Insecticides and Their Design[1]

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Pesticides and drugs originated from the need for controlling man's external and internal environment. Since the advent of agriculture, pests in the widest sense increasingly competed with man's best efforts in food, fiber, and timber production; urbanization accentuated the need for public health efforts, and animal husbandry necessitated advances in parasite control. Man responded to these challenges with pesticides and drugs. The chemical weapons used in this fight are part of the history of insect toxicology, pharmacology, and nematology.

At first, nature was man's best teacher and exclusive supplier of pesticides. With the increasing independence from nature came the push for synthetic substances, for procedures to make them, and for theories to understand their modes of action.

The interaction of man with pests is not static; it is highly dependent on natural

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and man-made changes. Early in this century man had to cope with phenomena like pest resistance to pesticides and drugs. This forced him to search for new approaches to control pests, and he soon left the scene of plants and minerals. Today, all possible sources for new compounds receive consideration (30,45,126,131).

PRINCIPLES AND LIMITATIONS OF APPROACH

Today we are still far from the ideal in pesticide development: the denovo synthesis of agents based on rational design (38,93). Limited knowledge of biochemical, pharmacological, and toxicological differences between man, insects, nematodes, and plants restricts the rational development. However, in a few selected examples, notably in the field of organophosphorus and carbamate insecticides, toxicologists are able to design pesticide analogs and, to a limited extent, predict their properties. In most other areas, our search strategies are still largely stochastic.

In the past, almost exclusive emphasis was given to the most effective agents with the highest acute toxicities. Two decades ago a subtle shift occurred toward environmentally benign compounds. Killing pests, let alone their eradication, was no longer the prime objective. Instead, rendering the pests unfit for reproduction became the goal.

In the course of the last two millenia, methods for pest control have evolved, first slowly, then, since the late 19th century, with accelerated pace. We realized that as we act on the pests they react in response to our actions. This forced us to rethink our strategies time and again. We probably will never gain more than a one-step advantage. The more progress we make, the greater the built-in pressure will become for pests to counteract. Resistant strains will occupy the niches vacated by the strains susceptible to our interventions (118).

By the end of 1975, 364 species of insects and mites were resistant, some of them multiply resistant, to all major insecticide groups (21,54). Starting in 1908, with the first observation of lime sulfur resistance of San Jose Scale in Washington, and in 1912 with the hydrocyanic acid resistance in the California Red Scale (137), the occurrence of documented cases of acquired resistance follows a predictable natural growth curve. By the turn of this century, more than 1,000 insect species may show some degree of resistance.

Since preceding papers of this symposium dealt with nematicides and herbicides, the scope of this paper will be restricted to the development, design, and evaluation of insecticides.

HISTORICAL REMARKS

Realgar (arsenic sulfide) was used by the Chinese for garden insect control as early as 900 A.D. In late Roman times, and thorugh the Middle Ages, sulfur, pitch, mineral oil, brine, lye, and soap were used as insect repellents. Records of these early uses are excellently reviewed by Shepard (137). Early insecticides utilized were the inorganic elements Hg, Pb, F, and As and compounds of these elements. These are broad spectrum biocides and can be equally harmful to insects, man, domestic animals, and plants. In hindsight, one wonders what ecological side effects occurred when lead arsenate was used in 1892 on a wide scale in an attempt to eradicate the gypsy moth in Massachusetts.

THE CONSIDERATION OF SELECTIVITY

The biochemical modes of action are known for a number of unselective poisons. Lesions occur at specific sites in the glycolysis pathway (GP), the tricarboxylic acid (TCA) cycle, and in the electron transport chain (ETC) (86,91). These sites are of ubiquitous importance for most animals. Examples of poisons in the GP are iodoacetamide, which interferes with the phosphorylation of fructose-6-phosphate to fructose-1,6-diphosphate; arsenous acid (145), which interacts with the ATP production in the conversion step of 3-phosphoglyceroylphosphate to 3-phospho-glycerate; and fluoride ion, which blocks the conversion of 3-phospho-glycerate to 2-phosphoglycerate. In the TCA cycle, fluoroacetamide blocks aconitase; chloropicrin interferes with the dehydrogenation of succinate to fumarate; tricyclohexyl tin hydroxide

impedes the first oxidative phosphorylation step in the ETC associated with flavoprotein and coenzyme Q; dinitro-*o*-cresol (DNOC) inhibits the subsequent two phosphorylation steps associated with cytochromes b and c; and HCN poisons the last step of electron transfer from the bivalent Fe in cytochrome A_3 (cytochrome oxidase) to molecular oxygen (74). Since the primary metabolism of all organisms is very similar, these metabolic poisons will affect most nontarget organisms including man.

Obviously, to achieve selectivity, we must turn our attention to other than metabolic poisons. The selectivity ratio, which is the quotient between the toxicity of a compound to the pest and to the host, or between the target and the nontarget, must be as high as possible. We can aim at differences in biochemistry, however small, provided we know them, and fine-tune the pesticide precisely to this difference; or we can identify differences in organismal design, like the presence (in all nematodes, invertebrates, vertebrates) or absence (in plants, fungi, bacteria) of a nervous system; or we can aim at major differences in the presence (e.g., chitin in insects, nematode egg shells, fungi) or absence of important skeletal building materials; or at differences in developmental (molting stages between larval and adult forms vs. nonmolting) or behavioral patterns (use of species-specific sex attractants). All of these approaches have been tried, and examples are given in the following pages.

THE PRESENT SITUATION

By the early part of the 21st century, the world population will have doubled. Food for the growing numbers will mainly come from increases in agricultural crop production. Undoubtedly, the demand for pesticides of a wide variety will increase at the same rate (98). Unfortunately, present development costs for insecticides are excessively high due to the low rate of success in finding marketable compounds (19,36). Costs are estimated at $20 million per compound (55,91). Only large international companies can afford capital investments of this magnitude for research and development alone. Collectively, they add about 16 new insecticides to the market each year. This number falls short of the anticipated need by the turn of the century. As a result, a demand exists for a more rational, predictable, and less expensive approach to insecticide development.

The "ideal" insecticide can be characterized by the following properties:

1) Specific for one target species only.
2) Highly efficacious.
3) Biodegradable, with water soluble, nontoxic, noncarcinogenic, and nonmutagenic residues.
4) Nonaccumulative in food chains.
5) Easy to synthesize, formulate, and apply.
6) Cheap to synthesize from readily available starting materials.
7) Free of selecting for resistant strains.

Most of the presently known compounds meet one or more of these criteria; no presently known compound is irresistible. In developing an insecticide, usually a compromise is being sought between scientifically achievable and economically feasible considerations.

MAJOR INSECTICIDE CLASSES

Until the early 1940s, inorganic compounds and botanical insecticides with a broad spectrum of activity provided the backbone of all chemical control efforts. Collectively, they are classified today as "first-generation insecticides." Between 1940 and the late 1960s, the "second-generation insecticides" consisting of the synthetic organophosphorus esters, the carbamates, and the environmentally persistent chlorinated hydrocarbons were introduced. Broad spectrum pyrethroids joined the group about 1970 when chlorinated hydrocarbons were being phased out. The history of discovery and the development of the second-generation insecticides will be discussed in the following sections. Table 1 provides a scheme and gives a short survey of the modes of their discovery. Subsequent sections deal with "third-generation insecticides," a chemically diverse group acting as modifiers of insect development; with "fourth-generation insecticides," characterized by their ability to modify insect behavior; and with a novel group of natural

Table 1: Some representative insecticides of the 1st to 5th generation and their modes of discovery.

Insecticide class	Discovery class†						
	1	2	3	4	5	6	7
FIRST-GENERATION INSECTICIDES:							
Minerals containing the elements As, Hg, F, P, Se, Cu, Pb, Ca, Ba and their compounds	*		*				A
Mineral oil and coal tar			*				
Raw plant products: tobacco, turpentine resin, powders of pyrethrum,							A
Quassia, Derris	*						A
SECOND-GENERATION INSECTICIDES:							
Organophosphorus esters				*	*		B
Organophosphates				*	*		
Phosphonates				*	*		
Carbamates	*			*	*		B
Sulfenylated carbamates as "pro" insecticides						*	D
Chlorinated hydrocarbons							
Lindane			*		*		
Toxaphene			*				
DDT, biodegradable DDT analogs				*	*	*	C
Cyclodienes			*	*	*		
Mirex, chlordecone			*				
Pyrethrin group							
Pyrethrins, natural	*						
Synthetic pyrethroids					*	*	
Hybrids between pyrethroids and DDT						*	
Minor classes of synthetic insecticides							
Formamidine group, chlordimeform			*		*		C
Nitromethylene heterocycles				*	*		
Botanical insecticides							
Alkaloids and nicotine	*	*					
Nonalkaloids and rotenone	*	*					
Insecticides from microbial origin							
Bacillus thuringiensis							E
Avermectins							E
Minor fungal metaoblites with insecticidal activity			*				
THIRD-GENERATION INSECTICIDES: (DEVELOPMENT MODIFIERS)							
Molting hormones							
Molting hormones from insects		*				*	
Molting hormones from plants		*	*				
Antimolting hormones					*	*	
Juvenile hormones (growth regulators)							
JH from insects		*				*	
Juvenoids from syntheses		*	*		*	*	
Chitin synthetase inhibitors of the benzoylphenylurea type				*			C
Precocenes		*	*				
FOURTH-GENERATION INSECTICIDES: (BEHAVIOR MODIFIERS)							
Antifeedants		*	*				
Pheromones		*				*	
FIFTH-GENERATION INSECTICIDES: (PROMISING LEADS FOR THE FUTURE)							
Novel natural products		*	*			*	
Brain hormone antagonists		*				*	

products that is still in the early stage of exploration and may tentatively be labeled as "fifth-generation insecticides."

This classification scheme is by necessity crude because it descriptively combines chemical, historical, and toxicological characteristics. Yet it will demonstrate the progress made in sophistication of approach and insecticide use within the last half century.

SECOND-GENERATION INSECTICIDES

Organophosphorus (OP) esters: These insecticides emerged from secret research on nerve gases before and during the second world war. The first OP insecticides were tetraethylpyrophosphate (TEPP) and the systemically active octamethylpyrophosphamide (schradan ®) (133). Developed in Germany as a substitute for nicotine, TEPP was targeted against the nervous system. Because of its high and indiscriminate toxicity to insects and mammals and because of its hydrolytic instability, it was replaced by parathion and methylparathion. In spite of their mammalian toxicity, the OP esters gained a 13% share of the U.S. insecticide market as inexpensive plant protectants. As a group, they approximately complied with requirements 2 through 6 of the "ideal" insecticide, but disappointingly failed with respect to numbers 1 and 7. Unfortunately, the compounds were not replaced when slightly more expensive but much safer OP analogs such as chlorothion and fenitrothion were discovered (99). In many European countries, China, Indonesia, and in Japan, the use of parathion and methylparathion is restricted because many accidental and deliberate cases of poisoning occurred.

Between 1945 and today thousands of OP compounds were described. Their total sales volume in the United States in 1971 was 50,000 tons (91). Many of the OP compounds have been extensively reviewed (133,144,153).

All OP compounds, including the very safe insecticides fenitrothion and malathion, work as cholinesterase inhibitors through a common, relatively well understood mechanism at cholinergic synapses (110,136,) (Fig. 1). The work of Murphy (110) illustrates the similarities between acetylcholine, the natural cholinergic neurotransmitter, and the OP compounds. Carbamates, with subtle differences, follow the same mechanism of action (Fig. 1). The more electropositive the phosphorus atom in the OP compound becomes, the higher is its phosphorylation potential, and, hence, the larger its reactivity with the serine hydroxyl group occupying the active site of acetylcholinesterase (AChE). A direct correlation exists between the lethal dose for 50% of the insects tested (LD_{50}) and substituent effects on aromatic rings attached to the OP group. Hammett's sigma constants are a measure of this substituent effect (48,49,72) (Fig. 2). Using graphs depicting this linear structure-toxicity correlation, the designer of new compounds can make quantitative comparisons and reasonable predictions.

Efforts to make OP compounds environmentally more stable lead to the introduction of methylated and halogenated substituents. It also led to the replacement of the labile OP triesters by diesters with one P-C bond (phosphonates). Unfortun-

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†Key for discovery class:
1 = original observation followed by chemical identification.
2 = screening of plants or organisms.
3 = pure accident.
4 = inspired guessing.
5 = synthesis, screening, structure optimization.
6 = enlightened research.
7 = other modes of discovery.
A: Observations from antiquity originating either in the Mediterranean, Indian, American Indian, or Chinese culture.
B: Quantitative structure-toxicity-relationships established by Hammett's constant.
C: Semiquantitative structure-toxicity-relationship data established by Hansch's π-constants.
D: Enlightened research supported by in-depth metabolic studies.
E: Discovered by observations of insect pathologists.

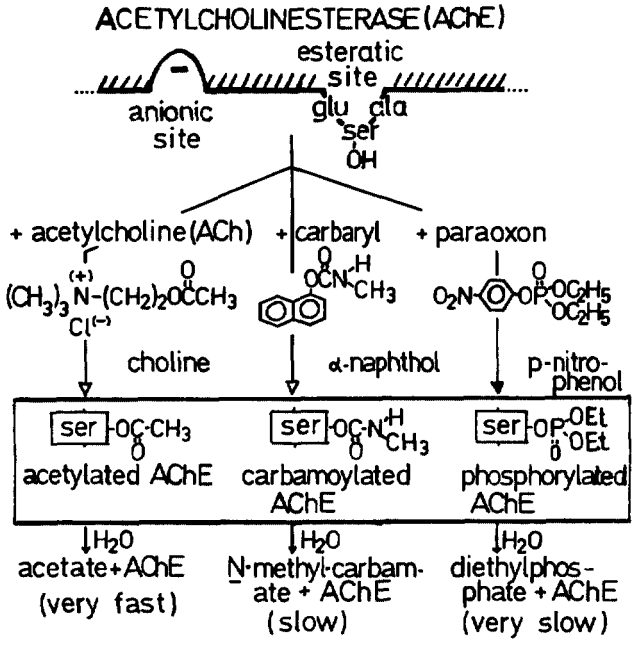


Fig. 1. Comparison of the biochemical interaction with the active site of AChE of the physiological neurotransmitter ACh, the carbamate insecticide carbaryl, and the OP compound paraoxon (modified from Murphy [110]). The aminoacid sequence -glu-ser-ala- denotes the active center of AChE; OH stands for the reactive hydroxy group of ser. The box emphasizes the similarity between the intermediately formed acylated AChE. Depending on the acyl-moiety, it has a half-life from msec to hours (for further explanations see the text).

ately, some members of the OP, phosphonate, and phosphonothioate series, such as leptophos, also act as delayed neurotoxins for mammals and birds (1,2,100,145). In addition to their moderate acute toxicity, they cause irreversible damage to myelinated nerve sheaths resulting in progressive ataxia (100). However, the phosphonate series also includes trichlorfon, which is safe and has the excellent environmental rating of 4.3 (101). The biological conversion of the phosphonate trichlorfon to the OP compound dichlorvos is a prime example of selective metabolic activation and toxication in insects and of inactivation in warm-blooded animals.

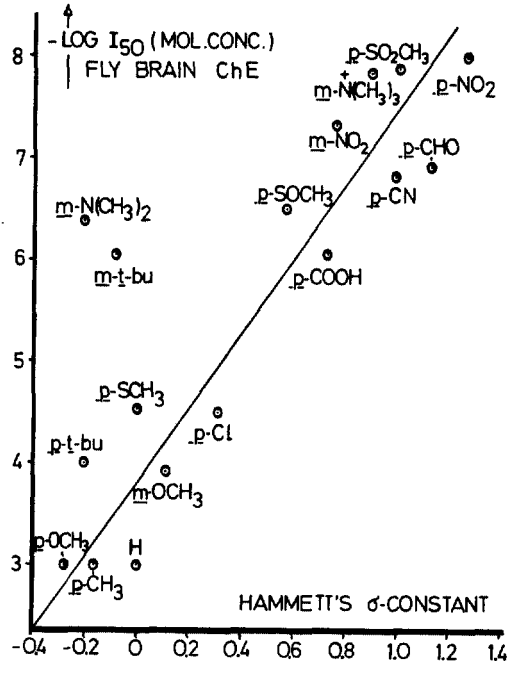


Fig. 2. Linear relationship between anticholinesterase activity and Hammett's sigma constants for substituted aromatic diethylphenylphosphates (48).

In addition to modification of the aromatic or aliphatic substituents, another avenue exists for gaining greater selectivity in OP compounds. Substitution of oxygen by sulfur leads to different metabolic activation patterns in insects and warm-blooded animals. As summarized by Murphy (110) (Fig. 3), phosphorodithioates and phosphothionates can be "toxicated" in insects to compounds binding to the critical AChE (toxic action). In mammals these compounds are metabolized to less toxic compounds that bind to noncritical enzymes or to sites where they can be eliminated before they reach dangerous levels (sparing action; see pathways II, III, IV, V, and VI in Fig. 3).

Carbamate insecticides: Unlike OP compounds, a few carbamates occur as natural products. The toxicological properties of the calabar bean *Physostigma venenosum* have been known since antiquity. The ac-

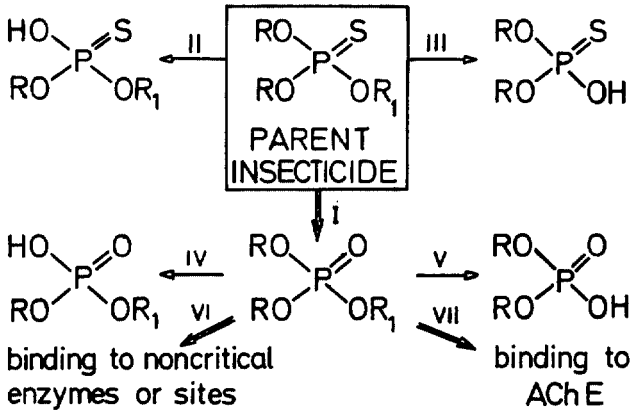


Fig. 3. Toxication (toxic action, pathways I plus VII) in *insect* tissues and detoxication (sparing action, pathways I plus VI) in *mammalian* tissues of dialkyl (R)-monoaryl-(R_1) phosphorothionate insecticides. Pathways II and IV (oxidative desalkylation) and III and V (hydrolytic cleavage) represent minor metabolic routes whose products do *not* inhibit AChE (modified after Murphy [110]).

tive principle, eserine, was chemically identified as a carbamate by Stedman and Barger (149) who also recognized the carbamic acid ester moiety -OCONHCH$_3$ as the toxophoric principle.

The introduction of a naphthyl group to carbamic acid ester produced carbaryl, a very effective insecticide with low mammalian toxicity (83). In 1971, 25,000 tons of carbaryl were produced in the United States (91). Between 1950 and 1970, industrial laboratories synthesized thousands of carbamates by analog synthesis in all thinkable variations (13,58) and for many uses.

Carbamates, like OP compounds, are inhibitors of AChE. Quantitative structure-toxicity correlations are known from the work of Kolbezen et al (83), Metcalf (97), and Kukuto (95,96). Toxicities, expressed as -log K_i values and plotted against Hammett's sigma values, follow straight lines for both the meta- and para-substituents (Fig. 4). Meta-substituents produce higher toxicities than do para-substituents (83).

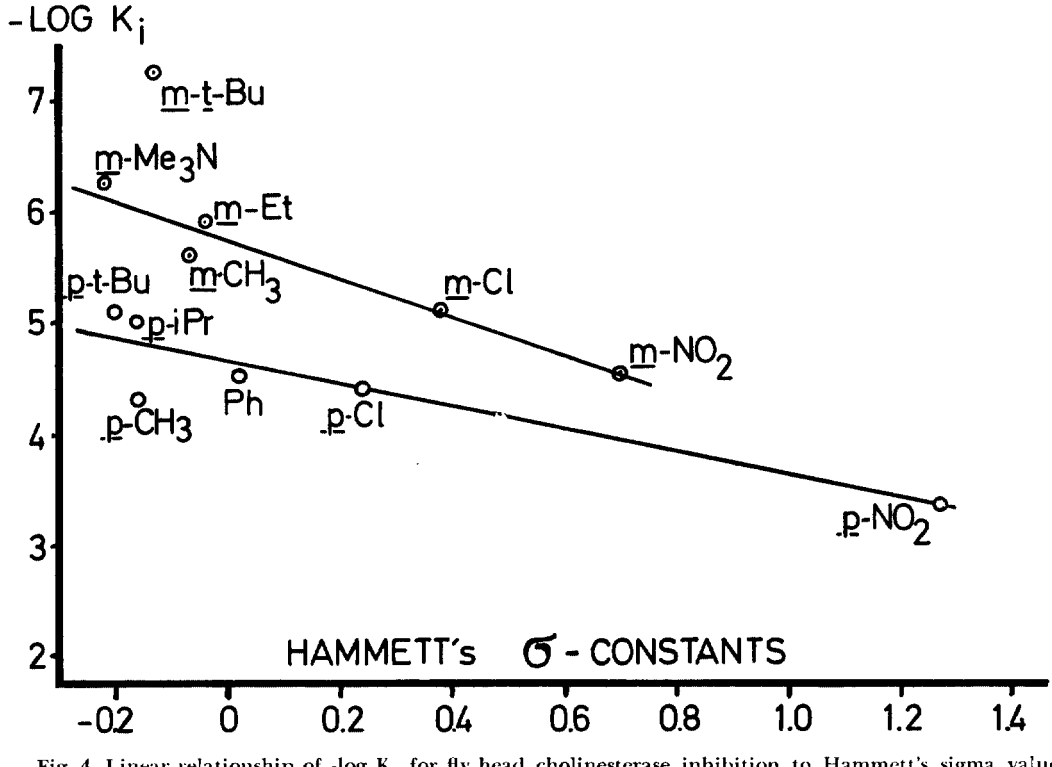


Fig. 4. Linear relationship of -log K_i for fly head cholinesterase inhibition to Hammett's sigma values for meta- and para-substituted phenyl *N*-methylcarbamates (modified after Kolbezen et al. [83]).

Unlike the situation in OP insecticides, addition of electron accepting substituents (e.g., the NO_2 group) to aromatic rings results in a reduction of inhibitory potency and thus insecticidal effectiveness, while electron donating substituents (e.g., OCH_3 and SCH_3) to the aromatic rings enhance the inhibitory power and hence the insecticidal potency. The negative slope of the straight lines is evident from the Fig. 4. Quantitative correlations of this kind assist in the design of analogs with desirable toxicological and environmental properties. Predictions are possible to a certain degree.

Another approach to selective toxicity is the design of "pro" insecticides in the carbamate family. Their active principles, the parent carbamates, are set free by different organisms at different rates. Both *N*-arylsulfenylated and *N*-alkylsulfenylated derivatives which operate by this principle are effective insecticides for mosquitos and houseflies (10).

N- (2-toluene sulfenyl) carbofuran (Fig. 5) is desulfenylated in the housefly to the more toxic parent compound carbofuran; in white mice and other mammals, competing reactions to nontoxic conjugates are faster, thus avoiding poisonous levels in these nontarget species (11). For example, *N*-(4-*t*-butylphenyl) sulfenyl-2-isopropoxyphenyl methylcarbamate has a selectivity ratio of 30 for the white mouse. Similarly, aminosulfenyl derivatives of the hazardous aldicarb are available (51) which offer selectivity ratios for mammals of 10 and are 7–8 times more toxic to mosquito larvae than the respective methylcarbamate. As a systemic insecticide, bisaldicarb sulfide is substantially more effective against cotton aphids, perforators, and mites than the parent compound (34,51). Higuchi and Stella (62) reviewed the progress already made in the related field of "pro" drugs. Fukuto (51) foresees major applications of proinsecticides and a future proliferation of the underlying toxicological principles.

Chlorinated hydrocarbons: This group, once believed to be the ultimate solution for insect control, rivals the proceding OP esters and carbamates both in production volume and price.

• Lindane (Fig. 6A). Hexachlorocyclohexane was first synthesized in 1825 by M. Faraday as a crude mixture of isomers (98). It took 117 years until research groups in

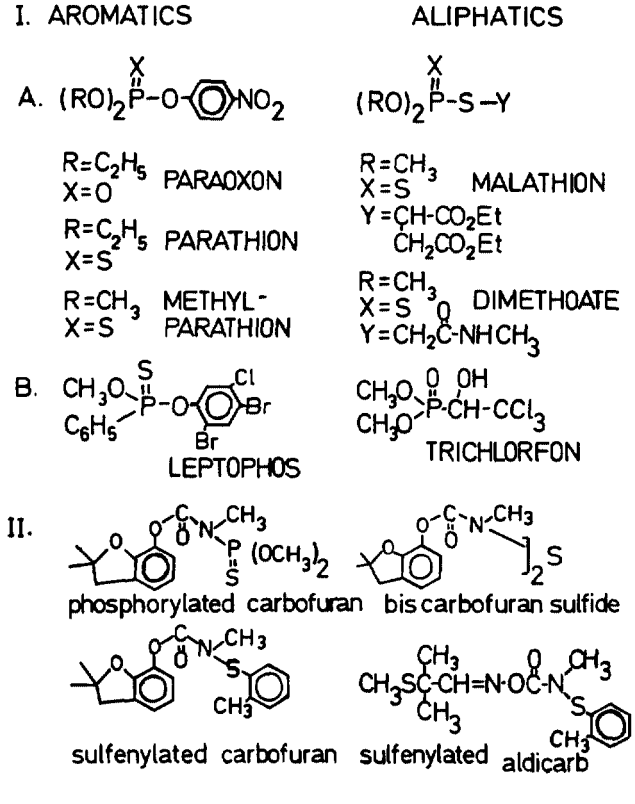
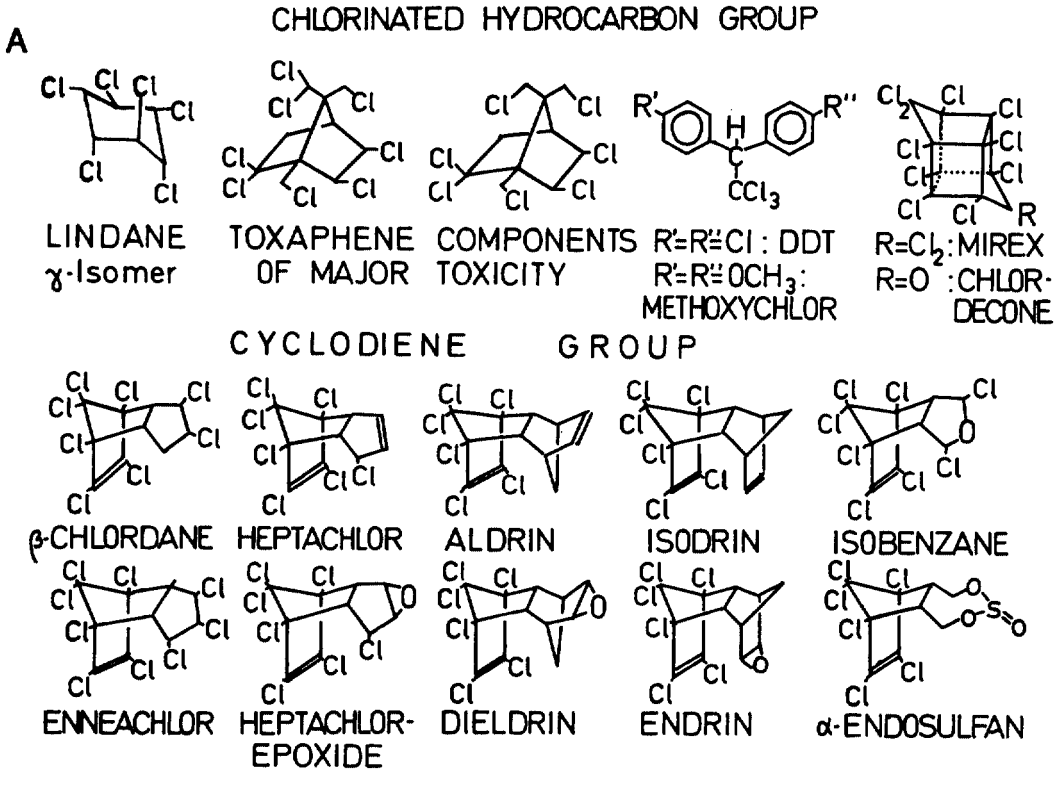


Fig. 5. Second-generation insecticides with built-in partial selectivity.

I. OP compounds. A = phosphate esters, B = phosphonate esters. The aliphatic members with Y = C_2H_4 S Et (demeton), Y = CH_2 S Et (phorate) share with dimethoate strong systemic action in plants.

II. Proinsecticides composed of the carbamates carbofuran and aldicarb with protective OP-, *o*-tolylsulfenyl-, and carbofuranoyl-moieties. Upon cleavage by insect tissue the parent carbamates are set free resulting in specific insect toxicity and a high mammalian selectivity ratio.



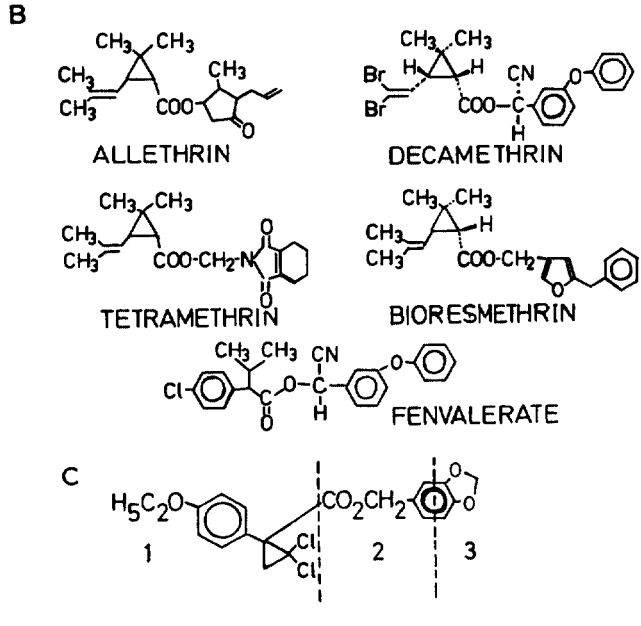


Fig. 6. Second-generation insecticides. A) Chlorinated hydrocarbons and cyclodienes. B) Synthetic pyrethroids. C) Holan's DDT-pyrethroid-hybrids (63,64). C 1 = DDT -analog part. C 2 = pyrethroid-analog part. C 3 = synergistic part.

France and England by chance and independently discovered its insecticidal properties. Of the seven isomers, only the gamma isomer, lindane, is appreciably active. Recently, synthesis conditions were adjusted to produce mainly the gamma isomer. In 1976, the cumulative world production of lindane had reached a total of I million tons. In spite of this impressive volume, the mode of action is insufficiently known. Several theories, ranging from metabolic interference with meso-inositol to CNS effects have been proposed (91). According to a brief review by Brooks (20), efforts in structure optimization had marginal success. Only some mixed halogen analogs with gamma configuration surpassed, and a gamma methoxychloro-analog came close to, the activity of lindane itself.

• Toxaphene (Fig. 6A). The success stories of lindane, DDT, and the cyclodienes paved the way for the preparation and testing of other chlorinated hydrocarbons. In 1948, camphene from pine tar, an unorthodox starting material, was selected for chlorination, and the polychlorinated terpene toxaphene, a mixture of 175 individual components, was produced (129). Compounds such as 2,2,5-*endo*-6-*exo*-8,9,10-heptachlorobornane were identified as insecticidal components (29); the most toxic component to mice, goldfish, and houseflies was the octachlorobornane homolog (Fig. 6A) (129).

More than 100 components, totalling 75% by weight in the crude toxaphene mixture, remain to be characterized. Since its discovery in 1948, 450,000 tons of toxaphene have been produced worldwide, mainly for use against cotton and livestock insects. But concerns with accumulation in food chains, its possible carcinogenicity in man, and its effects on immune responses in mice (4) prompted the EPA to restrict its use as of 1982 in the United States.

• DDT (Fig. 6A). Dichlorodiphenyltrichloroethane (DDT) can be considered as the forerunner of the chlorinated hydrocarbons insecticides. Its production in 1971 in the United States reached a total of 65,000 tons. DDT was first synthesised by Zeidler in 1874 via the then newly discovered Aivon Baeyer condensation reaction between chlorobenzene and trichloroacetaldehyde (158); its insecticidal properties were not discovered until 1939 (20,98,108). Research into public health applications of DDT went on in secrecy during World War II, but in 1944 DDT was already praised as the miracle insecticide that would solve all future insect problems. DDT, indeed, soon could show a spectacular success record in controlling insect vectors of malaria, typhus, and other debilitating diseases. Agricultural applications followed immediately. In 1961, a peak production year, 80,000 tons were synthesized. However, by 1971, production had dropped to 20,000 tons, a level that represented 30% of all chlorinated hydrocarbon insecticides (91,98). Environmental concerns (27), combined with the buildup of resistance (21,26) by all major insect pests, resulted in its discontinued use in the industrialized nations by 1973. More biodegradable, but more expensive, DDT analogs like methoxychlor (Fig. 6A) replaced it (33,98,102). DDT still is registered for emergency use in the United States in case of public health threats. In third-world countries, its low price still makes DDT the most attractive chlorinated hydrocarbon insecticide.

• Cyclodiene insecticides (Fig. 6A). Soon after World War II, great opportunities existed for use of newly discovered, cheap synthetic intermediates derived from petrochemicals. Around 1930, Diels and Alder had discovered the general 1,4-addition reaction named in their honor (66). This reaction facilitated simple, inexpensive, and previously unavailable routes of syntheses for chlorinated compounds. The group of cyclodiene insecticides (aldrin, dieldrin, isodrin, endrin, isobenzane, heptachlor and its epoxide, chlordane, endosulfan, mirex, and chlordecone) (Fig. 6A) are all derived from hexachlorocyclopentadiene by Diels-Alder reaction with a variety of dienophiles or by a dimerization reaction of the starting material. In 1944, Hyman (20) took credit for recognizing the potential of this simple synthetic route when he made chlordane, aldrin, and dieldrin, while Kearns et al. (79) first reported the insecticidal activity of chlordane. The precise biochemical lesions caused by cyclodienes never were clarified. They probably interfere with nerve axons and act as CNS stimulants. In spite of this lack of knowledge, many other cyclodienes were made by the manufac-

turers. As a group, cyclodienes reached record sale volumes comparable to DDT—20,000 tons in 1971 (91).

With the exception of endosulfan, the cyclodienes are all environmentally quite stable. Because of their lipophilicity they tend to accumulate in food chains and in nerve tissues. Reports of their detrimental effects on mammalian fertility, chronic interference with the electrical activity in the brain, and suspected carcinogenicity (27) lead to their gradual phase-out during the 1970s. Because of its reduced persistence, endosulfan can be considered the most benign of the group, although on Metcalf's scale (101) it ranks in category 9.7, comparable with mevinphos, azinphos-methyl, and lindane.

• Mirex and chlordecone (Fig. 6A). These highly chlorinated compounds are prime examples of "hard pesticides." Both compounds, synthesized by dimerization of hexachloropentadiene, were used for fire ant control. They are highly persistent, bioaccumulate in food chains, induce multifunction oxidase enzymes (150), and have poor environmental ratings (101). Chlordecone (kepone ®) has been linked to cases of reduced spermatogenesis and infertility in man (150).

Synthetic pyrethroids: The use of pyrethrum powder as an insecticide probably dates back to antiquity, but the natural product, contained in the flowers of *Chrysanthemum* sp. is still being extracted for commercial use (28,92,114). Its high price and limited environmental persistence stimulated efforts in several laboratories in Japan and Switzerland to extract and characterize the active principles. Given the crude analytical methods of the time, the chemical identification of pyrethrins by Staudinger and Ruzicka (147, 148) is considered a milestone in natural product chemistry. The full characterization of the numerous structural, geometric, and optical isomers took another 50 years. Schechter et al. (130) initiated the search for synthetic pyrethroids with improved stability and ease of preparation. They developed allethrin (Fig. 6B); less expensive, photostable, synthetic analogs were prepared in Japan, England, and France. Elliott et al. (39,41) synthesized bioresmethrine, the first compound more toxic than the natural esters. Subsequently, decamethrine was synthesized by systematic structure-toxicity optimization (40). With an LD_{50} of 0.01 mg/kg and effective application rates of 10–20 g/ha, it represented the then most effective insecticide. Developments since 1974 have been broadly reviewed (42). Several systematic improvements of other synthetic routes have been reviewed by Naumann (113). They led Japanese groups to tetramethrine and fenvalerate (Fig. 6B).

Simultaneous use of synergists (sesamin, piperonyl butoxide) can increase effectiveness of the natural pyrethrins by blocking metabolic degradation systems. One noteworthy approach is the chemical incorporation of the methylenedioxy moiety (the group confering synergism) into the insecticidal pyrethroid molecule (Fig. 6B), rather than physically mixing it into the formulated product. This principle is discussed further under "hybrid insecticides."

The primary targets of pyrethrins are the ganglia of the insect CNS. With the exception of criteria 1, 6, and 7, pyrethrins are close to the "ideal" insecticide. Gradual buildup of resistance by heavy selection pressure will, however, be unavoidable.

Hybrids between pyrethroids and DDT: A different avenue for the design of new insecticides has been suggested by Holan et al. (63,64). They identified "toxaphores" for pyrethroid analogs and for isosters of DDT, combined them in one chemical structure, and found 1) hybrid structures with considerable insecticidal activity and biodegradability, with the R-enantiomers being more toxic than the S-enantiomers (as commonly found in pyrethrins); 2) shifts of the site of action from the peripheral level (characteristic of DDT type compounds) to more central (but still unspecified) CNS sites; and 3) a strong potential for synergism by addition of the methylenedioxy moiety, a structural feature found in many mixed function oxidase inhibitors. The hybrids are nontoxic to mice. One example is the 3,4-methylenedioxybenzylester of 1-*p*-ethoxyphenyl-2,2-dichloropropane-1-carboxylate (Fig. 6C),

Although the hybrids between pyrethroids and DDT show cross-resistance with both parent compounds and will therefore not solve the crucial problem of irresistibility, they nevertheless point in the direc-

tion new developments may take. In summary, the pyrethrins, their synthetic analogs, and their hybrids provide one of the best examples to date for enlightened research leading to structural optimization.

The theme of hybrid insecticides will appear again in the section on third-generation insecticides, with Bowers' JH analogs (15,16) composed of features of JH and the synergistic 3,4-methylenedioxyphenyl moiety Fig. 8A.

MINOR COMPOUNDS

The search for new classes of compounds is an ongoing endeavor in many industrial laboratories. Of equal importance is the refinement of bioassay procedures. Originally, bioassays were designed to test for toxicity against fungi, weeds, mites, or nematodes, and only for short-term insect toxicity. Because of this blind screening strategy, promising leads were missed. Refined tests introduced within the last decade and long-term screening corrected this shortfall and rewarded the new initiative with the discovery of several new insecticides such as chlordimeform, the nitromethylene heterocycles, and the growth regulators.

Formamidines: This class of compounds was originally developed as acaricides. Later bioassays revealed excellent ovicidal activity. Also, the compounds could inhibit some Lepidoptera and Hemiptera larvae from consuming plant tissue treated with the compounds.

Chlordimeform (*N*-4-chloro-*o*-tolyl)-*N*, *N-dimethyl* formamidine) and a series of analogs have been reviewed (65,82,89). Today, the formamidines are extensively used for control of cotton and garden insects. In some situations, chlordimeform is preferred to broad spectrum pyrethroids which tend to kill insect predators and parasitoid populations and thus generate secondary outbreaks of new pests that are originally kept in ecological equilibrium.

The hyperexcitation and the "crawling off" reaction observed in treated larvae is explained by noncholinergic, central inhibitory effects of chlordimeform and some of its metabolites on the monoamino-oxidase system. Accumulation of biogenic amines like serotonin, norepinephrine, and octopamine (44) results in temporary hyperactivity with a chance for recovery. Other mechanisms, such as stimulation of mitochondrial ATP'ase activity and inhibition of oxidative phosphorylation (different from that caused by the uncoupler dinitrophenol), are discussed by Matsumura (91).

Problems may arise from the carcinogenic potential for bladder epithelial cells caused by chlordimeform degradation products like *p*-chloro-*o*-toluidine which is found in the urine of treated mammals.

Chlordimeform is an example of a promising class of compounds with various different activities. Its ability, at sublethal doses, to modify behavior, is somewhat reminiscent of behavior modifiers isolated from natural sources. Its discovery underscores our ability for developing new leads that may provide keys for entirely new modes of action.

Nitromethylene heterocycles (NMHs): NMHs originated in the Shell laboratories from structure optimization of unspecified synthetic compounds (142,143). In their toxicities for a number of insects, NMHs with the pyridyl moiety are comparable to parathion while being relatively safe to mammals. They are cholinergic agonists at the CNS level. Although they are fast acting "knockdown" agents like the pyrethroids and show a favorable weight-to-toxicity ratio, agricultural applications have been hampered by their environmental instability. Problems also arise from the fact that they have a zwitterionic charge distribution and are not readily taken up by the lipophilic surface of arthropod appendages. Field results during the last decade have been erratic, and the compounds, in spite of their promise, have not yet gained registration.

Minor botanical insecticides containing nitrogen: Like pyrethrins, the minor botanical insecticides have been used for centuries (37). Nicotine, nornicotine (Fig. 7) and anabasine occur in tobacco, *Nicotiana sp.,* and in the small perennial shrub *Anabasis sp.* In 1951, 750 tons of nicotine, the predominant alkaloid of this group, was sold in the United States and 2,800 tons worldwide. Although it was first isolated 150 years ago and synthesized only 75 years ago, its use as an aphicide can be documented in France in 1763 (137). Nicotine was the most toxic of all the synthetic

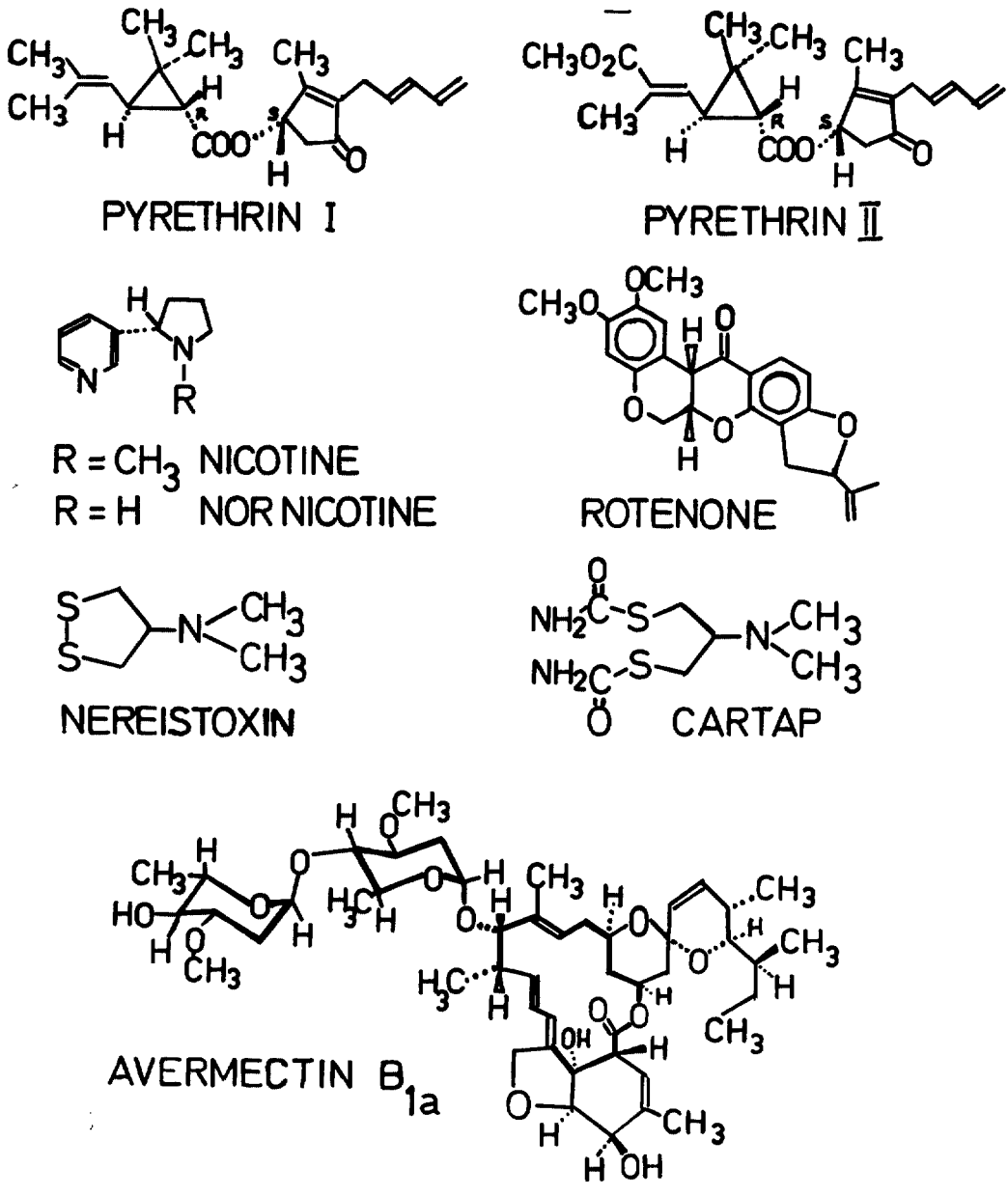


Fig. 7. Insecticides of botanical, marine, and microbial origin.

analogs investigated (157). Its high toxicity to warm-blooded animals is explainable by its easy skin and lung penetration and by its interaction with postsynaptic acetylcholine receptors. The broad range toxicity of these alkaloids, even when used as sulfate salts, calls for great caution in handling and limits their undisputed value as insecticides.

Veratrine alkaloids from hellebore roots (*Veratrum sp.*) and sabadilla seeds (*Schoenocaulon sp.*) gained commercial importance as insecticides against lice, plant feeding Hemiptera, and thrips. But their high cost, chemical lability, and toxicity to mammals limit their usefulness (94). Similarly, the root and stem of *Ryania sp.*, which contain ryanodine (30,94), have been applied for the control of European corn borers and other crop insects. The higher air and light stability and the improved residual activity of these plant extracts gave

them a temporary advantage over pyrethrum and rotenone.

Nonalkaloid botanicals: Water extracts from wood chips of the tropical tree *Quassia amara* contain quassin and neoquassin, tetracyclic diterpenes with considerable toxicity against sawflies and aphids (37). Today, they have only historical value.

Rotenoids have been described in 68 plant species of the family Leguminosae, including 12 species of *Derris* (137). Originally used as fish poisons, the insecticidal properties of the water soluble rotenoids were known as early as 1848. Rotenone, a pentacyclic flavonoid (30,47) (Fig. 7), was first isolated in 1902 and chemically characterized in 1932 by four independently working groups. The synthetic substance is too expensive for agricultural use, but even today the natural rotenoids are valued for their insecticidal properties on home and garden crops and for their low toxicities to plants and mammals. After the introduction of second-generation insecticides, U.S. imports of *Derris* roots dropped from 6,600 tons in 1947 to 2,300 tons in 1948 (137).

Insecticides from microbial origin: Microbial insecticides are accessible by large-scale fermentation and are relatively insect specific. Today they claim a minor but significant share of the market. Among the more than 1,500 known insect pathogens are several types of virus, microsporidia, and the spore-forming bacteria. The bacterium *Bacillus thuringiensis* (BT), discovered in 1915 by Berliner, has been extensively studied (90,112). Preparations of BT contain a crystalline toxic protein (δ-endotoxin), a thermostabile water soluble β exotoxin (30), and spores infective to insects (5). Commercial production of BT began in 1958.

In contrast to the fast acting chemical insecticides, microbials cause slow paralysis and eventual death by septicemia. The serotype *BT israelensis* specifically kills mosquitos and blackfly larvae and has considerable value in public health programs. BT preparations may be applied to crops shortly before harvest without human health or environmental hazards. In many respects, BT comes close to the ideal insecticide, even though problems have been encountered with its lability against sunlight; difficulties with standardization of the virulence obtained in different batches have also been reported.

Avermectins: These novel microbial insecticides are produced by cultured mycelia of the soil microorganism *Streptomyces avermitilis* (123). Originally, avermectins were discovered as broad spectrum anthelmintic agents for domestic animals with a very high activity in the range of 10–300 ppb (78). Later tests on confused flour beetles, sheep blowflies, and ectoparasites including mites and ticks encouraged further testing. Activity against all major orders of insects, as well as against plant-parasitic nematodes, was obtained at LD_{50} levels as low as 10 μg/kg. One of the distinctive features of avermectins is their novel chemical structure identified as a 16-membered pentacyclic lactone disaccharide (3). Eight different compounds were isolated, each with slightly different structure and activity spectrum (Fig. 7).

The symptoms of poisoning appear slowly and would have been missed by the classical short-term bioassay for toxicity. Paralysis of the caterpillar pseudopodia results in inhibition of movement on the plant and feeding. Egg production in fire ant queens is permanently inhibited by doses as low as 0.12 g/ha.

Avermectins have a unique mechanism of action. Unlike OP compounds and carbamates, avermectin has no cholinergic effects. Rather, it blocks transmission of electrical potentials between interneurons and excitatory motoneurons in the ventral nerve cord; it inhibits transmission between inhibitory motoneurons and muscle by opening the chloride channels on the membranes; but it has little effect on excitatory neuromuscular junctions. The block of interneuron to excitatory motoneuron transmission can be reversed by picrotoxin, a known gamma-aminobutyric acid (GABA) antagonist. Avermectins cause release of GABA from brain synaptosomes in rats (120). Interference with the chloride gate has been observed by Fritz et al. (46).

It is too early to assess the potential of avermectins. They certainly will stimulate more research and investments.

Fungal secondary metabolites with insecticidal activity: A recent example was described by Claydon and Grove (32). In

surface cultures, one strain of *Verticillium lecanii* produced pyridine-2,6-dicarboxylic acid. Its insecticidal activity against the blowfly *Calliphora erythrocephala* was determined as 50 μg/fly.

THIRD-GENERATION INSECTICIDES

This term was coined by Williams (156). It characterizes a chemically diverse group consisting of the ecdysteroids, the juvenile hormones and juvenoids, the chitin synthetase inhibitors, and the precocenes. Several feeding deterrent natural products have striking morphological effects, in addition to their ability to modify insect feeding behavior. They interfere with the molting process and are therefore included in the group of third-generation insecticides. Their example shows that the borderline to the fourth-generation insecticides is less clearcut than the systematic mind might wish it to be.

Ecdysteroids: Arthropods have relatively rigid exoskeleta. Growth and development from the larval to the pupal and adult stages requires periodic molting. This process is under tight control of the molting hormone ecdysone. It was originally isolated by Butenandt and Karlson (23) and structurally identified as a C_{27} steroid by Karlson et al. (76). The term "ecdysteroids" is now used for the entire family of closely related hormones which have been isolated from insects, crustacea, and plants (67).

A number of synthetic analogs (67) have toxic effects, prevent egg development, or interfere with cuticle hardening after molting. However, because the compounds were environmentally unstable, or would not penetrate the insect cuticle, or were too expensive, they did not gain acceptance. Moreover, insects do have the capacity to inactivate structurally identical, or similar, phyto-ecdysteroids contained in some of their food plants (141). Development of the juvenile hormones and juvenoids has been more successful.

Juvenile hormones and juvenoids (JHs): The discovery of a factor controlling insect differentiation and development occurred in 1937 (154). Twenty years later, an extract from male cecropia silkmoths was found to have potent juvenile hormone activity (155). JHs regulate molts at the juvenile or larval stage, in contrast to ecdysteroids which regulate molts at the pupal-to-adult stage. Insects treated with JHs do not reach adulthood; they are arrested in their development and eventually die without reproducing. Industrial scientists like to call the JHs "insect growth regulators." This alternative term is justified because JHs have no hormonal activity in warm-blooded animals.

After a painstaking purification procedure monitored by quantitative bioassays, Röller et al. (128) isolated and chemically identified the hormone as a terpenoid related to farnesol. Today, three more naturally occurring hormones are known (Fig. 8A), and hundreds of synthetic analogs have been prepared.

Since the discovery of the "paper factor" juvabione in balsam fir (*Abies balsamea*) (140) and the registration of methoprene (139) as a synthetic JH analog with improved environmental stability, progress in this field has been vigorous. Many reviews highlight our relatively high degree of knowledge (17,56,59,135,146) and sophistication. JHs are convincing examples for the success of enlightened research.

If JHs ultimately did not revolutionize the insecticide field, it is probably because of the formidable crux of resistance (21) and the impatience of the user who wants to see "dead insects" instantly after application. This is, however, a societal rather than a toxicological problem. By design, JHs come close to the ideal insecticide. Their specificity is limited, but it can be improved by appropriate formulations (84, 85).

The chitin synthetase inhibitor diflubenzuron: Chitin (poly-*N*-acetyl-glucosamine) is a structural component of the cell wall of pathogenic fungi and also adds strength to the inner proteinaceous cuticular layer of insect larvae. Inhibition of chitin synthesis will therefore interfere with growth and development of these organisms; insect larvae will be unable to molt properly.

The discovery of the fungicidal properties of polyoxin D (43,105) prepared the biochemical background necessary for the search for other compounds with similar activity. Diflubenzuron, an inactive analog obtained during screens in the herbicide synthesis program, turned out to be a po-

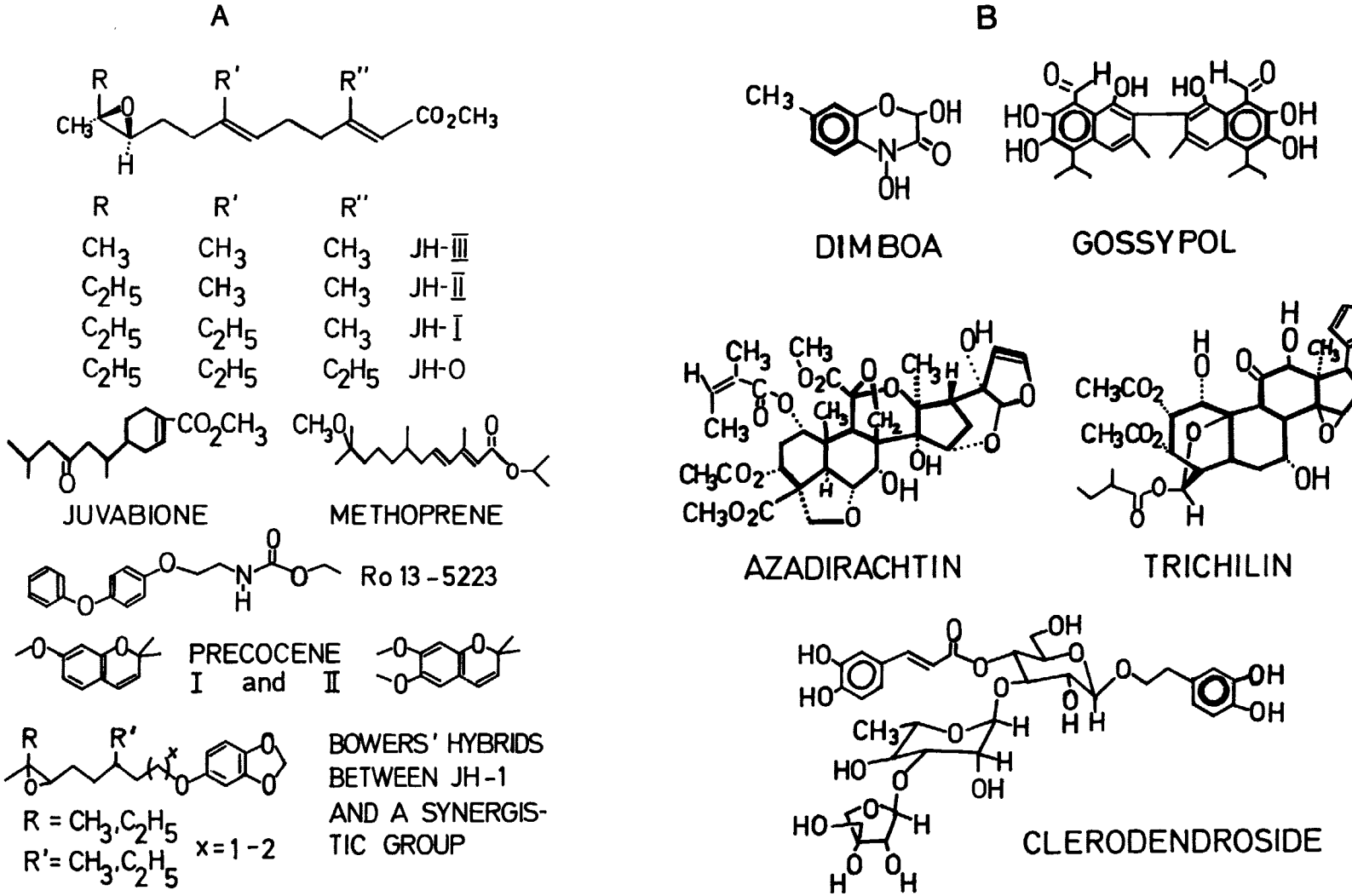


Fig. 8. Third-generation insecticides: Modifiers of insect development. A) Juvenile hormones. B) Feeding deterrants.

tent inhibitor of chitin synthetase in larvae of *Pieris brassicae* (107) and other insects (121). Rationales and procedures for selecting diflubenzuron as the compound for ultimate development have been reviewed by Verloop and Ferrell (152). As in the OP and carbamate series, Hammett's sigma constants and Hansch's π-constants were helpful in identifying trends within a series of analogs. Biodegradability was an important concern in selecting the difluoro-analog. It has favorable environmental properties (low bioaccumulation, moderate persistance) and is safe to mammals. As with other growth regulators, its effects are only visible several days after application. Diflubenzuron is another example of the carefully designed and optimized members of the third insecticide generation. It does not compete in price with the chlorinated hydrocarbons or the OP compounds.

Precocenes: Bowers et al. (17) discovered a new class of natural products with growth regulating activity. Extracts of the greenhouse plant *Ageratum houstontianum* produced developmental abnormalities in several insect species that paralleled *precocious* molts obtained after ecdysterone treatment. The compounds, named after their biological effect, were isolated, chemically identified, and synthesized; they are chromene derivatives (18) (Fig. 8A). Precocenes are oxidized in vivo to highly reactive expoxides with known alkylating power (122). They exhibit specific toxicity to the sensitive neurosecretory cells where they produce effects comparable to an allatectomy. This results in precocious metamorphosis to sterile or malformed adults or to intermediates between larval, pupal, and adult stages of development which are incapable of reproduction.

Insect antifeedants (Fig. 8B): Natural products with feeding deterrent activity against insects have been described in several plant species; e.g., DIMBOA (80), a compound from resistant hybrids of *Zea mays* which discourages larval feeding of the corn earworm *Heliothis zea* and the European corn borer *Ostrinia nubilalis*. According to Lukefahr and Martin (88), the pigment gossypol confers resistance to cotton plants against the bollworm and tobacco budworm. Other antifeedant compounds (61,71) have been identified as clerodendroside and trichilins (111) (Fig. 8B).

The most potent feeding deterrent known so far has been isolated from Neem (*Azadirachta indica*), a native tree of the Indo-African region. Among several dozen compounds of similar structure, azadirachtin, a complex tetranortriterpenoid, is the most active component. As Schmutterer et al. (132) point out, topical application of 1 μg azadirachtin per fourth-instar larva will interfere with the molting process. In addition, azadirachtin sterilizes adult female insects. Obviously, Neem extracts have several distinguishable modes of action. For centuries, Neem tree products were important as insecticides in India and Africa. Partially purified Neem fruit extracts have been proposed for use in developing countries as cheap but effective substitutes for synthetic insecticides (103).

FOURTH-GENERATION INSECTICIDES

Chemical modification of behavior is another recent approach to insect control. Chemical modifiers have in common that they interfere with normal behavior patterns and delay or prevent mating and producing offspring. Pheromones (75) (Fig. 9), also known as ecomones, sex attractants, and aggregants, are the prominent members of the fourth-generation insecticides. They occur in a wide variety of insects (69,106), 138,), spiders, mites, nematodes (14,125), aquatic invertebrates (109), and animals including primates (127). Examples of insect pheromones given in Fig. 9 include silk moth (24,77) and honeybee (53), gypsy moth (9), boll weevil (151), pink bollworm (68), bollworms (81), and corn rootworms (57). In terms of specificity and sensitivity, female moths produce the most striking behavioral effects with their sex pheromones (124). However, some male butterflies have reversed the sex roles and use pheromones as aphrodisiacs during courtship with females. Social insects like termites, ants, and bees communicate in their hives by pheromones, and bark beetles of both sexes use pheromones for marking aggregation sites.

Although chemically quite varied (70), all pheromones share a few common properties: volatility, specificity, potency, and nontoxicity. Synthetic pheromones can be

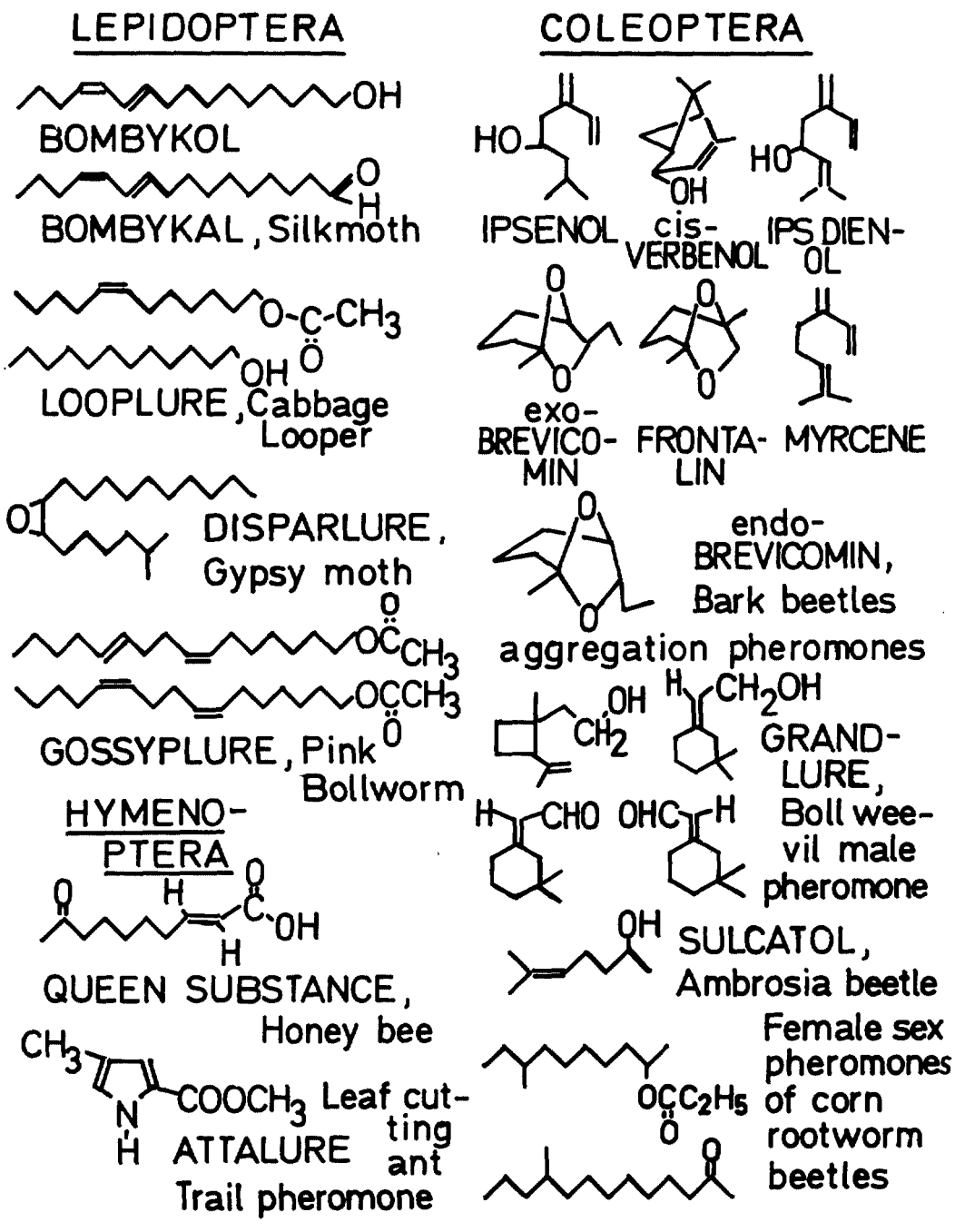


Fig. 9. Fourth-generation insecticides: Modifiers of insect behavior. Insect pheromones of Lepidoptera, Hymenoptera, and Coleoptera.

used to manipulate insect behavior in such a way that it will be maladaptive to the individual organism (69,106,116,119,138). Mechanisms include the saturation of antennal receptor sites with synthetic pheromones so that natural pheromones are not detected, thereby preventing mating. Alternative explanations for the observed effects are disorientation of males by the many artificial point sources which mask the females' natural signals. For a few selected agricultural pests (31,87,106), pheromone applications resulted in control levels that are economically competi-

tive with conventional second-generation pest control measures. Their environmental benignity is among the best of all insecticides.

Pheromone structural optimization has reached a high state of perfection through natural selection over many insect generations. The analytical chemist can, however, improve pheromone mixtures by quantitatively defining minor components (81). The synthetic chemist can identify less costly starting materials and new routes for production of pheromones of higher purity. The ecologist can further improve the efficacy of refined pheromone mixtures by developing better monitoring traps and by defining the best time of day and season for their deployment (69).

Novel formulation technology: Improved insecticides and behavior modifiers can be attained by providing new compounds and formulations and by developing new modes of application. Recent progress has been made in the field of microencapsulation techniques (25). Compounds like OP esters and certain carbamates previously considered hazardous to the applicator can now be handled without special precautions. Also, the formulated material has increased stability against oxidation, hydrolysis, and photolysis and will allow the user to realize savings by more judicious and sparing application. Controlled release of pheromones from hollow fibers and laminated sheets (84,85) represents progress in application technology as well.

The final success of fourth-generation insecticides depends on close cooperation and integration of the efforts of several disciplines. This price must be paid for the ever increasing sophistication of approach. It is a characteristic of all biorational strategies (38,93).

PROMISING LEADS

Novel natural products: Toxins are effectively used by insects in their own defense or as offensive weapons in their search for food and shelter (12). Dendrolasin, iridomyrmecin, and cantharidin (30) all have considerable activity. But analog synthesis has not yet produced useful insect control agents based on the leads suggested by nature.

The oceans cover over 71% of the earth's surface. Comparatively little is known about this huge ecosystem and its resources. Nereistoxin, a defensive substance produced by the marine annelid *Lumbriconereis heteropoda,* served as the model compound for the synthesis of the insecticide cartap (Fig. 7). Its metabolic activation in vivo generates nereistoxin, a synaptic blocking agent that binds, like nicotine, to ACh receptors.

Other new structures from diverse marine organisms are currently being intensively investigated (45,126,131). Potent antifungal, antibacterial, and antitumor drugs have already been found.

Contributions from the neurosciences: A promising target for new insecticides is the cholin acetyltransferase. Inhibitors of this enzyme would impede the synthesis of ACh (134). At the other end of the biochemical chain, the interaction of ACh with its receptor would provide a target for interference. The natural products nicotine and nereistoxin point in the direction research may take (73).

The glutamate transmitter system is only superficially understood (104). More research is needed to identify naturally occurring glutamate analogs and to design possible synthetic substances that focus on that system (60).

Neurotransmitters like ACh, GABA, and catecholamines produce postsynaptic effects quite rapidly. ACh excites the postsynaptic membrane across the 100-Å-wide synaptic cleft (136) within 40 msec and must be inactivated by AChE, one of the most active enzymes, before another excitatory event can take place. In contrast, newly discovered neurotransmitter peptides with molecular weights of about 1,000 Daltons are similar to the mammalian luteotropic hormone releaser hormone (LHRH). They act slowly, within 10 min, and by diffusion over distances of 10 μm (7). Inactivation sets in as slowly as activation takes place. Toxicological interference with this cell communication system seems possible, and investigations in this area could produce new types of insecticides (22,35,117). A lead already has been provided in the field of specific antibodies (115).

In this futuristic area, the pleas by Barend Ter Haar (6) and Corbett (36) for

interdisciplinary cooperation provide the key for success. Classical toxicology must join the neurosciences in its quest for new knowledge. If results from this research find practical applications, the compounds will justifiably be labeled "fifth-generation insecticides" because they will represent new approaches with respect to their discovery, their mode of action, their design, and their evaluation.

CONCLUSIONS

Short appraisals of the developmental histories of some discussed insecticides are summarized in Table 1. The majority of insecticides were developed by the "proven scheme" of random synthesis; screening and structure optimization were productive but time consuming and expensive. Cases of rational design and enlightened research, on the other hand, are still in the minority but increasing in frequency, as column 6 of Table 1 shows.

Up to 1970, searching and screening for compounds with higher and higher toxicity was the primary goal of insecticide research. With the age of environmental concerns, other qualtities—such as cost-effectiveness, biodegradability, environmental benignity, lack of delayed neurotoxicity, and high vertebrate and mammalian selectivity ratios—became increasingly desirable.

Some of the new "soft" insecticides of the third and fourth generations, the development and behavior modifiers, came into being when an entirely new philosophy was adopted. That philosophy aims at reducing the target pest population by manipulation of their development and behavior (not outright killing) while leaving nontarget species untouched.

Finally, nature still has vast treasures ready to be explored by man. These natural products with unprecedented structures and modes of action are incomparable with classical insecticides. Brain peptide hormones and their possible manipulation by exogenous factors offer opportunities for new insecticides. Solutions to the problem of insect resistance remains the ultimate challenge. The "ideal" insecticide may never be found. Yet, better approximations towards this ideal are forthcoming.

Future breakthroughs toward the rational design of new insecticides will hinge upon better knowledge of their modes of action. Target sites investigated so far include 1) the neuromuscular junction and the peripheral nervous system, 2) the CNS, 3) cuticle formation, 4) reproduction, and 5) behavior of host and mate finding. Other sites for increased future attention should include 1) manipulation of ionic nerve channels other than Na^+, 2) novel acylating agents for AChE (other than phosphorylating and carbamylating agents known today), 3) anti-JH, 4) cholinergic receptor agonists, 5) cholinacetyl transferase inhibitors, 6) glutamate analogs, and 7) antibodies as insecticides (8).

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