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Properties and Applications of Pyrethroids

by Michael Elliott*

Improved understanding of the factors determining the insecticidal activity, the mammalian toxicity, and the stability in air and light of natural and synthetic pyrethroids has led to a series of new compounds with a very favorable combination of properties. Their characteristics include outstanding potency to insects, low toxicity to mammals associated with rapid metabolic breakdown and, in appropriate cases, adequate stability on plant surfaces even in bright sunlight. Initial tests indicate that even the more stable compounds are degraded rapidly in soil, so if the trials at present in progress reveal no toxicological or environmental hazards, within a few years synthetic pyrethroids should be available to control a wide range of domestic, veterinary, horticultural, agricultural, and forest pests at low rates of application.

Introduction

The natural pyrethrins and related synthetic compounds have traditionally been recognized as excellent insecticides, harmless to mammals but too unstable and expensive to control pests of agricultural crops and forests efficiently and economically (*1–8*). This limited potential has changed dramatically in the past two to three years, for workers in Great Britain (*9,10*) and Japan (*11–13*) have shown that the photolabile centers of the molecular framework of pyrethroids may be replaced with alternative groups giving much greater overall stability in air and light, while the features essential for the great insecticidal activity and low mammalian toxicity are retained. As a consequence of these advances, a range of new insecticides is being developed. It now seems probable that by 1980, synthetic pyrethroids, with their combination of favorable properties, may have an importance comparable with organochlorine compounds, organophosphates, and carbamates as practical insecticides used on a large scale. Much evaluation, at present in progress, of the toxicological and environmental properties of the new compounds remains to be completed. However, preliminary results from these studies are favorable.

*Department of Insectides and Fungicides, Rothamsted Experimental Station, Harpenden, Hertfordshire, AL5 2JQ. Great Britain.

In summary, some characteristics of recent synthetic pyrethroids are: (1) greater stability in field than some organophosphates and carbamates, e.g., active after 2 weeks on leaf surface in bright sunlight; (2) rapid metabolism and elimination from mammalian systems, giving low toxicity; (3) limited persistence in soil (weeks, not years); (4) greater potency than other insecticides; low application rates which minimize environmental contamination and offset higher costs. It is therefore appropriate to discuss the new insecticides at a conference in 1975 on the current and future uses and potential human health effects of new approaches to insect pest control.

Present Situation

In contrast to the large quantities of organochlorine, organophosphate, and carbamate insecticides now used, the total consumption of natural and synthetic pyrethroids is below 500 tons (*14*) and comparable to that of nicotine, the only other important natural insecticide. However, the natural and the more active synthetic pyrethroids are generally more potent than other classes of insecticides (*8*) and, unless precluded by instability, or by lack of systemic properties, kill a wide range of insects efficiently by contact or as stomach poisons (*15*). Such broad activity may affect beneficial insects and predators as well as target species, but the instability, outstanding activity,

Table 1. Relative potencies of pyrethroid esters to the housefly (HF) and the American cockroach (AC).

	Alcoholic component[a]	Acid component	Approx. LD_{50}, μg/g HF	AC
Bioresmethrin	5B3F	(Me)(+)-*trans*[b]	0.6	1.7
Permethrin	3POB	(Cl)(±)-*cis, trans*[b]	1.0	0.5
Biopermethrin	3POB	(Cl)(+)-*trans*[b]	0.6	0.3
NRDC 167	3POB	(Cl)(+)-*cis*[b]	0.3	0.15
NRDS 161	α-CN-3POB	(Br)(+)-*cis*[b]	0.03	0.05
S 5439	3POB	4-Cl, α-isopropyl[c]	4.8	1.6
S 5602	α-CN-3POB	4-Cl, α-isopropyl[c]	1.6	0.74

[a] Alcoholic components: 5B3F = 5-benzyl-3-furylmethyl alcohol; 3POB= 3-phenoxybenzyl alcohol; α-CN-3POB = α-cyano-3-phenoxybenzyl alcohol.
[b]Substituents and configuration of 3-vinyl side chain on 2,2-dimethylcyclopropane carboxylate.
[c](±)-4-Chloro-α-isopropylphenylacetic acid.

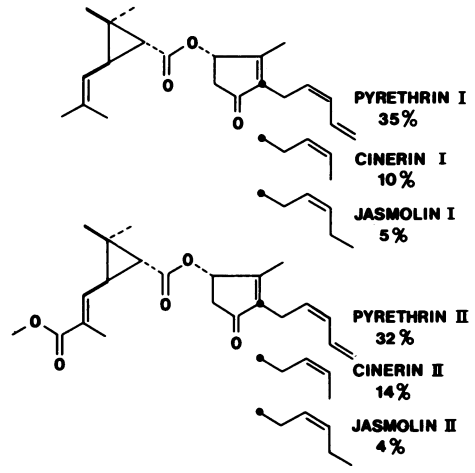
and low mammalian toxicity of pyrethroids can frequently be exploited to achieve effective and selective control not possible with more stable insecticides. Bioresmethrin (*7,16*) for example, which is a very potent insecticide, but has very low mammalian toxicity [ca. 8000 mg/kg oral toxicity, female rats (*17,18*)] is especially suitable for immediate preharvest treatment of food crops (*19*). These and other uses for the pyrethroids available at present are well documented (*20*). In this paper, therefore, new applications made possible by the greater stability, still combined with low mammalian toxicity, of the more recent compounds, will be emphasized. First, the development of the present range of pyrethroids will be discussed.

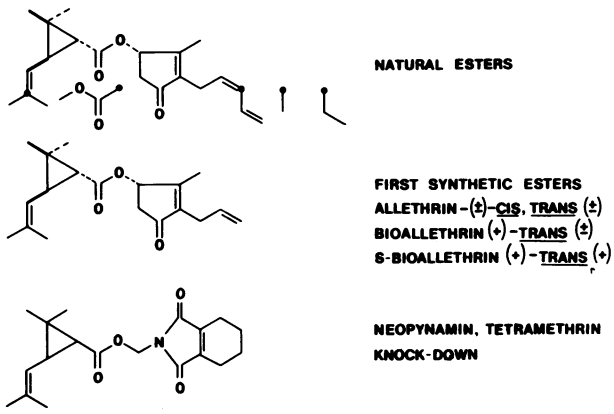
Structure and Insecticidal Activity

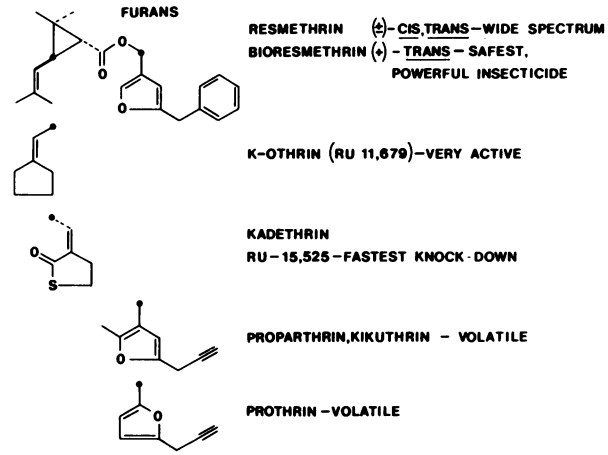
A typical extract of natural pyrethrum from *Chrysanthemum cinerariaefolium* contains pyrethrins, cinerins, and jasmolins. Pyrethrin I is the most important natural constituent for killing insects (*7,21*) while pyrethrin II provides much of the valued rapid knock-down action against flying insects (*22*). The structure of pyrethrin I is an appropriate basis for discussing the molecular features necessary for insecticidal activity, and for considering how these may be modified to increase potency, decrease toxicity to mammals and improve stability. This will illustrate the guiding principles which have led to the present range of synthetic pyrethroids.

The insecticidal activity of pyrethrin I depends on the overall structure of the ester, in particular on methyl groups at C-2 on the cyclopropane ring (*23*) maintained in a definite stereochemical disposition with respect to an unsaturated side chain at C-3 and the ester link at C-1 (*24–26*). Without steric constraint, the ester probably adopts an S-*trans* conformation (*2,25,26*) and, supported by the near-planar cyclopentenolone ring, the *cis*-pentadienyl side chain can adopt only certain orientations in space with respect to the features of the acid structure discussed above. High activity is related to the ability of the molecule to adopt an appropriate shape or conformation at the site of action, and this will be particularly influenced by the absolute configurations of the asymmetric centers at C-1 of the cyclopropane ring and at C-4 of the cyclopentenolone ring. In pyrethrin I, these configurations are, respectively, *R* and *S* (*27,28*), and inverting either diminishes or eliminates insecticidal activity.

A number of synthetic pyrethroids have been derived from the structures of the natural esters. The first important synthetic compound, still used today, was allethrin, developed by Schechter, Green, and La Forge in 1949 (*29*), by shortening and simplifying the pentadienyl side chain of the natural esters (*4,5*). Allethrolone, the alcoholic component, is now resolved on a commercial scale,







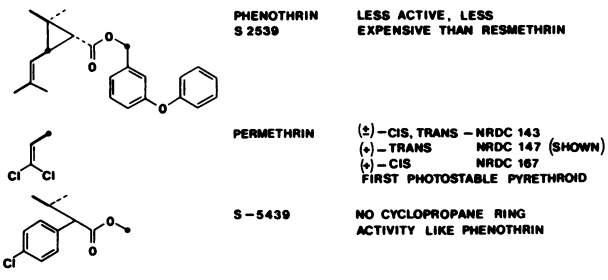
and the (+)- form, esterified with synthetic (+)-*trans*-chrysanthemic acid (*30–32*), gives *S*-bioallethrin, corresponding to pyrethrin I in stereochemical form. The quantity of allethrin, bioallethrin, and *S*-bioallethrin manufactured exceeds that of any other synthetic pyrethroid. When supplies of natural pyrethrum are restricted, allethrin is used as a substitute. Much allethrin is also used in mosquito coils, where its volatility and thermal stability, greater than the natural esters, is an advantage. *S*-Bioallethrin (*33*) is an outstandingly rapid knockdown agent against some insects, but like bioallethrin and allethrin lacks the broad spectrum of activity shown by the natural pyrethrins (*7*).

Neopynamin (tetramethrin) (*34*), reported in 1964, was the next synthetic pyrethroid produced commercially. The alcoholic component is not directly related by structure to other synthetic pyrethroids, and although neopynamin knocks insects down rapidly when incorporated into aerosols and comparable formulations, it is not generally a good killing agent (*7, 35*).

In 1966, (*16,36,37*), the first compounds that had properties superior to those of the natural ester were synthesized. The discovery of these esters of 5-benzyl-3-furylmethyl alcohol suggested that continued investigation of this group of compounds would be likely to lead to further practical insecticides. The furan alcohol was found by a systematic examination of the features essential for insecticidal activity in cyclopentenolone pyrethroids; the furylmethyl component, which, unlike the natural alcohol, had no asymmetric center, reproduced the stereochemistry of the cyclopentenolone nucleus and the phenyl group the function of the unsaturated olefinic side chain. An additional valuable property of the furylmethyl esters, especially that from (+)-*trans*-chrysanthemic acid (bioresmethrin) was that the great insecticidal activity was combined with very low mammalian toxicity (*7*). These favorable properties merited commercial production of resmethrin and bioresmethrin.

The same furan alcohol is a component of other practical pyrethroids. The ethanochrysanthemate (K-othrin, RU 11,679) (*38–40*) has even greater insecticidal activity against some insect species than bioresmethrin, though the mammalian toxicity is also higher (*7*). Kadethrin (*41*) (RU 15,525) has a thiolactone ring *cis* to the ester function and knocks down insects more rapidly than any other compound yet reported. The change in biological properties from K-othrin to Kadethrin with minor alteration of chemical and stereochemical features illustrates well the potential for developing a wide range of insect control agents in the pyrethroid group. Two other more volatile pyrethroids derived from furan alcohols with propargyl side chains, proparthrin and prothrin (*35, 42–44*) have been developed in Japan as useful constituents of aerially dispersed insecticidal sprays, but the propargyl side chain is less effective than benzyl in giving the esters a wide spectrum of activity (*44*).

A further advance in developing synthetic pyrethroids was made independently in Great Britain and Japan in 1969 when it was recognized that *m*-substituted derivatives of benzene could reproduce the stereochemistry of the furylmethyl unit and a phenoxy group could replace the benzyl side chain (*7,9,11*). 3-Phenoxybenzyl alcohol gives esters highly active against insects with a smaller



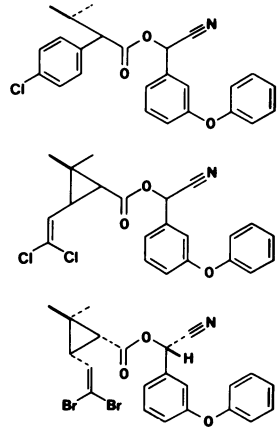
range of acids than 5-benzyl-3-furylmethyl alcohol—for example, the *cis*-thiolactone ester corresponding to Kadethrin is not a good knockdown agent (*45*). The chrysanthemate (phenothrin) is one third to one half as active as the 5-benzyl-3-furylmethyl ester to most insect species (*7,11*). However, 3-phenoxybenzyl alcohol is accessible by a variety of routes and is less expensive, compensating in some circumstances for the lower insecticidal activity of its esters.

At Rothamsted Experimental Station in 1972 an exceptionally valuable combination of properties was found in the esters (permethrin) of 3-phenoxybenzyl alcohol with the *cis*- and *trans*-dichlorovinyl acids (*9,10,46,47*) analogs of chrysanthemic acid with chlorine in place of methyl in the isobutenyl side chain. Not only was permethrin more active against many insect species than would have been predicted from experience with other esters of the acidic and alcoholic components, but it was also very much more stable in air and light than other potent pyrethroids and had lower mammalian toxicity than the 5-benzyl-3-furylmethyl esters of the same acid (*9,17,18,48*). Although all the synthetic pyrethroids discussed so far, from allethrin to resmethrin and related compounds have been valuable additions to the armory of pyrethroidlike insecticides, they did not greatly extend the range of applications established for the natural pyrethrins, their main advantage being that some, like bioresmethrin, provided an even greater margin of safety. Permethrin, however, retains most of the favorable characteristics of earlier synthetic compounds and is, in addition, stable enough to control insects in the field as efficiently as established organophosphates, carbamates, and organochlorine compounds, many of which it surpasses in potency.

A further outstanding advance (*12,13*) was disclosed by Japanese workers in 1974. With a suitably substituted aromatic ring in a steric position corresponding to the unsaturated side chain in chrysanthemates, the methyl groups adjacent to the ester link need not be supported on a cyclopropane ring and α-isopropylphenylacetates of established pyrethroid alcohols such as 5-benzyl-3-furylmethyl and 3-phenoxybenzyl alcohols have insecticidal activity comparable with the dimethylcyclopropane esters. The two series of compounds probably owe their insecticidal activity to common structural features, because both the *S*-isopropylphenylacetic acids and 1-*R*-dimethylcyclopropanecarboxylic acids, which correspond with one another in absolute configuration, give more esters than their optical isomers (*12,49*). Insufficient data are as yet published to permit precise comparison of the insecticidal activity attainable with the traditional cyclopropane carboxylates with that of corresponding α-isopropyl arylacetates, but the most active diahalovinylcyclopropanecarboxylates appear to be two to three times more potent to some insect species than the *S*-α-isopropyl 4-chlorophenylacetates, for which there are most results. The discovery of the potency of esters of these acids without cyclopropane functions enormously increases the scope for developing useful synthetic insecticides related to the pyrethrins.

Finally esters derived from 3-phenoxybenzaldehyde cyanhydrin (*50*) have been shown to be two to three times more active than those from 3-phenoxybenzyl alcohol. The dihalovinylcyclopropane ester of 3-phenoxybenzaldehyde cyanhydrin (NRDC 149) is more active (P. E. Burt, A. W. Farnham, P. H. Needham, personal communications) than the α-isopropyl 4-chlorophenyl acetate (so relative potencies of the esters are similar to those previously found with other alcohols). By using 1-*R*, *cis*-2,2-dimethyl-3(2,2-dibromovinyl)cyclopropanecarboxylic acid as resolving agent (*51*), the two optically isomeric cyanhydrins were separated. The crystalline isomer derived from the *S*-cyanohydrin (NRDC 161) (*51,52*) has quite exceptional insecticidal activity (on a molar basis, approximately 1700 times that of pyrethrin I to normal susceptible houseflies and at a level of ca. 0.03 mg/kg to other insect species), demonstrating the great potential latent in the pyrethroid group (*26*).

To summarize this discussion of the development of practical pyrethroids, Table 1 shows the relative insecticidal activities of some of the more recent compounds to houseflies and American cockroaches. The data are typical of results obtained by topical application of measured drops of insecticide solution to other species. References to



S 5602 2-5 TIMES AS ACTIVE AS PHENOTHRIN

NRDC 149 MIXED ISOMERS 2-3 x BIORESMETHRIN

NRDC 161 MOST ACTIVE INSECTICIDE 20-30 x BIORESMETHRIN

the relative potencies of other natural and synthetic pyrethroids are given in earlier publications (*7,8*).

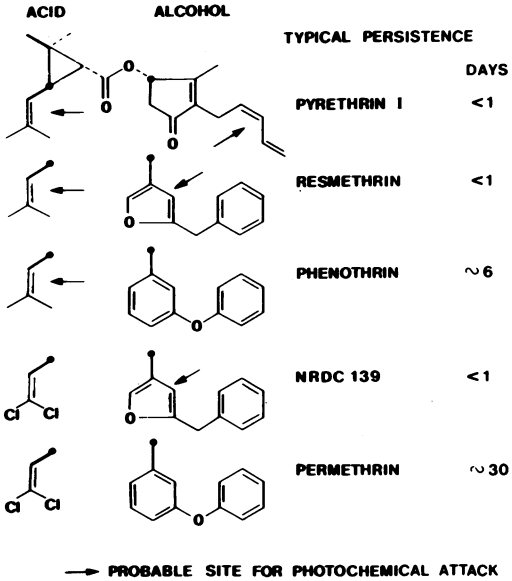
Future Developments

The wide variety of structural features and high level of insecticidal activity of natural and synthetic pyrethroids shows the scope for developing many potent new compounds. If limited to applications where instability in light was not a disadvantage, few new uses for these compounds could be foreseen. However, the discovery, in the past few years, of structural variations giving increased stability in light has greatly extended the scope of the group. Relative stabilities for some pyrethroids under typical conditions of exposure to air and light in the field are shown in Table 2 to illustrate the principles now recognized for designing more photo-stable compounds.

The photochemical degradation products from chrysanthemates (*53,54*) indicate that the isobutenyl side chain is attacked and the pentadienyl side chain of pyrethrins I and II is another reactive position; the presence of at least two photosensitive centers in the same molecule explains the observed instability in air and light of pyrethrin I. In 5-benzyl-3-furylmethyl esters the photochemical decomposition products show that the furan ring reacts as a dienophile with oxygen (*55,56*) so that like pyrethrin I, resmethrin has two sensitive positions and is unstable. In phenothrin (*11*), a stable aromatic center replaces the furan ring but the isobutenyl side chain remains, so that stability is still limited. Substituting chlorine for the methyl groups on the isobutenyl side chain of chrysanthemic acid increases insecticidal activity and inhibits photochemical attack, so that in NRDC 139 (*48*) only the furan ring remains for photochemical reaction, but this is sufficient to confer instability. However when all sites at which photochemical reaction is initiated are removed, in permethrin, the compound is adequately stable, as results discussed below demonstrate.

3-Phenoxybenzyl α-isopropyl aryl acetates similarly lack photosensitive centers (*12,13*) so that these two series of very potent pyrethroid insecticides are adequately stable to give residual control of pests in the field. Which particular compounds are most suitable for further development depends on a combination of factors, such as cost of production, insecticidal potency and spectrum of activity, stability required to give adequate control of the target pest and toxicity to mammals and other nontarget organisms.

Table 2. Photostabilities of some pyrethroids.



Physical Properties of Pyrethroids and Other Insecticides

Some insight into the effects on the environment of introducing more stable pyrethroids to control insect pests in field and forest may be gained by comparing the physical properties of the newer compounds with those of established insecticides and extrapolating from experience with the known compounds. Table 3 lists the octanol–water partition coefficients of some representative insecticides (G. G. Briggs, personal communication; *57,58*). Both behavior in the environment and type of action exerted in mammalian and insect systems will be influenced by this property. The three pyrethroids, bioresmethrin, permethrin, and K-othrin are lipophilic compounds, and resemble, in

Table 3. Physical properties of some insecticides.

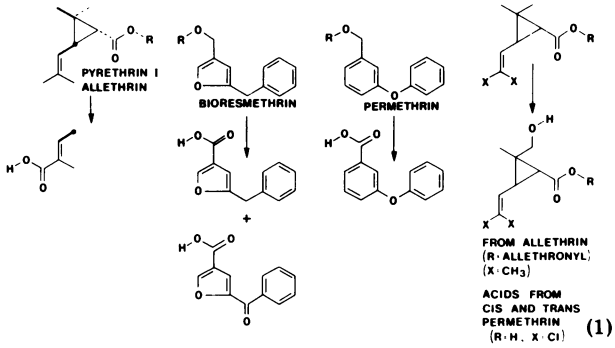
Compound	Logarithm of octanol–water partition coefficients (*P*)
Aldicarb	1.2
Dimethoate	1.5
Carbaryl	2.3
Parathion	3.1
Bioresmethrin	6.2
Dieldrin	6.2
Permethrin	6.5
DDT	6.8
K-othrin RU 11 679	7.0
Aldrin	8.0

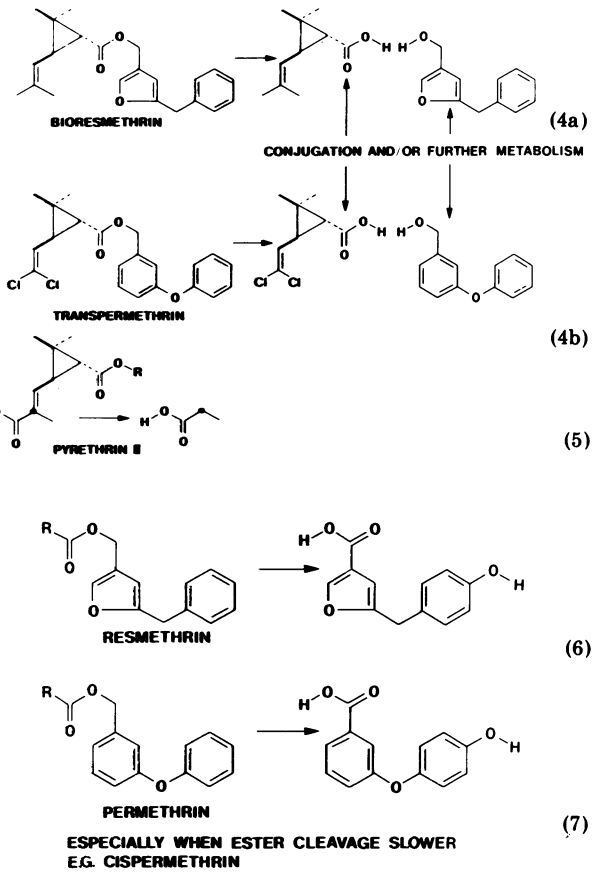
the properties listed here the chlorinated hydrocarbons rather than the organophosphates and carbamates. Permethrin, as would be predicted, has little systemic, fumigant, or translaminar activity (C.N.E. Ruscoe, personal communication).

The less desirable properties of chlorinated hydrocarbon insecticides are associated with their lipophilicity and inert chemical structures so that they are stored in the fatty tissues of organisms rather than being metabolized and eliminated. Although pyrethroids are similar to the chlorinated hydrocarbons in some of their physical properties, much evidence from research in the past decade (*59–68*) suggests that the structural features of pyrethroids render them susceptible to mammalian detoxification systems, so that by one or more of several possible pathways they are rapidly converted to more polar compounds and are excreted in the urine or feces.

This explains their low toxicity to mammals and probably their selective potency to insects which are not able to detoxify them and prevent penetration to the nervous system on which pyrethroids act. In contrast, Barnes, Verschoyle, and White (*18*) consider that observations on rats poisoned with pyrethroids indicate that, although the nervous systems of these mammals may also be sensitive to their toxic effects, such compounds are very rapidly metabolized after absorption, preventing an effective concentration being reached at the sensitive sites of mammals.

The mammalian toxicity of a pyrethroid is related to the facility and speed with which the compound is metabolized. Typical detoxification routes are reactions at methyl and methylene groups [eq. (1)] and at unsaturated centers [eqs. (2) and (3)] and cleavage, especially of unhindered esters of primary alcohols [eqs. (4) and (5)]. Ester cleavage is especially important and cannot take place with the chlorinated hydrocarbon insecticides; where this cleavage reaction is hindered sterically other pathways are involved, for instance, hydroxylation in the 4-position of benzyl or phenoxy substituents [eqs. (6), (7)]. This hydroxylation reaction will be suppressed on aromatic rings deactivated by halogen substituents as in the chlorinated hydrocarbon insecticides and elsewhere, but phenoxy groups seem especially susceptible (*65,68*). This may contribute to the extremely low mammalian toxicity of phenothrin (*11,65*) and, in the important instance of permethrin, partly explain the lower oral toxicity which Barnes and Verscholyle (*9,18*) found for both *trans* and *cis* isomers compared with the corresponding isomers of the 5-benzyl-3-furylmethyl esters. An interesting recent observation (*68*) is that when oxidation of the *trans*-methyl group in the isobutenyl side chain of chrysanthemates, the first





metabolic reaction established for pyrethroids (*59,62*) is not possible, as in dichlorovinylcyclopropane esters, one of the adjacent *gem*-dimethyl groups on the cyclopropane ring is attacked eq. (1)

No reports have yet been published of the mammalian toxicity or the nature of the metabolic products from the α-isopropyl aryl acetates, although from general considerations of chemical reactivity, ester cleavage should be relatively hindered in this series of compounds.

Insecticidal Properties and Applications of Pyrethroids

The outstanding potency and other favorable properties of pyrethroids are especially significant with the more stable compounds potentially available (*69*). Table 4 shows the potency of permethrin and of other common insecticides against the adult desert locust (*70*) and the rat. The ratios in the third column indicate the relative effectiveness and safety of the compounds, and permethrin is at least twenty times superior to the organophosphate, sumithion, which most closely approaches it.

Other insect species give similar results (*47,71*), so if larger-scale production and low application rates make general and economic use of pyrethroids possible, these compounds should contribute to pest control at levels which will diminish appreciably the risk of contaminating the environment. As an example, *Aedes taeniorhynchus* was controlled satisfactorily with only 1.5 g/ha of even the unstable pyrethroid bioresmethrin (*72*).

Lepidoptera, especially the larval stages, are serious pests affecting economically important crops such as cotton, maize, tobacco, rice, sugar beet, and sugar cane throughout the world and enormous quantities of insecticides are used to control them (Table 5). The natural pyrethrins are very active against lepidopterous larvae but in the past instability, even when specially formulated has precluded use in practice. The synthetic pyrethroids are even more potent than the natural esters to these insects; Ford, Reay, and Watts (*73*) have projected that efficient and economic control of *Spodoptera littoralis* is possible with ultra-low volume applications of permethrin. Synthetic pyrethroids, including permethrin, are extremely active against the third instar larvae of an insecticide-resistant strain of the tobacco budworm *Heliothis virescens* (F.) (F. W. Plapp, personal communication). In laboratory tests, permethrin was more toxic than methyl parathion to this insect, to the bollworm, *H. zea* (Boddie) and to the boll weevil, *Anthonomus grandes* Boheman. In the field, it controlled *Heliothis* spp. as well as did methomyl and monocrotophos (*74*), so the prospects for practical use against cotton pests are promising. The α-isopropyl acetate, S-5439, also has very good residual activity against the tobacco cutworm (army worm) (*Spodoptera litura* Fabricius) (*13*), and the corresponding α-cyano ester S-5602 is more than twice as toxic as lannate in a pot test to this insect.

Table 6 shows the relative stabilities and toxicities to codling moth larvae of permethrin and other insecticides (J.G. Allen, East Malling Research Station, personal communication) and toxicities to female rats of these compounds. The data show that under practical conditions permethrin has much greater activity, low mammalian

Table 4. Relative toxicities of insecticides to *Schistocerca gregaria* (mature males) and rats.[a]

	Approximate LD_{50} values		Ratios
	Insects, μg/g	Rats, mg/kg	rat/insect
Toxaphene	100+	69	1
DDT	100+	250	2
Chlordane	50	500	10
Carbaryl	31	540	17
Malathion	31	1400	45
DNOC	13	45	4
BHC	9	190	21
Aldrin	8	44	6
Sumithion	6	375	62
Diazinon	5	185	37
Dichlorvos	2	65	33
Parathion	1	11	11
Permethrin	0.7[b]	1000+	1400

[a]Similar results with other insect species.

[b]Result from M. G. Ford and R. C. Reay (personal communication).

Table 5. United States production (1971) of ten important insecticides.

	Tons	Rat oral toxicity, mg/kg
Carbaryl	25,000	700
Toxaphene	23,000	70
DDT	20,000	250
Methyl parathion	20,000	14
Malathion	14,000	5,000
Chlordane	11,000	500
Parathion	7,000	4
Methoxychlor	4,500	6,000
Diazinon	4,500	200
Aldrin	4,500	60

toxicity and a useful stability (estimated by bioassay) more than twice as long as the next most active compound, methidathion. As a spray (250 ppm) on cabbage leaves permethrin gave a greater than 50% mortality of *Pieris brassicae* (Lep) larvae (IV instar) for 19 days, azinphosmethyl (Gusathion, Guthion) for 9 days and bioresmethrin for 2 days (C.N.E. Ruscoe, Jealotts' Hill Research Station, personal communication).

Permethrin also shows promising activity against other insect pests. It gave excellent control under field conditions of larvae and pupae of the mosquito *Culex peus* Speiser at 0.025–0.05 lb/acre and good control of *Aedes nigromaculis* Ludlow at 0.01–0.025 lb/acre (*75*). An unexpected result was demonstrated at Rothamsted Experimental Station, where permethrin as a dressing on wheat seeds gave protection without phytotoxic effects against wheat bulb fly larvae (Table 7) comparable with the best organophosphorus insecticide, isophenphos. Under these conditions permethrin probably remained in the waxy coating on the seed from December to March. This is the first successful seed treatment against this pest by other than organochlorine compounds or organophosphates (D. C. Griffiths, personal communication). Such persistent activity as a seed coating does not imply long life for permethrin in soils however, where microorganisms would be expected to decompose it rapidly. In another investigation, F. T. Phillips, P. Etheridge, and G. C. Scott (personal communication) found that permethrin, microencapsulated to delay toxic action, was as effective against two species of leaf cutting ants (*Atta sexdens* and *Atta cephalotes*) at 0.005% as pirimiphos methyl at 0.1%.

Table 6. Relative stabilities and toxicities to codling moth larvae (Carpocapsa pomonella) and female rats of permethrin and other insecticides.

	LD_{50}		
	Larvae $\mu g/cm^2$	Rats, mg/kg	Stability, days[b]
Phosmet	0.25	230	15
Phosalone	0.22	135	21
Azinphos-methyl (Gusathion)	0.79	16	Not available
Tetrachlorvinphos (Gardona)	0.066	4000+	16
Phentriazophos	0.055	82	20
Fenitrothion (Sumithion)	0.023	250	19
Diazinon	0.023	250	Not available
Methidathion	0.019	25+	29
Permethrin	0.004	1000+	70

[a]Acute oral LD_{50}, female rats (standard references).
[b]Effective life of insecticides on apple surface.

Table 7. Control of wheat bulb fly larvae *Leptohylemyia coarctate* (Fall.).[a]

Seed treatment (A.I. 0.2 g/100 g seed)	Damaged shoots, %	Plants with live larvae, %	Healthy shoots/ sample
Control	32	36	50
Pirimiphos ethyl	13	13	72
Permethrin	11	12	101
Chlorfenvinphos	9	6	95
Fonofos	6	2	94
Isophenphos	6	0	104
Triazophos	5	1	73
Standard error of difference	4.0	4.1	14.8

[a]Seed sown Dec. 10, 1974; sampled March 25, 1975.

Although control of agricultural pests, discussed above, will probably most greatly extend the use of more stable pyrethroids there may be further applications in the domestic, horticultural and veterinary fields (*76*). Preliminary results indicate that in hand spray applications to the entire body surface of lactating dairy animals, at a level needed for adequate fly control, residues of permethrin in milk are unlikely to pose a problem; permethrin also shows a wide range of activity against veterinary parasites (Wellcome Research Laboratories, Berkhamsted, personal communications). Wickham and Chadwick (*20*) discuss new applications for pyrethroids including permethrin, which they found to have a quite remarkable residual life on plywood. A deposit of 300 mg/m^2 on plywood gave 100% kill of *Blatella germanica* after 12 months exposure in the sun on the windowsills of a laboratory. They note that few compounds in the organophosphorus group last 2 weeks under such circumstances, and the results suggest a promising residual use against mosquitoes, stored products, insects and cockroaches particularly as the compound has low mammalian toxicity and is also apparently biodegradable. Although only limited results are available so far on the effects of permethrin on wildlife, no lethal effect was observed when male Japanese quail received 5 g of permethrin/kg-day for 3 consecutive days. (Pest Infestation Control Laboratory, Worplesdon, personal communication).

Synergists

Synergists (*77,78*) such as piperonyl butoxide are valuable in extending the economic use of the

natural pyrethrins and some synthetic pyrethroids. However, resmethrin, permethrin and related compounds are relatively less well synergized (*7,69*), and producing a formulation for agricultural use, where the synergist and toxicant must be presented together to the target pest, is relatively difficult. Complications also arise from the necessity to establish safety under all conditions for the toxicant and synergist, so clearance trials are more expensive. For these reasons, unless much more effective and stable synergists are discovered, which can be appropriately formulated for the field, more extensive use of these adjuvants is unlikely.

Resistance

Where natural and synthetic pyrethroids have been used intensively, especially to control insects resistant to most of the commonly used insecticides (for example, flies in Denmark) (*79*) resistance to all insecticides, including pyrethroids has developed. Dyte (*80*) has discussed the problems associated with resistance in stored products pests of which some laboratory selected strains are tolerant to pyrethroids. Although resistance in pests of agricultural crops is less well documented, there is no reason to suppose that the mechanisms involved will not extend to any pest continually exposed to a toxicant new, or well established. Keiding (*81*) showed that resistance genes have a seemingly unlimited persistence which precludes reuse of insecticides against populations apparently susceptible again. Therefore, if more stable pyrethroids are introduced to control pests in new situations, research on treatment regimes likely to minimize the rate of resistance development is essential. (R. M. Sawicki, personal communication)

Summary and Conclusions

Knowledge of the relationship between chemical structure and insecticidal activity, toxicity to mammals and photostability of pyrethroids has developed rapidly in the past decade. This has been applied to designing lipophilic insecticides with, in some respects, more favorable combinations of properties than are possessed by any other naturally occurring or synthetic group of compounds; further application and extension of these principles should provide a wide range of compounds with properties appropriate for controlling many pests under any given circumstances. However, although preliminary examination of the environmental properties and behavior in non-target organisms has not yet disclosed any significant or insuperable problems (*82*), much more evaluation remains to be completed, and industrial processes to produce the compounds economically must be developed. Great caution is necessary lest overenthusiastic initial application lead to rapid development of resistant field species which prudent deployment might avoid. In favorable circumstances however, synthetic pyrethroids should help to control more insect pests in the future with smaller hazard to man and the environment than earlier, widely used pesticides.

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