SESSION VIII

SYNTHETIC PYRETHROIDS

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The Relationship between the Structure and the Activity of Pyrethroids

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There is considerable scope for developing new non-persistent insecticides with little hazard for man and mammals by modifying the structures of the natural pyrethrins. New compounds already synthesized are more effective against some insect species than are the natural compounds, are even less hazardous to mammals, and do not need synergists to supplement their insecticidal action. Other examples show considerable insect species specificity. These compounds may help to control insect vectors when other insecticides are no longer effective because resistance has developed or because their residues can no longer be tolerated.

When the detailed chemical structures of the natural pyrethrins were established, the foundation for rational structure–activity studies was laid and it might then have been predicted that related compounds, as toxic or more toxic to insects, would be discovered by persistent investigations. However, it was unforeseen and welcome to find that some of the new compounds with greatest insecticidal activity are also considerably less toxic to mammals than are the natural pyrethrins. Table 1 shows that one synthetic compound is more toxic than parathion to houseflies, but much less toxic to rats. Such results justify continued work with these non-persistent compounds.

Table 1

Toxicity of parathion and bioresmethrin to the housefly and the rat

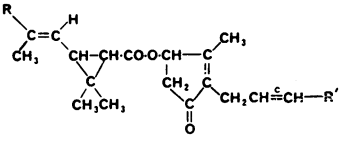
Compound	LD_{50} (mg/kg) to	
	housefly [a]	rat [b]
parathion	1	5
bioresmethrin	0.25	8 000

[a] Topical application.
[b] Oral administration.

The insecticidal compounds (Fig. 1) in pyrethrum extract (Crombie & Elliott, 1961) are esters of cyclopropanecarboxylic acids with alkenylmethyl cyclopentenolones. Investigations of the metabolism of these esters in insects (Yamamoto et al., 1969) and in mammals (Casida et al., 1971) have detected no hydrolysis products of the cyclopropane ester link. This and other evidence (Elliott, 1969) indicates that these compounds act against insects as intact esters. An essential feature of this action seems to be that the ester bond is difficult to cleave, and it probably provides a position of appropriate polarity at the centre of the molecule.

Fig. 1

Structures of the natural pyrethrins



	R	R'
Pyrethrin I	CH_3-	-CH=CH_2
" II	$CH_3O.CO$-	-CH=CH_2
Cinerin I	CH_3-	-CH_3
" II	$CH_3O.CO$-	-CH_3
Jasmolin I	CH_3-	-CH_2CH_3
" II	$CH_3O.CO$-	-CH_2CH_3

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Fig. 2 shows the structural features at present considered essential for powerful pyrethrin-like activity. All compounds as active as or more active than the natural pyrethrins contain the unit B substituted in various ways at A; thus they are derived from *gem*-dimethyl-substituted cyclopropane acids. Natural chrysanthemic acid has a *trans*-isobutenyl group at C-3 on the cyclopropane ring, but other substituents there produce greater or more rapid action. Even with no substituents at C-3 on the cyclopropane ring, appropriate alcohols give esters with considerable insecticidal and knock-down action (Barlow et al., 1971).

The exact nature of the substituent A at C-3 on the cyclopropane ring is, therefore, not critical for toxicity to insects, so this position is probably not directly involved in the poisoning process, in contrast to the *gem*-dimethyl group on C-2. Substituents at C-3 on the cyclopropane ring influence the reactivity and physical properties of the molecules and partly determine the ease with which the compounds are detoxified in insect and mammalian systems.

A second structural feature common to all potent pyrethroids examined so far is the ability of the O-acyl bond in the ester to adopt a position approximately parallel to a line or plane through the units C, D, and E (for a more detailed discussion, see Elliott, 1969). In practice this means that the carbon atom bearing the acyloxy group AB must be tetrahedral. Thus, in all pyrethroids based on cyclopentenolones (the natural esters, allethrin, furethrin, etc.), the unit C is the asymmetric methine group at C-4 of the 5-membered ring, but in acetylenic, benzylic, and heterocyclic chrysanthemates, and in tetramethrin, O–acyl is attached to the CH_2 group and there is no centre of asymmetry in the alcohol.

When C is CH, D is the rest of the cyclopentenolone ring; when C is CH_2, D is a unit such as C_6H_4, furan, or $C{\equiv}C$, so that, in both cases, the carbon atoms in C, D, and E are co-planar.

The unit E is $-CH_2-$, $-O-$, or $-CO-$, or a sterically equivalent link, such that an unsaturated centre F (an olefinic or acetylenic bond, a conjugated system of double bonds, or an aromatic ring) can adopt a position skew to the direction defined by C, D, and E. If no unsaturated centre F is present, as in the methylbenzyl chrysanthemates (Barthel, 1961, 1964; Elliott, Ford & Janes, 1970; Elliott, Janes & Jeffs, 1970), dimethrin (Barthel, 1964), trimethrin (Elliott et al., 1965a), barthrin (Barthel, 1964), and tetramethrin (Kato et al., 1964) insect killing power is limited to a lower level.

Such requirements for insecticidal potency can be satisfied in many structures, and those compounds most active against insects have the appropriate physical properties to penetrate and remain active inside the organism and the fewest positions at which they are attacked by detoxifying systems. Active but easily detoxified compounds are frequently recognized by a great increase in toxicity in the presence of a synergist to inhibit the mixed-function oxidase system (Casida, 1970). With houseflies, this inhibition is conveniently achieved by pretreatment of each insect with a constant large dose (2 μg) of sesamex, irrespective of the amount of insecticide (Sawicki & Farnham, 1967, 1968). Numerous results obtained in this way are discussed in the present paper; the best example of an outstanding insecticide that is easily deactivated in houseflies is pyrethrin I, for which a synergistic factor (LD_{50} without synergist/LD_{50} with synergist) of 350 was obtained (A. W. Farnham, personal communication).

A specific application of the generalized structure (Fig. 2) is the relationship seen (Elliott, 1967; Elliott et al., 1965a; Elliott, Janes & Pearson, 1967; Elliott et al., 1967b) between allethrin (Fig. 3) (Schechter et al., 1949) and substituted benzyl chrysanthemates such as piperonyl chrysanthemate (Staudinger & Ruzicka, 1924; Synerholm, 1949); barthrin, 6-chloro-

Fig. 2

Structural requirements for pyrethrin-like activity

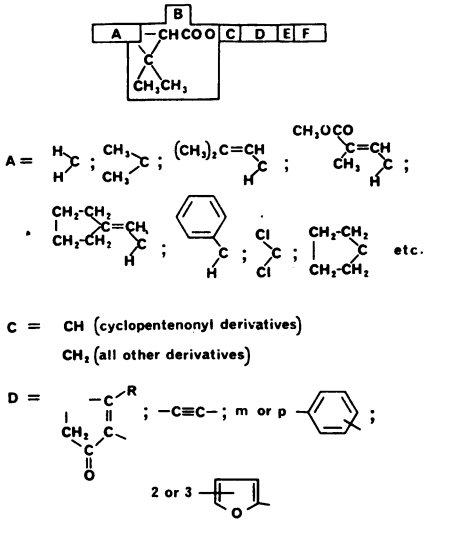
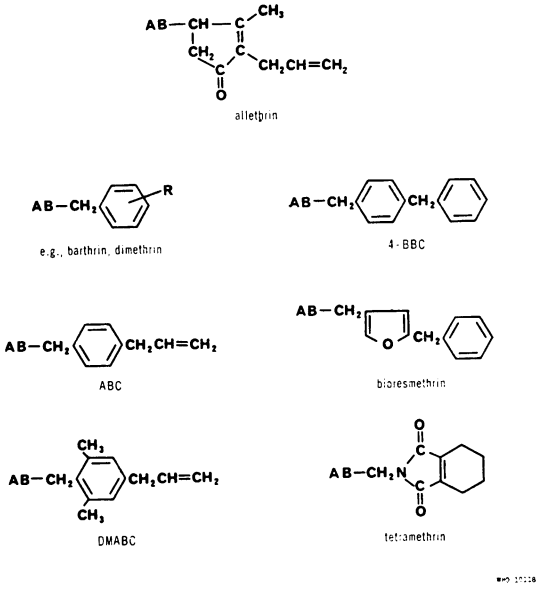


Fig. 3

Structures of synthetic pyrethroids



piperonyl chrysanthemate (Barthel & Alexander, 1958); dimethrin, 2,4-dimethylbenzyl chrysanthemate (Barthel, 1958; Barthel et al., 1959; Piquett & Gersdorff, 1958); and other methylbenzyl chrysanthemates (Elliott et el., 1965a; Elliott, Ford & Janes, 1970; Elliott, Janes & Jeffs, 1970). This led from 4-allylbenzyl chrysanthemate (Fig. 3) and 2,6-dimethyl-4-allylbenzyl chrysanthemate (Elliott et al., 1965a, 1965b; Elliott, 1967) to 4-benzylbenzyl chrysanthemate and 5-benzyl-3-furylmethyl chrysanthemate (Elliott et al., 1967a, 1967b, 1971). A parallel line of progress evolved *N*-hydroxymethyl chrysanthemates such as tetramethrin (Kato et al., 1964), which has rapid knock-down action. Table 2 shows the relative toxicities of these compounds and of a natural pyrethroid to houseflies and mustard beetles.

Since 5-benzyl-3-furylmethyl (+)-*trans*-chrysanthemate (bioresmethrin) is more active against insects than other synthetic pyrethroids, it and related compounds were investigated further, as follows. The xanthenylmethyl chrysanthemate (Fig. 4) was

Fig. 4

Structures of different chrysanthemates

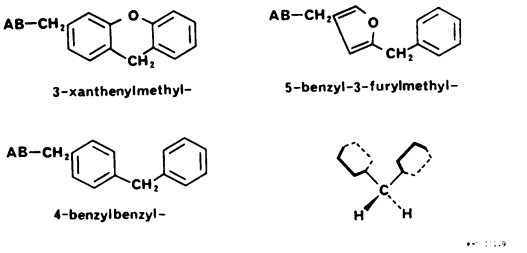


Table 2

Relative toxicities of pyrethroids to the housefly and the mustard beetle

Compound		Relative toxicity [a] to	
(+)-*trans*-chrysanthemate of:	other designations	housefly	mustard beetle
(+)-pyrethrolone	pyrethrin I	12	1 600
2,4-dimethylbenzyl alcohol	dimethrin	19	7
6-chloropiperonyl alcohol	barthrin	20	5
4-benzylbenzyl alcohol	4-BBC	15	20
N-hydroxymethyltetrahydrophthalimide	tetramethrin	60	58
(+)-allethrolone	(+)-(+)-allethrin	100	42
4-allylbenzyl alcohol	ABC	190	3
2,6-dimethyl-4-allylbenzyl alcohol	DMABC	190	50
5-benzyl-3-furylmethyl alcohol	bioresmethrin	1 000	1 000

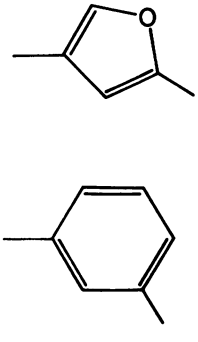
[a] Toxicity by topical application, relative to that of bioresmethrin taken as 1 000.

synthesized because it resembled the furan superficially and was also related to 4-benzylbenzyl chrysanthemate, but it had no insecticidal activity. This suggested that the toxicity for insects of the 4-benzylbenzyl compound and, by implication, of the 5-benzyl-3-furylmethyl chrysanthemate, is associated with the ability to act in a conformation in which the two aromatic rings are non-planar. In substituted diphenylmethanes the benzene rings are rotated by 52° about the axes containing the *p*, *p'* positions in opposite senses from a hypothetical planar conformation (data obtained for 3,3'-dichloro-4,4'-dihydroxydiphenylmethane: Sutton, 1958), and the lack of steric hindrance in phenylfuryl methanes, such as 5-benzyl-3-furylmethyl esters, would make a similar disposition possible. The potency of the furan chrysanthemate may depend on this property.

Another feature of the structure of 5-benzyl-3-furylmethyl chrysanthemate is the angle, approximately 145°, between the bonds from the 3 and 5 positions of the furan ring. The angle between the plane containing the OH group of cyclopentenolones and the 2-position bearing the alkenyl substituent is also close to 145°, and this is not far removed from that between the *m*-positions of a benzene ring (Fig. 5). Consequently, 3-benzylbenzyl

Fig. 5

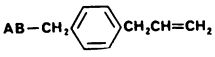
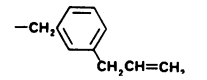
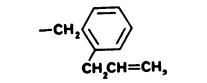
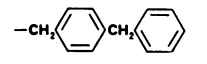
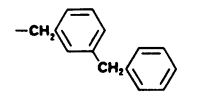
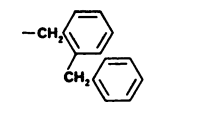
Bond angles in 3,5-substituted furan (top) and *m*-substituted benzene (bottom)



chrysanthemate (*m*-substituted) was synthesized and it was found to be more toxic (Table 3) than the *o*-benzylbenzyl and *p*-benzylbenzyl chrysanthemates. This suggested not only that it is important for the unsaturated centres to be at an angle to one another, as in diphenylmethanes, but also that the disposition of the side chain, relative to the acid, influences toxicity. The finding that a benzyl substituent is most effective in the *m*-position contrasted with the earlier result with allylbenzyl chrysanthemates, where the *p*-compound was found to be most effective.

Table 3

Relative toxicities of allylbenzyl and benzylbenzyl chrysanthemates to the housefly and the mustard beetle

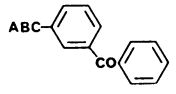
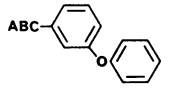
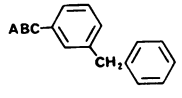
Structure of compound [a]	Relative toxicity [b] to	
	housefly	mustard beetle
	85	0.9
	13	2.4
	<2	0.7
	9.3	5.4
	100	100
	<2	<1

[a] For an explanation of group AB, see Fig. 2.
[b] By topical application.

Because the insect toxicity of 4-phenoxybenzyl chrysanthemate is much lower than that of 4-benzylbenzyl chrysanthemate, it was earlier concluded that the $-CH_2-$ group between the rings is important for toxicity (Elliott, 1969). But in *m*-substituted aromatic chrysanthemates, the *m*-benzyl, *m*-benzoyl, and *m*-phenoxy compounds were all active and, moreover, when synergized (Table 4), all three esters attained considerable toxicity to houseflies. In these com-

Table 4

Effect on toxicity of varying group E * in 3-substituted benzyl chrysanthemates

Structure of compound *	LD_{50} (μg/insect) to the housefly [a]		Synergistic factor	LD_{50} (μg/insect) to the mustard beetle (unsynergized) [a]
	Unsynergized	Synergized		
	~0.4	0.0045	~90	0.0030
	0.022	0.0025	9	0.0012
	0.028	0.0013	23	0.00052

* For an explanation of " group E ", and of groups ABC in the structural formulae, see Fig. 2.
[a] Topical application.

pounds the two aromatic rings are in similar relative steric positions to each other and the cyclopropane ring of the acid is also comparably disposed. Similar relative spatial positions can also be attained by the acidic moieties and the alkenyl side chains of cyclopentenolone chrysanthemates such as pyrethrin I, pyrethrin II, and allethrin, and by the two aromatic rings and the acid in 5-benzyl-3-furylmethyl chrysanthemate.

Toxicity for insects is therefore found in many compounds (Fig. 2) where an unsaturated side chain F is held by a group E at an angle to links C and D to the acid. From the results given in Table 5, with the benzyl side chain (units E and F) common to a number of compounds, it is apparent that the 3-furylmethyl ring has the best spatial and electronic characteristics found so far to provide the junctions C and D. The only noncyclic unit that confers appreciable toxicity is the acetylenic system, which is more effective with the benzyl side chain than with the allyl side chain investigated earlier (Elliott et al., 1965a).

Insecticidal activity is drastically lowered by the substitution of the CH_2 group in esters of 5-benzyl-3-furylmethyl chrysanthemate to give α-methyl esters. A methyl group in this position obtrudes into the plane of the furan ring and would interfere with any close contact necessary there. Toxicity for insects is thus closely related to the size and nature of the ring and is greatest in furan or cyclopentenolone derivatives.

The furylmethyl ring reproduces almost exactly the size and shape of the methylcyclopentenonyl ring in the natural esters, but there is no group in the furan ester equivalent to the methyl group in the cyclopentenone. To determine whether this methyl group is essential for toxicity, we synthesized the norbenzyl ester (Table 6) and compared it with the benzyl ester. The new compound, conveniently called benzyl northrin, not only killed houseflies as well as did bioallethrin, but showed a much greater response to synergism and had better knock-down action against houseflies than the furylmethyl ester. It is particularly significant that the toxicity of this compound to mustard beetles is about 8 times that of bioallethrin. Within this limited area of comparison, therefore, it is clear that the methyl group on the cyclopentenolone ring is not essential for toxicity.

The discussion so far has mainly concerned variations of the alcoholic component of the esters. In the few compounds where the acid–alcohol link has been changed, the modified compounds are considerably less toxic than the parent esters. This topic has been investigated and reviewed by Berteau & Casida (1969), and the relative toxicities of 5 com-

Table 5

Effect of varying groups C and D on the toxicity of chrysanthemates

Groups C and D [a]	Relative toxicity [b] to	
	housefly	mustard beetle
$-CH_2 \cdot CH_2CH_2-$	10	1
$-CH_2 \cdot CH=CH-$	5	0.3
$-CH_2 \cdot C\equiv C-$	5	8
$-CH_2 \cdot$ 	40	20
$-CH_2 \cdot$ 	150	520
$-CH_2 \cdot$ 	100	40
$-CH_2 \cdot$ 	480	110
$-CH_2 \cdot$ 	1 000	1 000
$-CH(CH_3) \cdot$ 	7	2

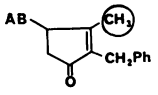
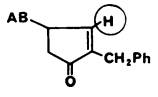
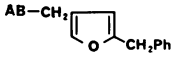
[a] Group D is attached to units E and F (– CH_2Ph); for further explanation see Fig. 2.
[b] By topical application.

pounds for which comparable data are available are shown in Table 7. Any departure from the ester link reported so far results in great diminution in toxicity for insects; this may be associated with the greater ease with which the alternative structures are attacked by detoxifying systems and with the absence of the conformational rigidity given by an unstrained ester bond (for further discussion, see Elliott, 1969).

5-Benzyl-3-furylmethyl alcohol (Elliott et al., 1971) is a good esterifying alcohol for investigating changes in insecticidal activity with subtle variations in structure of the acidic part of the molecule, because it

Table 6

Effect of the methyl group on the toxicity of cyclopentenonyl esters

Structure of compound [a]	Relative toxicity [b] to	
	housefly	mustard beetle
	7	50
	72	170
	1 000	1 000

[a] For an explanation of groups AB, see Fig. 2.
[b] By topical application.

has no complicating asymmetry and apparently is not a centre for detoxification. The 2,2-dimethyl cyclopropanecarboxylate (Fig. 6) of 5-benzyl-3-furylmethyl alcohol is approximately as toxic as pyrethrin I or allethrin to houseflies, has quite good

Table 7

Effect on toxicity of varying the acid-alcohol link *

Link [a]	Relative toxicity to the housefly [b]
—CO—O—CH_2—	1 000
—CO—CH_2—CH_2—	47
—CHOH—CH_2—CH_2—	<1
—CO—NH—CH_2—	13
—CH_2—O—CO—	<1

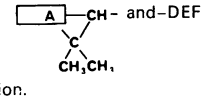
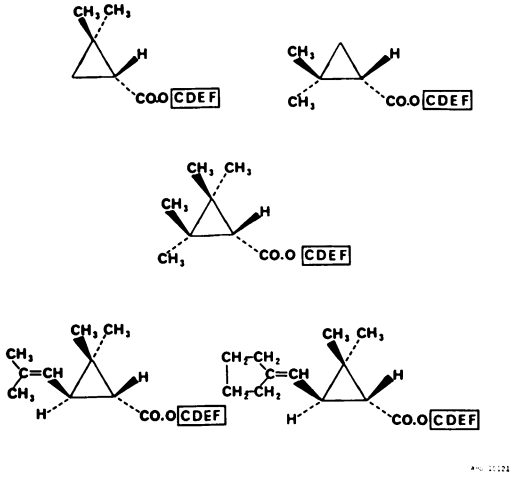
* Data of Bertrau & Casida (1969).
[a] The link between  and-DEF
[b] By topical application.

Fig. 6
Variations of the acid in chrysanthemate analogues



knock-down action, and is also active against mustard beetles, whereas the compound without methyl groups is completely without activity. Esters from the two optically active forms of 2,2-dimethyl cyclopropanecarboxylic acid differ very little in toxicity, providing direct evidence that the absolute configuration at C-1 of the cyclopropane ring is not important. If the two methyl groups on the cyclopropane ring and some part of the alcoholic structure of the ester must be in a definite orientation for insecticidal action, molecular models show that without a substituent on C-3 of the cyclopropane ring esters of either enantiomeric form of the acid are likely to be able to fulfil almost equally well the steric requirements. However, when a bulky group such as isobutenyl (as in chrysanthemic acid) is introduced at C-3 either *cis* or *trans* to the carboxyl group, with one optical form this will be at a side of the molecule remote from the surface of action of the dimethyl group, and so it might be expected that the insecticidal activity of the ester will not be too greatly altered. On the other hand, a large group at C-3 in the other isomer will obtrude its bulk to prevent access of the dimethyl group to the surface of action. It is, indeed, known that esters of one of the pairs of both *cis* and *trans* chrysanthemic acids are almost inactive. Tetramethylcyclopropanecarboxylic acid (Matsui & Kitahara, 1967) has *gem*-dimethyl groups that are appropriately oriented for activity whatever the steric attitude of the molecule. The ester of tetramethylcyclopropanecarboxylic acid with 5-benzyl-3-furylmethyl alcohol (Berteau & Casida, 1969; Barlow et al., 1971) approaches the (+)-*trans*-chrysanthemate in toxicity for houseflies, but it is relatively less active against other insects. The (+)-pyrethrolone ester of tetramethylcyclopropanecarboxylic acid shows four times the toxicity to houseflies, but only one-seventeenth of the toxicity to mustard beetles, of pyrethrin I, the (+)-pyrethrolone ester of (+)-*trans*-chrysanthemic acid (Barlow et al., 1971).

The greatest activity in pyrethrin-like esters therefore depends on the presence of a *gem*-dimethyl group on the cyclopropane ring, and the substituent at C-3 gives appropriate physical and chemical properties to the molecule. The only acid that gives esters with 5-benzyl-3-furylmethyl alcohol having greater potency against insects than (+)-*trans*-chrysanthemic acid is (+)-trans-2,2-dimethyl-3-cyclopentylidenemethylcyclopropanecarboxylic acid, which was the most effective of many acids synthesized by Velluz, Martel & Nominé (1969) (Lhoste & Rauch, 1969; Lhoste et al., 1969). The activity of the (+)-*trans*-ethanochrysanthemate against houseflies and mustard beetles is about 1½ times that of the (+)-*trans*-chrysanthemate, and its activity against cockroaches is about 4 times that of the latter compound. If substituents at C-3 on the cyclopropane ring contribute to toxicity for insects only by indirect influence, the most probable explanation for the greater potency of the ethanochrysanthemate is decreased susceptibility to detoxification, for it lacks the *trans*-methyl group on the isobutenyl side chain. This is the position found to be most susceptible to detoxification in insects (Yamamoto et al., 1969) and mammals (Casida et al., 1971).

It is therefore relevant to consider evidence of the relative susceptibility to detoxification of various pyrethroids. Table 8 shows the toxicities to houseflies of 11 compounds with and without sesamex, as found by Farnham. The results separate the compounds into three classes. Esters of 5-benzyl-3-furylmethyl alcohol show considerable toxicity without the synergist, and their potency is increased only 7–15-fold when detoxification is suppressed. Next, esters of cyclopentenolones without a diene side chain (allethrolone and benzyl norrethrolone) have synergistic factors in the range 50–90. Finally, pyrethrin I with a *cis*-pentadienyl side chain in the alcohol has the outstanding factor of 300. Clearly, interaction between the properties of the acidic and alcoholic components of the esters determines the

Table 8

Effect of potentiation with sesamex (pretreatment technique) on the toxicity of pyrethroids to the housefly *

Chemical name of ester	Other designations	LD_{50} for housefly (mg/♀)[a]		Synergistic factor
		unsynergized	synergized	
5-benzyl-3-furylmethyl (+)-*trans*-chrysanthemate	bioresmethrin	0.0054	0.00057	9
5-benzyl-3-furylmethyl (+)-*cis*-chrysanthemate	NRDC 119	0.027	0.0018	15
5-benzyl-3-furylmethyl (+)-*trans*-ethanochrysanthemate	RU 11 679	0.0037	0.00054	7
(+)-pyrethronyl (+)-*trans*-chrysanthemate	pyrethrin I	0.33	0.0011	300
(+)-pyrethronyl (+)-pyrethrate	pyrethrin II	0.21	0.0043	49
5-benzyl-3-furylmethyl (+)-pyrethrate	NRDC 106	0.027	0.0011	25
3-benzylbenzyl (+)-*trans*-chrysanthemate	3-BBC	0.030	0.0013	23
5-benzyl-3-furylmethyl 2,2,3,3-tetramethylcyclopropanecarboxylate	NRDC 108	0.0063	0.00077	8
(+)-pyrethronyl 2,2,3,3-tetramethylcyclopropanecarboxylate		0.072	0.00084	85
(±)-allethronyl (+)-*trans*-chrysanthemate	bioallethrin	0.096	0.0017	55
(±)-2-benzylcyclopent-2-en on-4-yl (+)-*trans*-chrysanthemate	benzyl northrin	0.055	0.00061	90

* A. W. Farnham, unpublished data, 1968-70.
[a] By topical application.

Table 9

Toxicity of pyrethroids to the rat and the housefly *

Compound	Approximate LD_{50} (mg/kg)		LD_{50} ratio (rat/housefly)
	female rat[a]	housefly[b]	
natural pyrethrins	580	15	38
allethrin	770	10	77
bioallethrin	860	4.0	210
resmethrin	1 400	0.6	2 300
5-benzyl-3-furylmethyl (+)-*trans*-chrysanthemate (bioresmethrin)	8 000	0.25	32 000
5-benzyl-3-furylmethyl 2,2,3,3-tetramethylcyclopropanecarboxylate (NRDC 108)	150	0.32	470
benzyl northrin	>1 600	2.8	>570
5-benzyl-3-furylmethyl 2,2-dimethylcyclopropanecarboxylate (NRDC 115)	>1 600	10	>160
5-benzyl-3-furylmethyl (+)-pyrethrate (NRDC 106)	>10 000	1.0	>10 000
5-benzyl-3-furylmethyl (+)-*trans*-ethanochrysanthemate (RU 11 679)	63	0.2	130
5-benzyl-3-furylmethyl (+)-*cis*-chrysanthemate (NRDC 119)	100	0.7	140

* Data for mammals by courtesy of the Cooper Technical Bureau, Berkhamsted, Herts., England, and Roussel Uclaf SA, Romainville, France.
[a] Oral administration.
[b] Topical application.

overall susceptibility of the molecule to detoxification. The situation may be comparable with the interaction between factors of resistance in a strain of the housefly, where Sawicki (1970a, 1970b) found that, although no single factor could explain the great resistance developed to organophosphorus insecticides, several mechanisms of detoxification, each barely significant alone, gave considerable immunity when combined.

Mammals also differ greatly in their ability to detoxify pyrethroids, as shown by the wide spread of LD_{50} values for rats in Table 9. Small changes in stereochemistry produce considerable changes in toxicity for mammals; a most remarkable result is that the (+)-*cis*-chrysanthemate of 5-benzyl-3-furylmethyl alcohol shows much greater toxicity than the (+)-*trans* ester. Both the ethanochrysanthemate and the tetramethylcyclopropanecarboxylate are also relatively toxic to rats. On present evidence, therefore, slight toxicity to mammals seems to depend on the presence of an isobutenyl side chain *trans* to the carboxyl group on the cyclopropane ring, so that the *trans*-methyl group there is accessible for attack. The other compound in Table 9 that shows very little toxicity for mammals, the pyrethrate, also has a group (methoxycarbonyl) that is susceptible to hydrolytic attack in this position. Thus, surprisingly, the low toxicity for mammals that is traditionally associated with pyrethroids is seen to be delicately balanced, and it is indeed fortunate that the natural (+)-*trans*-chrysanthemic acid, now synthesized commercially, is the only acid found so far that gives esters with great potency against insects combined with the expected very slight hazard to mammals.

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DISCUSSION

WEIDEN: With respect to the absolute requirement for a *gem*-dimethyl group, does the removal of one or both of the methyl groups lead to a compound that is readily hydrolysed *in vivo*? Can the pyrethroids be synergized against the mustard beetle?

ELLIOTT: We have not examined the hydrolysis of esters of cyclopropanecarboxylic acids under biological conditions. Under conditions in which it is possible to obtain synergistic factors of up to 300 with sesamex † against houseflies, the greatest factor that can be achieved with mustard beetles is about 4. However, the data that have already been presented indicate that the response of mustard beetles is different from that of houseflies; many pyrethroids that are toxic for houseflies are relatively ineffective against mustard beetles and it is not so easy to observe rapid knock-down action with the latter.

FUKUTO: It would be helpful to have information on pyrethroid structures that are inactive as well as on those that are active. We synthesized a number of compounds that, although interesting in structure, showed reduced insecticidal activity. We later learned from Dr Elliott that his group had synthesized similar compounds and found similarly reduced insecticidal activity. Information on negative results would be very useful in avoiding such duplication of effort.

ELLIOTT: Rothamsted Experimental Station is an independent research institution and all results are published as rapidly as possible; the earliest notice frequently appears in the annual report, but publication is sometimes delayed for reasons associated with patenting.

NARAHASHI: Would it be possible to stabilize pyrethroids by formulation?

ELLIOTT: Many workers have attempted to stabilize natural and synthetic pyrethroids by suitable formulations, including ultraviolet-screening agents and antioxidants. However, I would agree with Mr Barthel that much remains to be done in improving formulations. Another method of formulating the synthetic pyrethroids so as to produce greater persistence and to make them available only at the site of action is microencapsulation; this is being investigated at Rothamsted.

† Names against which this symbol appears are identified in the Glossary on pages 445-446.