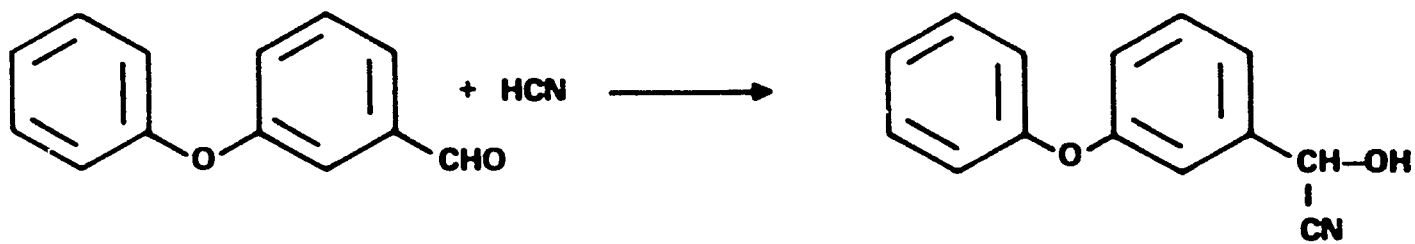


Figure 23

SUGGESTED FENVALERATE PROCESS CHEMISTRY

A. ALCOHOL



B. ACID CHLORIDE

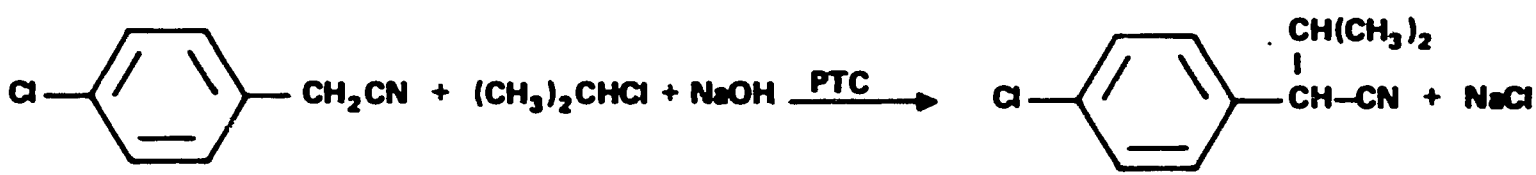
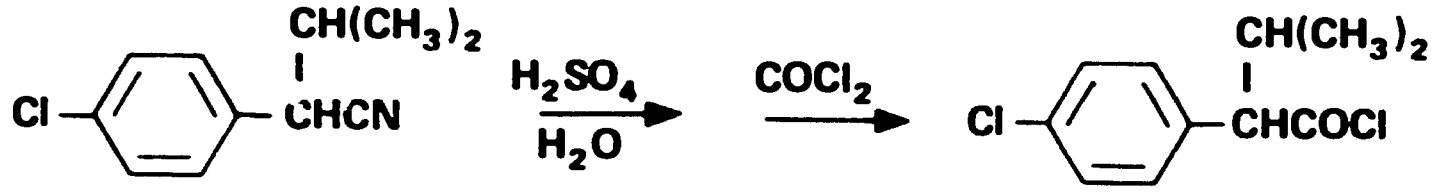


Figure 24

SUGGESTED FENVALERATE PROCESS CHEMISTRY



C. ESTER FORMATION

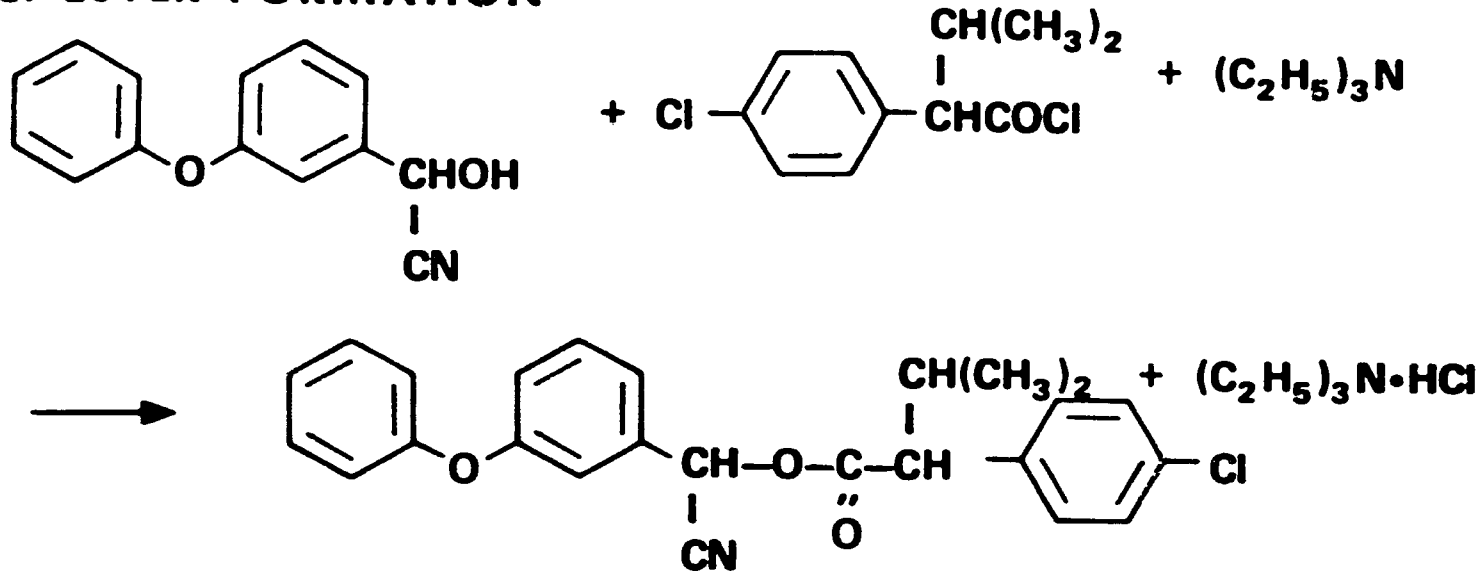
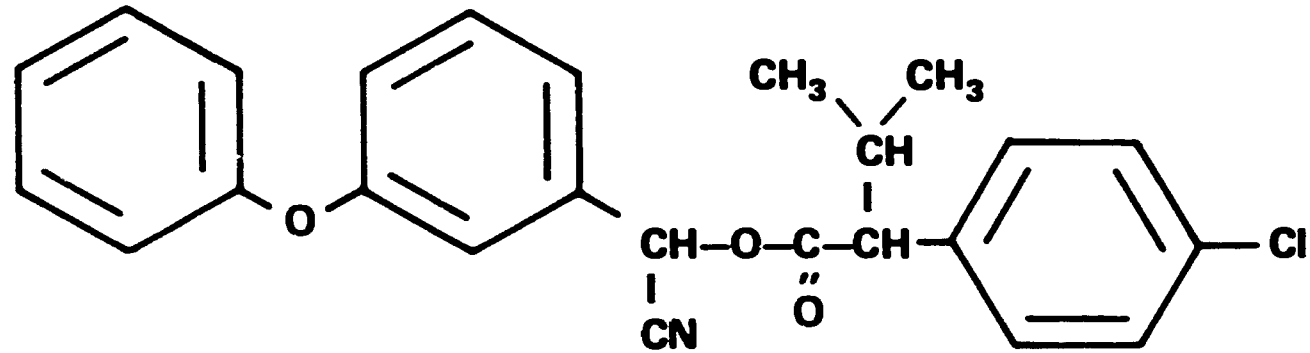
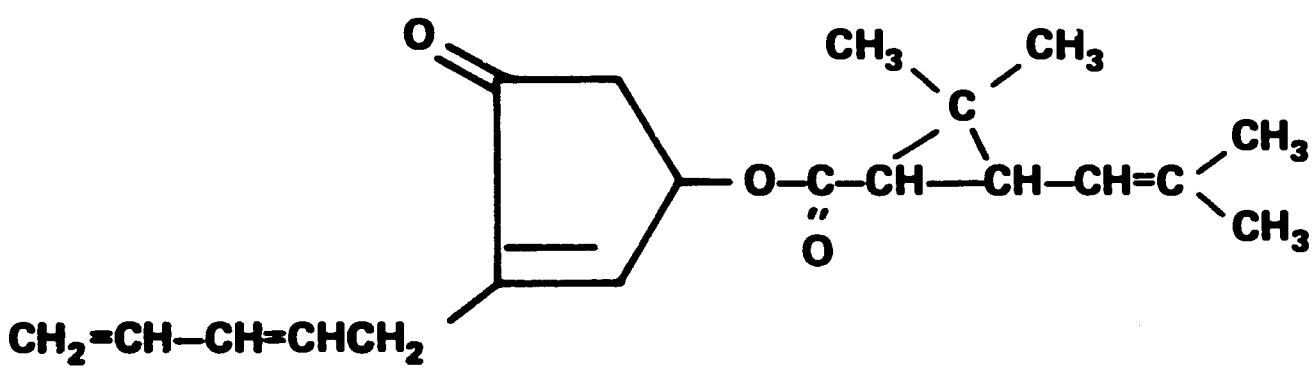


Figure 24 A



FENVALERATE

Sumicidin® Insecticide
S 5439



PYRETHRIN I

Figure 25

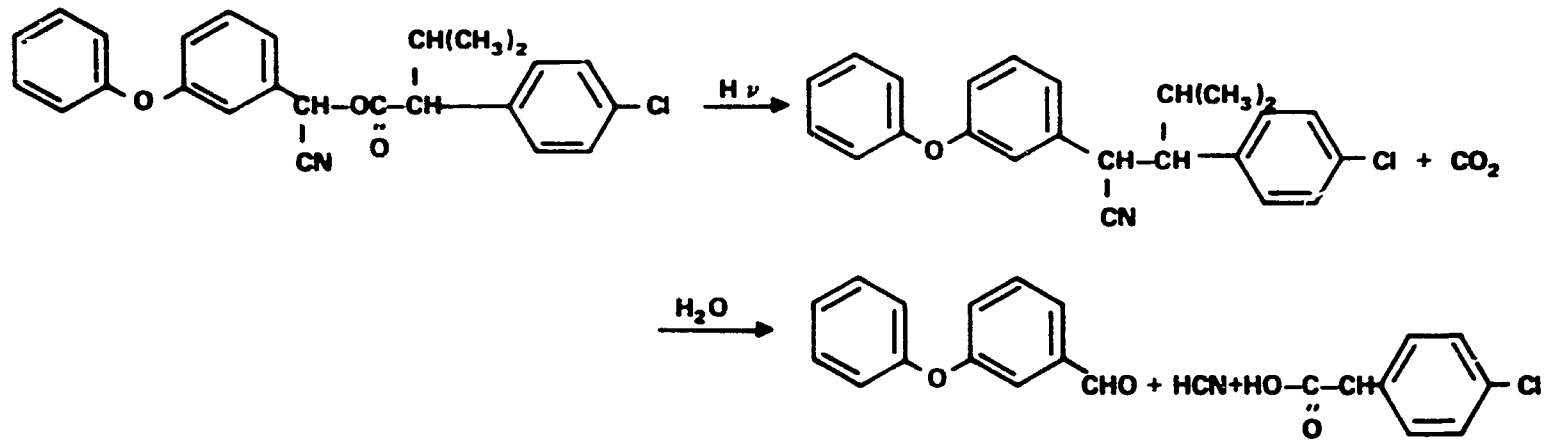

CH(CH3)2
CH–OC–CH
CN
O
Cl
H ν
CH(CH3)2
CH–CH
CN
Cl + CO2
H2O
CHO + HCN+HO–C–CH
O
Cl

Figure 26

ACUTE TOXICITY
INSECTICIDES OF IMPORTANCE IN EGYPT

Product	Acute Oral LD_{50} In Male Rats mg/kg	Dermal LD_{50} In Rabbits mg/kg
CHLORPYRIFOS	163	~ 2000
DIFLUBENZURON	> 2000	> 2000
MEPHOSFOLAN	8	9
PHOSFOLAN	8	240 (Formulated)
PROFENOFOS	358	~ 3000

Figure 27

SOIL METABOLISM

- Aerobic
- Anaerobic
- Anaerobic, Fine Textured Soil
- Additional Broad Residue Studies

SOIL PERSISTENCE

- Persistence
- Persistence, Direct Incorporation
- Long-Term
- Leaching
- Photodegradation

TRANSLOCATION IN WATER

- Hydrolysis
- With Suspended Solids
- With Bottom Sediments
- Photodegradation

Figure 28

TRANSLOCATION IN WATER

- Water To Crop And Aquatic Plants
- Irrigation Water
- Moving Water

AIR

- Photodegradation
- Volatility

LIVESTOCK AND POULTRY

- Drinking Water, Milk Tissues, Egg Residues

FISH

- Uptake From Moving Water
- Uptake From Soil-Modified Water

Figure 29

INDUSTRIAL HYGIENE PROGRAM

- RECOGNIZATION OF INTERRELATIONS
- EVALUATION OF IMPAIRMENT
- RECOMMENDATIONS FOR ALLEVIATION OF PROBLEMS

Figure 30

INDUSTRIAL HYGIENE REQUIREMENTS

- EXAMINATION OF DATA
- INTERPRETATION OF DATA
- CONTROL MEASURES
- CREATION OF STANDARDS
- PRESENTATION OF DATA
- PREPARATION OF WARNINGS
- EDUCATION OF WORK COMMUNITY
- CONDUCT EPIDEMILOGIC STUDY

Figure 31

ندوة الكيمياء

ينظمها

المركز القومى للبحوث

والجمعية الكيميائية الأمريكية

٢٨ نوفمبر - ٨ ديسمبر ١٩٧٧

القاهرة

جمهورية مصر العربية