Synthetic Pyrethroids – A New Class of Insecticide

By M. Elliott and N. F. Janes
DEPARTMENT OF INSECTICIDES AND FUNGICIDES, ROTHAMSTED EXPERIMENTAL STATION, HARPENDEN, HERTS., AL5 2JQ

1 Introduction

Pyrethroid insecticides have evolved in a classical sequence: activity observed in a natural extract, compounds responsible isolated and identified, increasingly active analogues synthesized. Recent synthetic pyrethroids are among the most potent pesticides known, and at present are being evaluated for many applications and as possible replacements for some of the organophosphate, carbamate, or organochlorine insecticides now considered unacceptable. Few classes of biologically active compound have such great potential for structural variation with retention or enhancement of potency.

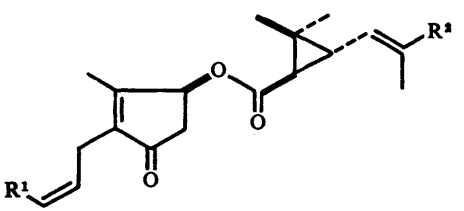
The insecticidal properties of the powder from pyrethrum flowers (*Chrysanthemum cinerariaefolium*) were being exploited in Europe by the 19th century[1] when few effective insecticides were available. Therefore as soon as the nature of the active constituents was known[2] synthetic analogues were investigated[2] in attempts to elucidate the principles governing their activity and to discover simpler or more potent insecticides. New compounds have been discovered with greater insecticidal activity or faster knockdown than the natural esters and, in some cases, enhanced photostability and diminished mammalian toxicity.

This survey traces the development of the present wide range of synthetic compounds, and the growing comprehension of the principles which govern their activity. It reviews most relevant publications up to Spring 1978; the profusion of information, especially in patents published in the past three years, has made detailed coverage of all topics impracticable. Previously, the chemistry of the natural esters,[3,4] the relationship between structure and activity[5–8] and the

[1] C. B. Gnadinger, 'Pyrethrum Flowers'. McLaughlin Gormley King Co., Minneapolis, 1936.
[2] H. Staudinger and L. Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 177, 201, 212, 236, 245, 390, 448.
[3] L. Crombie and M. Elliott, *Fortschr. Chem. org. Naturstoffe*, 1961, **19**, 120.
[4] M. Elliott and N. F. Janes, in 'Pyrethrum—the Natural Insecticide', ed. J. E. Casida, Academic Press, New York, 1973, p. 56.
[5] M. Elliott, *Pyrethrum Post*, 1951, **2** (3), 18.
[6] M. Elliott, *Chem. and Ind.*, 1969, 776.
[7] M. Elliott, *Bull. World Health Organ.*, 1971, **44**, 315.
[8] M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and D. A. Pulman, in 'Mechanism of Pesticide Action', ed. G. C. Kohn, ACS Symposium Series No. 2, American Chemical Society, Washington, DC., 1974, p. 80.

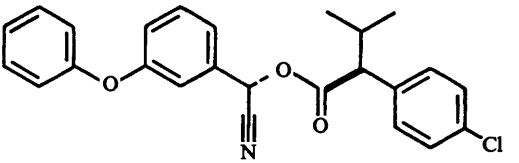
potential of pyrethroids as economic insecticides[9–11] have been reviewed. Proceedings of recent symposia on 'Synthetic Pyrethroids' and 'Newer Applications of Pyrethroids' have been published.[12,13] Two valuable alerting services cover the subject.[14,15]

Large areas of pyrethrum are cultivated in high altitude regions of Kenya, Tanzania, and Ecuador, for commercial extraction of the natural insecticide. The structures and absolute configurations (Figure 1a) of the six insecticidal esters in the extract have been fully confirmed by physical techniques.[16–19]



R^1	R^2	
$CH_2{=}CH-$	$-CH_3$	Pyrethrin I
CH_3-	$-CH_3$	Cinerin I
$CH_3{-}CH_2-$	$-CH_3$	Jasmolin I
$CH_2{=}CH-$	$-CO_2CH_3$	Pyrethrin II
CH_3-	$-CO_2CH_3$	Cinerin II
$CH_3{-}CH_2-$	$-CO_2CH_3$	Jasmolin II

(a) natural esters



(b) most active isomer in fenvalerate

Figure 1 (*a*) *The six natural esters;* (*b*) *a recent synthetic pyrethroid*

2 Definition

Although it is accepted that pyrethroids interfere with nerve action, the precise

[9] M. Elliott, in 'The Future for Insecticides: Needs and Prospects', ed. R. L. Metcalf and J. J. McKelvey, jun., Wiley, New York, 1976, p. 163.
[10] M. Elliott, N. F. Janes, and C. Potter, *Ann. Rev. Ent.*, 1978, **23**, 443.
[11] M. Elliott, *Env. Health Persp.*, 1976, **14**, 3.
[12] 'Synthetic Pyrethroids', ACS Symposium Series No. 42, ed. M. Elliott, American Chemical Society, Washington, DC., 1977.
[13] *Pesticide Sci.*, 1977, **8**, 236–330.
[14] Bibliography of Insecticide Materials of Vegetable Origin, Tropical Products Institute, London.
[15] Research Service Bibliographies, Series 4, 'Pyrethrins and Pyrethrum Insecticides', Public Library of South Australia, Adelaide.
[16] A. F. Bramwell, L. Crombie, P. Hemesley, G. Pattenden, M. Elliott, and N. F. Janes, *Tetrahedron*, 1969, **25**, 1727.
[17] L. Crombie, G. Pattenden, and D. J. Simmonds, *J.C.S. Perkin I*, 1975, 1500.
[18] G. Pattenden, L. Crombie, and P. Hemesley, *Org. Mass Spectrometry*, 1973, **7**, 719.
[19] M. J. Begley, L. Crombie, D. J. Simmonds, and D. A. Whiting, *J.C.S. Perkin I*, 1974, 1230.

system attacked in insects is not known, neither is their mode of action well enough understood to provide a basis for recognising an insecticide as a pyrethroid.

When developments since 1974 are considered, basing a definition on structural affinities is also problematical, for, with the exception that they are both esters, little superficial connection is apparent between pyrethrin I and a recent important active compound, fenvalerate[20,21] (Figure 1). However, strong evidence for a definite relationship (to be discussed) suggests that fenvalerate and pyrethrin I should both be considered members of the same class.

3 Structural Variations and Insecticidal Activity

Almost all active pyrethroids are esters. The constituent acids and alcohols, and simple derivatives of them, are practically inactive, as Staudinger and Ruzicka[2] demonstrated in their remarkable pioneering work. Much evidence suggests that high insecticidal activity depends on the overall shape of the molecule,[22] with certain key structural features appropriately disposed; other properties such as electron density and polarizability are of secondary importance. Almost every part of the parent molecule has now been replaced by a unit of analogous structure without losing insecticidal activity; yet other changes, apparently no more drastic, produce inactive compounds. Because of this strong dependence of the activity of pyrethroids on structural shape, the effects of structural variation are analysed in relation to the segmented structure of pyrethrin I as shown in Figure 2. In the following sections different structures are represented as combinations

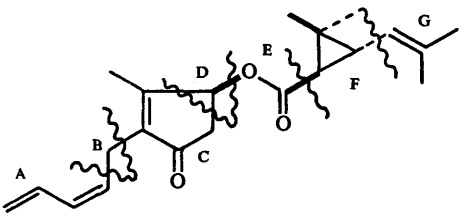


Figure 2 *Segmentation scheme for pyrethrin I*

of units directly comparable to those in pyrethrin I, and the most active natural ester, and the importance of each unit is indicated approximately by a one- to three-star rating of its overall performance. This modular approach to systematize the discussion of structural variations reflects a practical basis for designing

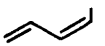
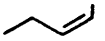
[20] N. Ohno, K. Fujimoto, Y. Okuno, T. Mizutani, M. Hirano, N. Itaya, T. Honda, and H. Yoshioka, *Pesticide Sci.*, 1976, **7**, 241; Jap. P. 73 06 528.
[21] A. N. Clements and T. E. May, *Pesticide Sci.*, 1977, **8**, 661.
[22] M. Elliott, in ref. 12.

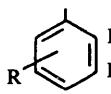
synthetic pyrethroids which has led to a succession of potent insecticides[23–27] and helped to establish the principles, reviewed here, underlying activity.[28]

As in other applications of additivity principles to interpret the results of variations assumed to be independent, conclusions must be qualified by recognizing that effects of altering one segment of the molecule may be influenced by the nature of the other groups present and may differ markedly between species of insect. Relative activities are often difficult to assess because many bioassay procedures emphasize knockdown rather than kill, and many patents lack data useful for external comparisons.

Segment A.—A centre of unsaturation at this site in the molecule is essential for high activity, but the structures of the natural esters (I—III), all active insecticides, show that variation is possible. Synthetic analogues with vinyl (IV) or ethynyl (VI) groups here have extended the range, but substituents on them (V, VI) do not improve activity.

Segment A

Variation	*Rating*	*Ref.*
I 	* * *	natural esters (Fig. 1a)
II 	* *	
III 	* *	
IV 	* * *	23, 29
V (Cl)*n* 	*	30, 31

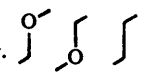
Variation	*Rating*	*Ref.*
VI 	*	30, 32—34
VII  R = H	* * *	see text
R = other	*	35

[23] M. Elliott, N. F. Janes, K. A. Jeffs, P. H. Needham, and R. M. Sawicki, *Nature*, 1965, **207**, 938.
[24] M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and B. C. Pearson, *Nature*, 1967, **213**, 493.
[25] M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and D. A. Pulman, *Nature*, 1973, **244**, 456.
[26] (*a*) M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, D. A. Pulman, and J. H. Stevenson, *Nature*, 1973, **246**, 169; (*b*) 'Proceedings of the seventh British Insecticide and Fungicide Conference (Brighton)', 1973, p. 721.
[27] M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and D. A. Pulman, *Nature*, 1974, **248**, 710.
[28] M. Elliott, N. F. Janes, and I. J. Graham-Bryce, 'Proceedings of the eighth British Insecticide and Fungicide Conference (Brighton)', 1975, p. 373.
[29] M. S. Schechter, N. Green, and F. B. LaForge, *J. Amer. Chem. Soc.*, 1949, **71**, 3165.
[30] W. A. Gersdorff and N. Mitlin, *J. Econ. Entomol.*, 1951, **44**, 70.
[31] P. D. Bentley and N. Punja, in ref. 12.
[32] M. Nakanishi, T. Mukai, S. Inamasu, T. Yamanaka, H. Matsuo, S. Taira, and M. Tsurada, *Botyu-Kagaku*, 1970, **35**, 87.
[33] H. Ogami, Y. Yoshida, Y. Katsuda, J. Miyamoto, and T. Kadota, *Botyu-Kagaku*, 1970, **35**, 45.
[34] C. Corral and M. Elliott, *J. Sci. Food Agric.*, 1965, **16**, 514.
[35] M. Elliott, N. F. Janes, and B. C. Pearson, *J. Sci. Food Agric.*, 1967, **18**, 325.

The most important unsaturated unit identified so far is phenyl (VII), present in all recently discovered potent pyrethroids (see Table 1 in Section 4) as a phenoxy or benzyl group (O or CH_2 in segment B); substitution on phenyl[36–38] or its replacement by a hetero-aromatic ring[39] usually diminishes activity.

Segment B.—This unit is methylene in the natural esters and in many active synthetic compounds (see Table 1). Its function is steric rather than chemical, for replacement by O generally produces a favourable change of properties of great practical importance when segment A is phenyl.[7,40] Other replacements (III—VI) usually diminish activity.

Segment B

Variation	*Rating*	*Ref.*	*Variation*	*Rating*	*Ref.*
I	* * *	see text	IV 	* *	7
II 	* * *	see text	V 	*	37, 41
III 	*	40	VI *e.g.* 	*	42, 43

When segments A and B are combined as a cyclopentenyl (cyclethrin,[44]) or a penta-1,3-dienyl (isopyrethrin I,[45]) side-chain, activity is also less.

Segment C.—Recognition of the significance of this structural unit has been very important in the discovery of the newer synthetic pyrethroids.

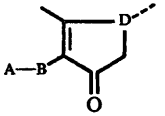
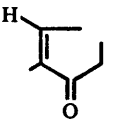
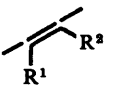
The methyl group on C-3 of the cyclopentenone ring (a consequence of the biosynthetic route, which may involve acetate[46]) apparently affects activity little, for one normethyl compound was more potent than the parent (benzyl substituted in segments A and B). Apart from this variation, no pyrethroids in which segment D is incorporated in the same ring as segment C show significant activity.

However, with segment D outside the ring, there are many effective variations (III—VIII) with planar or near planar aromatic heteroaromatic rings or acyclic

[36] M. Elliott, N. F. Janes, and M. C. Payne, *J. Chem. Soc.* (*C*), 1971, 2548.
[37] M. Elliott, A. W. Farnham, N. F. Janes, and P. H. Needham, *Pesticide Sci.*, 1974, **5**, 491.
[38] T. Matsuo, N. Itaya, T. Mizutani, N. Ohno, K. Fujimoto, Y. Okuno, and H. Yoshioka, *Agric. Biol. Chem.*, 1976, **40**, 247.
[39] M. Matsui, F. B. LaForge, N. Green, and M. S. Schechter, *J. Amer. Chem. Soc.*, 1952, **74**, 2181.
[40] K. Fujimoto, N. Itaya, Y. Okuno, T. Kadota, and Y. Yamaguchi, *Agric. Biol. Chem.*, 1973, **37**, 2681.
[41] W. A. Gersdorff and N. Mitlin, *J. Econ. Entomol.*, 1954, **47**, 888.
[42] Fr. P. 2043019/1971.
[43] M. Elliott, A. W. Farnham, N. F. Janes, M. M. Petersen, and P. H. Needham, unpublished results.
[44] H. L. Haynes, H. R. Guest, H. A. Stansbury, A. A. Sousa, and A. J. Borash, *Contrib. Boyce Thompson Inst.*, 1954, **18**, 1.
[45] M. Elliott, *J. Chem. Soc.*, 1964, 888.
[46] Ref. 4 p. 108.

units. By finding that an ester of piperonyl alcohol had insecticidal activity, Staudinger and Ruzicka[2] established a precedent for replacing cyclopentenonyl by benzyl. An increase in activity when an unsaturated substituent was placed at position 4 [3,23] confirmed the structural analogy. Later, some 3-substituted benzenes (IV) were shown to be even more active.[7,40] Heteroaromatic replacements, especially furan, close in size and shape to cyclopentenone, also have activity, which is greatest when 3,5-substituted.[5,24] Other heterocyclic variations such as thiophene,[47] and rings with two heteroatoms, are generally less insecticidal.

Segment C

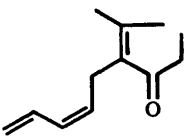
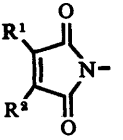
	Variation	*Rating*	*Ref.*		*Variation*	*Rating*	*Ref.*
I		* * *	natural esters	V	 X = O, S	* * *	see text
II		* *	36	VI		* *	48
III		* *	see text	VII		*	49, 50
IV		* * *	see text	VIII	 esp. R^1 = H R^2 = Cl, CH_3	* *	51, 52

Many acyclic compounds have been investigated (VI—VIII) but, although relatively easily synthesized, in general they are less active insecticides than the cyclic compounds.

Segments A + B + C.—Some insecticidal esters are derived from alcohols which are not obvious combinations of the segments discussed, yet are clearly pyre-

[47] B.P. 1265437/1972.
[48] B.P. 1226788/1971.
[49] B.P. 1313554/1973.
[50] *Rothamsted Ann. Rep.* 1971, Pt. I, p. 188.
[51] K. Sota, T. Amano, M. Aida, K. Noda, A. Hayashi, and I. Tanaka, *Agric. Biol. Chem.*, 1971, **35**, 968; **37**, 1019.
[52] *Rothamsted Ann. Rep.* 1973, Pt. I, p. 169.

Segments A + B + C

	Variation	Rating	Ref.
I		* * *	natural esters
II	 esp. $R^1 + R^2 = (CH_2)_4$	* *	53

throids because they are only active when they incorporate pyrethroid acids. Tetramethrin, the prototype, is a strong knockdown agent, and many alternatives for R^1 and R^2 are patented. Other variations in this category are based on benzofurans[54] and dihydrofurans.[55]

Segment D.—All active pyrethroids reported so far are esters in which the carbon atom joined to the ester oxygen is sp^3 hybridized; it is either incorporated in a cyclopentenone ring (variation I) or connects, for example, a benzene ring to the ester oxygen, when it is either primary (II) or secondary (IV—V). Phenyl esters (III) where it is sp^2 hybridized are much less active.

Segment D

	Variation	Rating	Ref.
I		* * *	natural esters
II		* * *	see text
III	—	*	6, 23

	Variation	Rating	Ref.
IV	 —C≡C—R	* *	56
	—C≡N	* * *	27, 38
	other	*	38, 57

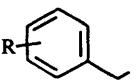
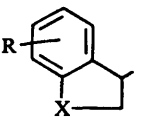
In the benzene and furan series, esters with an unsubstituted CH_2 group (variation II) are effective, but especially in 3-phenoxybenzyl compounds, introduction of cyano produces dramatic changes in activity. When the absolute configuration of the —CH(CN)— group is *S*, activity is increased up to 15-fold[27] over the unsubstituted compound (depending on the acid component present), whereas in the opposite configuration activity is *depressed* by as much as eight times;[58] the pure esters required for this study were separated from diastereo-

[53] T. Kato, K. Ueda, and K. Fujimoto, *Agric. Biol. Chem.*, 1964, **28**, 914.
[54] B.P. 1271771/1972; U.S.P. 3816469/1974.
[55] Ger. Offen. 2108932/1972; 2555581/1974.
[56] B.P. 1270315/1972.
[57] Ger. Offen. 2407024/1974; 2609704/1976.
[58] M. Elliott, N. F. Janes, D. A. Pulman, and D. M. Soderlund, *Pesticide Sci.*, 1978, **9**, 105; M. Elliott, A. W. Farnham, N. F. Janes, and D. M. Soderlund, *Pesticide Sci.*, 1978, **9**, 112.

isomeric pairs chromatographically. The C-4 epimers of cyclopentenolone esters apparently differ less in activity (see discussion[58]). The α-ethynyl compounds (IV) are also active.

Segments C + D.—If appropriate sectors of the flexible pyrethroid structure could be maintained by suitable additional connections in the conformation adopted at

Segments C + D

	Variation	*Rating*	*Ref.*		*Variation*	*Rating*	*Ref.*
I		* * *	benzyl esters	II	 X = O, S, CH_2, CO	*	59

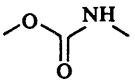
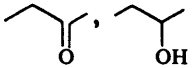
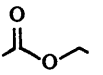
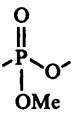
the site of action, particularly active compounds might be produced. In variation (II), several alternative extra connecting units have been examined. Activity was generally small, comparable to that of esters of most other benzyl alcohols with α-substituents (above); the most interesting compound (II, X = O, R = 7-Me) has moderate activity.[60]

Segment E.—Even small alterations in this unit at the centre of the molecule would be expected to produce large overall stereochemical differences with consequent effects on potency; the variations listed (II—VIII) do indeed diminish or remove activity.

In addition, there is evidence from physical properties such as dipole moments[67] that in esters one of the two conformations in which all four bonds are coplanar is strongly preferred. *X*-ray analytical evidence for all pyrethroids examined[19,68,69] shows this to be a consistent feature, therefore the ester unit in pyrethroids may have properties not reproduced by alternative structures. The relative ease of ester cleavage also exerts an important influence on mammalian toxicity (see below).

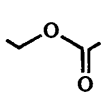
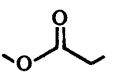
[59] B.P. 1274595/1972; U.S.P. 3647857/1972; Jap. Kokai, 74 26421-2; M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and B. C. Pearson, unpublished results.
[60] Y. Inoue, S. Ohono, T. Mizuno, Y. Yura, and K. Murayama, in ref. 12.
[61] P. E. Berteau and J. E. Casida, *J. Agric. Food Chem.*, 1969, **17**, 931.
[62] M. R. Altamura, L. Long, and T. Hasselstrom, *J. Org. Chem.*, 1962, **27**, 594.
[63] M. H. Black, in ref. 12.
[64] M. Matsui, K. Yamashita, M. Miyano, S. Kitamuka, Y. Suzuki, and M. Hamuro, *Bull. Agric. Chem. Soc. Japan*, 1956, **20**, 89; Belg. P. 852082.
[65] Jap. P. 61 8498.
[66] J. R. Reid and R. S. Marmor, *J. Org. Chem.*, 1978, **43**, 999.
[67] L. E. Sutton, in 'Determination of Organic Structures by Physical Methods', ed. E. A. Braude and F. Nachod, Academic Press, New York, 1955, Vol. I. p. 405.
[68] J. D. Owen, *J.C.S. Perkin I*, 1975, 1865.
[69] J. D. Owen, *J.C.S. Perkin I*, 1976, 1231.

Segment E

	Variation	*Rating*	*Ref.*		*Variation*	*Rating*	*Ref.*
I		* * *	esters	V		*	62
II		*	22, 23, 61	VI		*	63
III		*	61	VII		*	64
IV		*	61	VIII		*	65
				IX		*	66

Segments D + E.—As in the previous section, the evidence available indicates that compounds in which the central ester link is reversed show little or no activity.

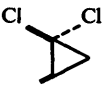
Segments D + E

	Variation	*Rating*	*Ref.*		*Variation*	*Rating*	*Ref.*
I		* * *	*e.g.* benzyl esters	II		*	61

Segment F.—Both methyl groups (I) are present in the most active compounds[72] but that *cis* to segment E has been shown,[74] in some cases, to be the more important; all known cyclopropyl esters with no substituents here are inactive. The function of the methyl groups in the active molecules is probably related more to their steric than to their chemical characteristics, because dichloro-(II)

[70] J. J. K. Novak, J. Farkas, and F. Sorm, *Coll. Czech. Chem. Comm.*, 1961, **26**, 2090.
[71] Ger. Offen. 2553991/1976; 2712333/1977.
[72] F. Barlow, M. Elliott, A. W. Farnham, A. B. Hadaway, N. F. Janes, P. H. Needham, and J. C. Wickham, *Pesticide Sci.*, 1971, **2**, 115.
[73] P. E. Burt, M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and D. A. Pulman, *Pesticide Sci.*, 1974, **5**, 791.
[74] T. Sugiyama, A. Kobayashi, and K. Yamashita, *Agric. Biol. Chem.*, 1974, **38**, 979.

Segment F

	Variation	Rating	Ref.		Variation	Rating	Ref.
I		* * *	natural esters	III		* *	71
II		* *	70	IV		*	72, 73

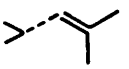
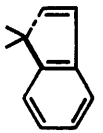
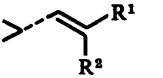
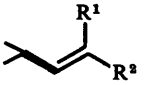
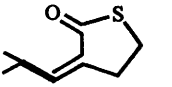
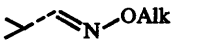
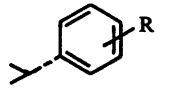
and spiro-(III) substituted cyclopropanes show significant insecticidal activity, but esters with larger groups are less active. Inversion of stereochemistry at C-1 (IV) eliminates or greatly diminishes insecticidal activity in all dimethylcyclopropane esters, except when there is no substituent at C-3. Cyclopropanes with an additional group at C-1,[75] dimethyl aziridines,[76] cyclopropenes,[77] and cyclobutanes[78] have little activity.

Segment G.—Many compounds with diverse substituents in this segment are active, showing considerable latitude in requirements; however, certain small changes here can influence activity profoundly. Activity increases with the number of C-3 methyl groups. As with segment F, alternative groups (III, IV) with steric properties similar to (II) are effective.

However, only compounds with unsaturation in the substituent at C-3 are highly active. In the homologous series (VI) the but-1-enyl analogue (R^1 = H, R^2 = Et) with the same number of carbon atoms as the parent chrysanthemate (I), and possibly optimum polarity,[85] is most active. Ethano-bridged compounds (VI; $R^1 + R^2 = (CH_2)_4$) are also more potent than the corresponding chrysanthemates.[86] 3-Dienyl substituents (VI; R^1 or R^2 = alkenyl) give outstandingly active esters,[25] the most effective being buta-1,3-dienyl and penta-1,3-dienyl, without a 1′-methyl group.[87] Compounds with substituents containing hetero-

[75] R. G. Bolton, *Pesticide Sci.*, 1976, **7**, 251.
[76] M. P. Sammes and A. Rahman, *J.C.S. Perkin I*, 1972, 344.
[77] Jap. P. 71 21 373
[78] P. J. Crowley, Ph.D. Thesis, University of Manchester, 1974.
[79] M. Matsui and T. Kitahara, *Agric. Biol. Chem.*, 1967, **31**, 1143.
[80] R. H. Davis and R. J. G. Searle, in ref. 12; U.S.P. 3823177/1974.
[81] U.S.P. 3962458/1976.
[82] M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and D. A. Pulman, *Pesticide Sci.*, 1976, **7**, 492.
[83] J. Farkas, P. Kourim, and F. Sorm, *Chem. Listy*, 1958, **52**, 695.
[84] J. Lhoste and F. Rauch, *Pesticide Sci.*, 1976, **7**, 247.
[85] G. G. Briggs, M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, D. A. Pulman, and S. R. Young, *Pesticide Sci.*, 1976, **7**, 236.
[86] L. Velluz, J. Martel, and G. Nominé, *Compt. rend.*, 1969, **268**, 2199.
[87] Ger. Offen. 2231436/1973; M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and D. A. Pulman, *Pesticide Sci.*, 1976, **7**, 499.

Segment G

	Variation	*Rating*	*Ref.*
I		* * *	natural 'I' esters
II		* * *	61, 72, 79
III		* *	72
IV		* *	7, 80, 81
V		* *	81
VI	 (*trans*)	* * *	see text
VII	 (*cis*)	* * *	see text
VIII		* *	84
IX		* *	82
X		* *	83

atoms (VI; R^1 = CH_2OMe, CO_2Me, *etc*; R^2 = Me, halogen) are more polar, and especially active as knockdown agents.[88]

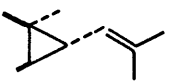
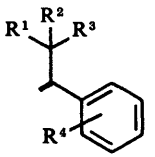
The activity of both *cis*-(VII; R^1 = R^2 = Me) and *trans*-chrysanthemates indicates the broad steric latitude within which unsaturated groups on C-3 confer activity. Replacing the methyl groups in either isomer with halogens (VI or VII; R^1 = R^2 = halogen) gives a considerable increase in insecticidal activity[25–27,89,90] and, with appropriate alcohols, the very valuable property of photostability (see Section 6). Variation (VIII) is present in the most powerful known knockdown agent.

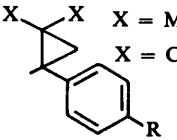
Of other variations reported, only the methoxyimino ether (IX) is more active than isobutenyl (I). Substituted ethynyl[91] and alkenylidene[92] groups give esters of low activity. Substitution of methyl groups into otherwise active compounds greatly diminishes potency, a result ascribed to disturbance of the optimum conformation for activity.[93]

[88] Ger. Offen. 2109010/1971; 2449643/1975.
[89] M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and D. A. Pulman, *Pesticide Sci.*, 1975, **6**, 537.
[90] D. G. Brown, O. F. Bodenstein, and S. J. Norton, *J. Agric. Food Chem.*, 1973, **21**, 767; 1975, **23**, 115; *Botyu-Kagaku*, 1976, **41**, 1.
[91] M. Yoshimoto, N. Ishida, and Y. Kishida, *Chem. Pharm. Bull.*, 1972, **20**, 2593; *Rothamsted Ann. Rep.* 1976, Pt. I, p. 163.
[92] Jap. Kokai 74 80242.
[93] M. Elliott and N. F Janes, in ref. 12.

Segments F + G.—Ohno *et al.*[42] recently made the important discovery that acyclic units (II) can function as acidic components of esters with typical pyrethroid alcohols. The most effective compounds were *p*-substituted 3-methyl-2-phenylbutyric acids (II, $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = p$-Cl, p-CH_3, or 3,4-methylenedioxy). Of the two optical forms of each of these acids, that related

Segments F + G

	Variation	*Rating*	*Ref.*
I		* * *	natural esters
II		* * *	20, 94

	Variation	*Rating*	*Ref.*
III	 X = Me	*	22
	X = Cl	* *	95

sterically to the (more active) (1*R*)-chrysanthemate gives the more active esters. The discovery of this variation not only provides significant evidence of the features essential for activity in this group of insecticides, but also considerably increases the potential range of practical insecticides; numerous replacements for the substituted phenyl group have already been described in patents. Variation (III) is particularly interesting because it may indicate a structural connection between DDT-type compounds and pyrethroids.

Summary of structure–activity relationships.—The relative insecticidal activities of the many structures summarized in the previous sections are most straightforwardly interpreted by assuming that the action of pyrethroids involves approach of an intact molecule to a site in the nervous system of the insect; a metabolic activation (comparable to the thion → oxon transformation of organophosphates) is probably not involved. Greatest potency depends on at least two centres having appropriate chirality. For example, in chrysanthemates the configuration at C-1 must be [*R*], in 3-methylbutyrates the sterically equivalent [*S*] and in alcohols, for cyclopentenolones [*S*] at C-4, and for α-cyano-3-phenoxybenzyl alcohol [*S*] at C-α. These conditions imply chirality in the interacting system at an important stage in the process of poisoning. Two centres of unsaturation at the extremities of the molecule (segments A and G) and a *gem*-

[94] N. Ohno, K. Fujimoto, Y. Okuno, T. Mizutani, M. Hirano, N. Itaya, T. Honda, and H. Yoshioka, *Agric. Biol. Chem.*, 1974, **38**, 881; M. Miyakado, N. Ohno, Y. Okuno, M. Hirano, K. Fujimoto, and H. Yoshioka, *Agric. Biol. Chem.*, 1975, **39**, 267; Ger. Offen. 2335347/1974.

[95] G. Holan, D. F. O'Keefe, C. Virgona, and R. Walser, *Nature*, 1978, **272**, 735.

dimethyl group or its steric equivalent β to the ester group are features of all potent pyrethroids so far described. Other segments of the molecule can be replaced by a wide range of sterically equivalent groups whose function may be to influence preferences for the relative conformations between segments, whilst maintaining suitable molecular polarity.

4 Chronological Survey of Effective Combinations

The sequence of compounds in Table 1 reflects the progressive advance in understanding structure–activity relationships and the associated development of commercially important insecticides. Although some compounds may be especially active against one particular pest at one stage in the life cycle (*e.g.* the 3-methyl-2-phenylbutyrates against lepidopterous larvae),[20] experience has shown that the levels of activity against the two chosen species of insect in the Table provide a useful general indication of the practical value, where appropriate, of the compound.

By the compounds they synthesized and tested for insecticidal activity, Staudinger and Ruzicka[2] showed remarkable insight into the structure–activity relationships of pyrethroids, and provided the foundation for modern concepts of the essential requirements for activity. However, the first major advance towards a commercially important synthetic pyrethroid was the versatile synthesis of cyclopentenolones by Schechter *et al.*[29] who developed allethrin (4J), containing all eight possible stereoisomers. Later one- and two-isomer preparations (3B, 4B) were developed commercially. Combining Chen and Barthel's observation[101] of activity in various benzyl chrysanthemates with the need for unsaturation in segment A led to 4-allyl and 4-allyl-2,6-dimethylbenzyl chrysanthemates (6J and 7J). This investigation was pursued by showing that benzene could be replaced by furan when benzyl was substituted for allyl, the optimum orientation found being in 5-benzyl-3-furylmethyl esters (9).

In a parallel development, the chrysanthemate (8J) of *N*-hydroxymethyltetrahydrophthalimide, a relatively inexpensive alcohol, was shown to have excellent knockdown action against flying insects, though relatively low insecticidal toxicity.

5-Benzyl-3-furylmethyl alcohol was then used to examine the relative activities of esters of novel acids. The tetramethylcyclopropane carboxylate (NRDC 108, 9L) is the most effective pyrethroid with no chiral centre. Ethanochrysanthemates (*e.g.* 9N) are generally somewhat more active than the corresponding chrysanthemates. Inverting stereochemistry at C-3, as in the *cis*-chrysanthemate (9F), increases activity to some species. The *cis* thiolactone compound, RU 15525 (9M)

[96] L. Crombie, S. H. Harper, and F. C. Newman, *J. Chem. Soc.*, 1956, 3963.
[97] W. A. Gersdorff and N. Mitlin, *J. Econ. Entomol.*, 1953, 46, 999.
[98] W. F. Barthel, *Adv. Pest Control Res.*, 1961, 4, 33.
[99] B.P. 1223217/1971.
[100] M. Elliott, A. W. Farnham, M. G. Ford, N. F. Janes, and P. H. Needham, *Pesticide Sci.*, 1972, 3, 25.
[101] Y. L. Chen and W. F. Barthel, *U.S. Dept. Agric. ARS*, 33-23/1956.

Table 1 *Relative toxicities of pyrethroids to two insect species*

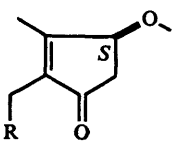
*Name**	*Formula†*	*First Synthesized*	*Ref.*	*Relative Toxicity‡* (Bioresmethrin = 100) *to Houseflies*	*Mustard beetles*
Pyrethrin I	(2B)	1956	96	2 (+KD)	150
Allethrin	(4J)	1949	29	3 (+KD)	1
'Bioallethrin'	(4B)	1949	29	5 (+KD)	2
'S-Bioallethrin'	(3B)	1953	97	9 (+KD)	4
Dimethrin	*a*	1958	98	0.3	0.2
Tetramethrin	(8J)	1964	53	2 (+KD)	2
'ABC'	(6J)	1965	23	7	0.1
'DMABC'	(7J)	1965	23	7	2
Resmethrin	(9J)	1967	24	42	37
Bioresmethrin	(9B)	1967	24	100	100
'NRDC 108'	(9L)	1968	61, 72	74	30
Prothrin	*b*	1967	33	7	1.2
'Ethanoresmethrin'	(9N)	1969	86	150	180
Proparthrin	*c*	1970	32	6	—
Cismethrin	(9F)	1971	72	42	52
'3BBC'	*d*	1971	7, 99	15	53
Phenothrin	(10J)	1971	7, 40	31	72
'Benzylnorthrin'	(5B)	1971	36	7	17
Butethrin	*e*	1971	51	14	—
'Cyano phenothrin'	(11J)	1973	38	180	110
'NRDC 134'	(9D)	1973	25	240	280
Permethrin	(10K)	1973	26	69	140
Biopermethrin	(10D)	1973	26	86	240
'RU 15525'	(9M)	1973	81	39 (+KD)	52
Fenvalerate	(11Q)	1973	20	47	100
'NRDC 167'	(10H)	1974	72	200	160
Decamethrin	(12I)	1974	27	2800	5500
'NRDC 173'	(9C)	1975	92, 93	390 (+KD)	180
Cypermethrin	(11K)	1975	92	260	430

*The name by which the compound is referred to in at least one publication. If not in quotes, it is a proposed or accepted common name; †Esters are designated by a number–letter combination to indicate the alcohol [formulae (1—12)] and acid [formulae (A—Q)] components, respectively; ‡Measured by topical application and probit analysis as described;[100] molar basis [a–e](±)-*cis,trans*-chrysanthemates of the following alcohols: [a]3,4-dimethylbenzyl; [b]5-propargylfurfuryl; [c]2-methyl-5-propargyl-3 furylmethyl; [d]3-benzylbenzyl; [e]3-chloro-4-phenylbut-2-enyl

is the most powerful knockdown agent yet described, but the *trans* isomer, and the corresponding 3-phenoxybenzyl esters, are not comparably active.

Of the many mono- and poly-heterocyclic alcohols with a structural similarity

(1)

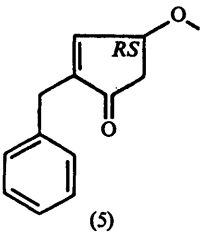


R

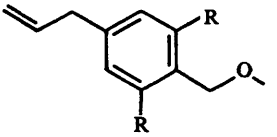
(2)

(3)

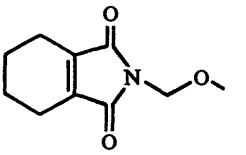
(4) (*RS* at C-4)



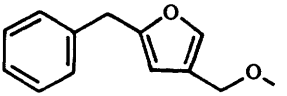
(5)



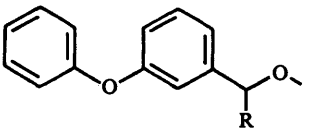
(6) R = H
(7) R = CH_3



(8)

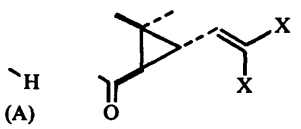


(9)



R

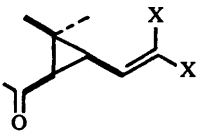
(10) H
(11) CN (*RS*)
(12) CN (*S*)



(A)

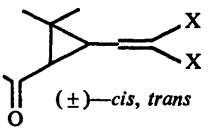
(1*R*, *trans*)

(B) X = Me
(C) X = F
(D) X = Cl
(E) X = Br



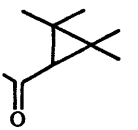
(1*R*, *cis*)

(F) X = Me
(G) X = F
(H) X = Cl
(I) X = Br

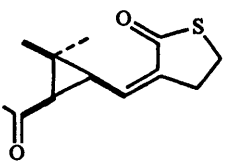


(±)—*cis*, *trans*

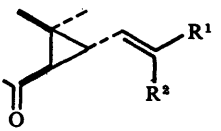
(J) X = Me
(K) X = Cl



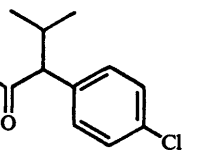
(L)



(M)



(N) $R^1 + R^2 = (CH_2)_4$
(O) R^1 = H, R^2 = Me
(P) R^1 = H, R^2 = Et



(Q)

to 5-benzyl-3-furylmethyl alcohol, only the propargyl compounds are significantly active, especially against flying insects. Butethrin with an acyclic unit for segment C shows useful activity to a limited number of species.

In 1969, two research groups independently recognized the significance of the structural similarity between 5-benzyl-3-furylmethyl alcohol and benzyl alcohols with *m*-substituents such as benzyl and phenoxy. Esters from 3-phenoxybenzyl alcohol (10) were generally less active than those from 5-benzyl-3-furylmethyl alcohol (9) but activity in esters of α-ethynyl alcohols having been detected, α-cyano-3-benzylbenzyl and -3-phenoxybenzyl esters, *e.g.* (11B) were examined and found to have increased insecticidal activity.

Initial indications of the valuable influence of changing the 3-substituent in dimethylcyclopropanecarboxylates (variations in segment G) stimulated synthesis and examination of analogues with a diverse range of groups at this position. Acids with dichloro- and dibromo-vinyl side chains formed exceptionally effective combinations with the three most powerful alcohols, (9A), (10A), and (11A). The last two were not photolabile, so combining them with the comparably stable dihalovinyl acids produced the first group of synthetic pyrethroids sufficiently persistent to control insect pests of agricultural and horticultural crops in sunlight. Of all the possible combinations in this group, the diastereoisomeric pair of esters (11I) from the racemic cyanohydrin of 3-phenoxybenzaldehyde and [1*R*,*cis*]-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid was exceptionally active insecticidally, due almost entirely to one isomer (decamethrin; NRDC 161; 12I) which was separated by crystallization.[27,58] Further, decamethrin is one of the few biologically active compounds suitable without modification for heavy atom *X*-ray analysis to establish absolute configuration.[68] Other combinations being developed for practical applications are the (±)-*cis*-,*trans*-dichlorovinyl esters of 3-phenoxybenzyl alcohol (permethrin; NRDC 143; 10K) and of α-cyano-3-phenoxybenzyl alcohol (cypermethrin; NRDC 149; 11K). The [1*R*, *trans*]-difluorovinyl ester of 5-benzyl-3-furylmethyl alcohol (9C) has a unique combination of rapid knockdown action against houseflies and killing power greater than bioresmethrin.

The ester of α-cyano-3-phenoxybenzyl alcohol with 2-(4-chlorophenyl)-3-methylbutyric acid (fenvalerate; S-5602; 11Q) now being introduced also has valuable potential as an insecticide for agricultural use. The four named compounds (10K, 11K, 12I, and 11Q), after extensive field trials throughout the world, are at present considered to have the most favourable combination of properties and prospects for practical application.

5 Synthesis of Components of Pyrethroid Esters

A. Alcohols.—*Cyclopentenolones.* The original route[29] (or a variation[102]) to (±)-allethrolone (4A) is still used commercially, despite numerous published alter-

[102] Fr. P. 1434224/1966.

natives, some originating in the prostaglandin field; for reviews, see ref. 103. (*S*)-allethrolone (3A), obtained by resolving the hemi-succinate[104] or -phthalate[105] is necessary for the manufacture of *S*-bioallethrin (3B). The (*R*)-allethrolone can be recycled by racemization of a derivative,[106] or more directly, the *R* alcohol, as its mesyl derivative, undergoes an S_N2 reaction with sodium chrysanthemate with inversion to give the required (4*S*) ester.[107]

N-*hydroxymethyl Imides.* The alcoholic component (8A) of tetramethrin (8J) is readily accessible at low cost from condensation of maleic anhydride and butadiene, followed by rearrangement, imide formation with urea, and hydroxymethylation with formaldehyde.[108]

Substituted Benzyl Alcohols. The alcoholic components of the benzyl chrysanthemates needed for structure–activity investigations were made by reaction of aryl Grignard reagents with formaldehyde, by reducing appropriate aldehydes or acids, or by the sequence $—CH_3 \rightarrow —CH_2hal \rightarrow —CH_2OH$.[35] The alcoholic function was protected when necessary as the tetrahydropyranyl derivative whilst a bromo substituent was converted into allyl, benzyl, *etc.* 2,6-Dimethyl-4-allylbenzyl alcohol was also made by a special route[109] in which *N*-allyl-2,6-xylidine was rearranged in xylene in the presence of zinc chloride to 2,6-dimethyl-4-allylaniline, and then converted into the alcohol by conventional reactions.

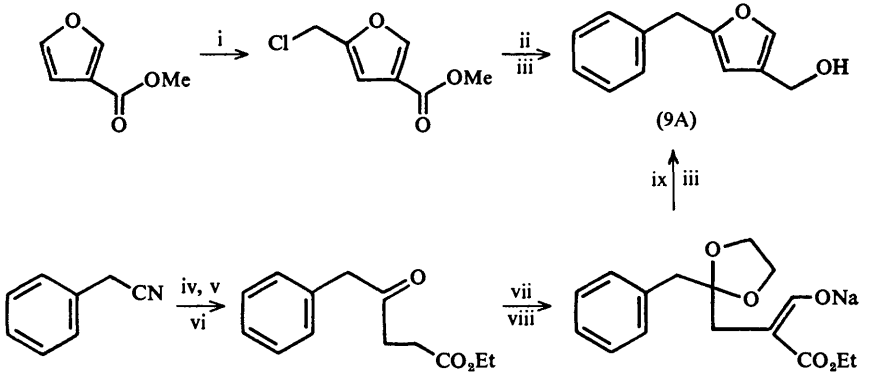
5-*Benzyl*-3-*furylmethyl alcohol.* Furans with functional groups at the 3-position are relatively inaccessible[110] but an established synthesis of 3-furoic acid[111] gave the starting material for the route[112] to the alcohol (9A) shown in Scheme 1.

The second route shown in Scheme 1 was developed later and adapted for commercial production;[112] alternatives for reagents iv—vii have been patented.[113]

The importance of this alcohol (9A) has stimulated development of several alternative syntheses[114] one of which (Scheme 2) was subsequently adapted to form the insecticidal ester (R = chrysanthemoyl) directly.

3-*Phenoxybenzyl Alcohols.* These are the most important alcoholic components of

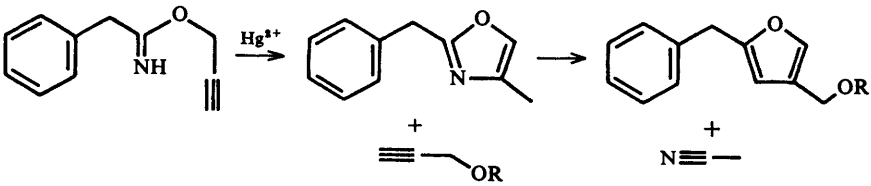
[103] R. A. Ellison, *Synthesis*, 1973, **7**, 397; G. Pattenden, in 'Aliphatic Chemistry', ed. A. McKillop (Specialist Periodical Reports), The Chemical Society, London, 1977, vol. 5, p. 231.
[104] Ger. Offen. 2263880/1973.
[105] Ger. Offen. 2414794/1974.
[106] Ger. Offen. 2535766/1976; B.P. 1485082/1977.
[107] Ger. Offen. 2740701/1978.
[108] Jap. P. 65 22658; M. E. Bailey and E. D. Amstutz, *J. Amer. Chem. Soc.*, 1956, **78**, 3828.
[109] M. Elliott and N. F. Janes, *J. Chem. Soc.* (*C*), 1967, 1780.
[110] P. Bosshard and C. H. Eugster, *Adv. Heterocyclic Chem.*, 1966, **7**, 377.
[111] E. Sherman and E. D. Amstutz, *J. Amer. Chem. Soc.*, 1950, **72**, 2195; F. Korte, R. Heinz, and D. Scharf, *Chem. Ber.*, 1961, **94**, 825.
[112] M. Elliott, N. F. Janes, and B. C. Pearson, *J. Chem. Soc.* (*C*), 1971, 2551; Anon, *Chem. Eng. News*, 1971 (2), 32.
[113] B.P. 1178897/1970; B.P. 1196202/1970; U.S.P. 3755368/1973.
[114] B.P. 1213850/1970; G. R. Treves and P. A. Cruickshank, *Chem. and Ind.*, 1971, 544; Ger. Offen. 1935009/1971; 2122661/1972; 2122822—3/1972; U.S. 3781308/1973; Y. Naoi, T. Nakano, K. Sakai, K. Fujii, and M. Wakaomi, *Nippon Kagaku Kaishi*, 1977, **9**, 1365.



Reagents: i, CH_2O, HCl; ii, Benzene, $AlCl_3$; iii, LAH; iv, NaOEt + $(CH_2CO_2Et)_2$; v, H_3O^+; vi, EtOH–HCl; vii, H^+, $(CH_2OH)_2$; viii, NaH, HCO_2Et; ix, aq, HCl

Scheme 1

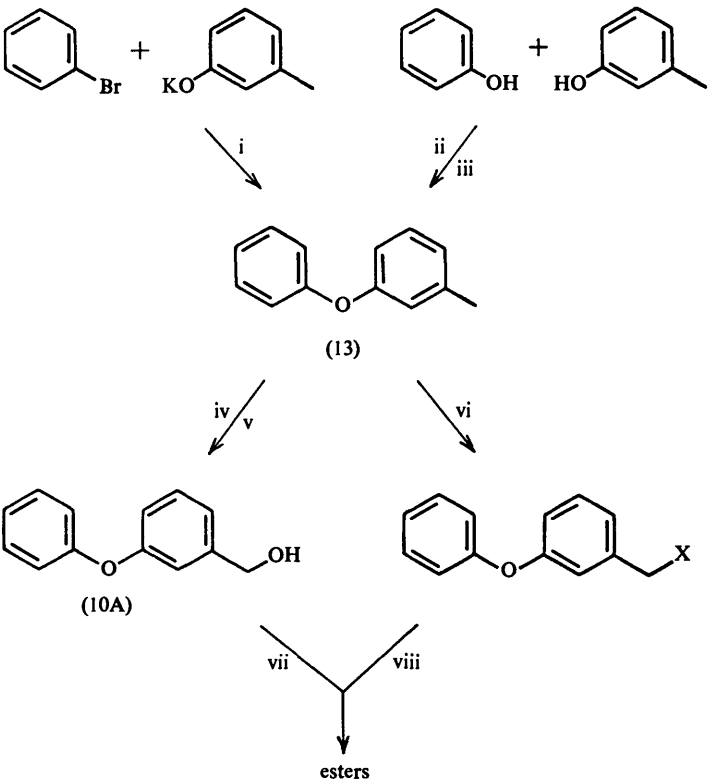
the recent generation of synthetic pyrethroids. Although esters from 3-phenoxybenzyl alcohol (10A) are less active than those from 5-benzyl-3-furylmethyl alcohol (9A) many are photostable and being more readily synthesized, are less expensive. Esters from α-cyano-3-phenoxybenzyl alcohol (11A) are among the most powerful insecticides known.



Scheme 2

3-Phenoxybenzyl alcohol (10A) is made by several routes (Scheme 3), most of which involve the intermediate, 3-phenoxytoluene (13) originally made[115] by condensing potassium cresate with bromobenzene, but more recently by a process[116] more suitable for an industrial plant. Oxidation of the methyl group in (13) with either permanganate[115] or oxygen and catalyst[117] gives 3-phenoxybenzoic acid, which can then be reduced to the alcohol (10A). In a more direct route[118] the methyl group is halogenated and the monohalide, with the appropriate acid in the presence of a tertiary amine, gives the insecticidal ester, *e.g.* phenothrin.

[115] Fr. P. 1394557—8/1965.
[116] B.P. 1496821/1975.
[117] Jap. Kokai 73 61450; B.P. 1489325/1977.
[118] Ger. Offen. 2402457/1974; 2437882/1975.



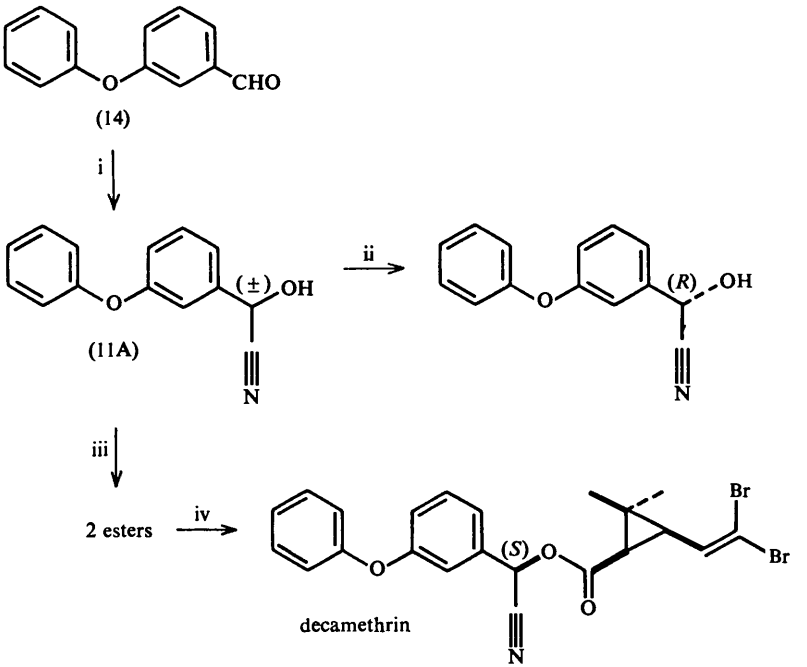
Reagents: i, Cu; ii, thoria (450 °C); iii, fractionate; iv, oxidant; v, reductant; vi, halogen; vii, RCOCl; viii, RCO_2H + NR^1_3

Scheme 3

α-Cyano-3-phenoxybenzyl alcohol (11A) is made from 3-phenoxybenzaldehyde (14) available by oxidation of the alcohol[27] or by an Ullman reaction.[119] Reaction of (14) with HCN gives the racemic alcohol; in the presence of D-oxynitrilase one epimer is preferentially destroyed producing predominantly the less active *R*-form (Scheme 4).[27,58] The problem of isolating esters of this alcohol with the more active *S*-configuration (12) at this centre was first solved[27,58] using the **1*R*,*cis***-dibromovinyl acid (1I) as resolving agent; the required insecticidal enantiomer [(12I); NRDC 161; decamethrin] crystallized from hexane leaving the other diastereoisomer in solution (Scheme 4). The configuration at C-α is epimerized by base[120] so the inactive diastereoisomer can be inverted to provide more decamethrin, without cleaving the ester. α-Cyano-3-phenoxybenzyl bromide is a

[119] Belg. P. 842177/1976; see also A. Bader, *Aldrichimica Acta*, 1976, **9**, 49.
[120] Belg. P. 853866—7/1977; Ger. Offen. 2718038—9/1977.

potentially useful intermediate for preparing esters of labile acids *via* their sodium or amine salts.[121]



Reagents: i, HCN; ii, D-oxynitrilase; iii, acid chloride of (11); iv, crystallization from hexane

Scheme 4

B. Acids.—*Chrysanthemic Acid and Analogues.* Recent elegant syntheses[122] have not significantly influenced the commercial production of (±)*cis*,*trans*-chrysanthemic acid (1C), the most direct route to which remains the addition of ethyl diazoacetate to 2,5-dimethyl-hexa-2,4-diene (for a review of many routes, see ref. 4). The established route to (±)-*trans* acid by addition of the methyl-propenyl unit (presented as a sulphone) to seneceoic ester has been modified.[123] An efficient asymmetric addition of ethyl diazoacetate to the diene in the presence of a chiral copper catalyst gives a product 80:20 *trans*:*cis* and predominantly (80%)

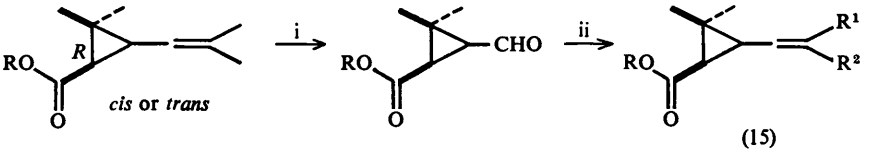
[121] Ger. Offen. 2619321/1976.

[122] B.P. 1416804/1975; H. Hirai, K. Ueda, and M. Matsui, *Agric. Biol. Chem.*, 1976, **40**, 153, 161, 169; M. J. Devos, L. Hevesi, P. Bayet, and A. Krief, *Tetrahedron Letters*, 1976, 3911; A. S. Khanra and R. B. Mitra, *Indian J. Chem.*, 1976, **14B**, 716; A. J. Ficini and J. d'Angelo, *Tetrahedron Letters*, 1976, 2441; S. C. Welch and T. A. Valdes, *J. Org. Chem.*, 1977, **42**, 2108.

[123] J. Martel and C. Huynh, *Bull. Soc. chim. France*, 1967, 985; Hung. Teljes 8014/1974.

1*R*.[124] Chirality in the alkyl diazoacetate has less influence.[125] New procedures separate optical and geometrical isomers[126] and racemize less active forms[127] for recycling.

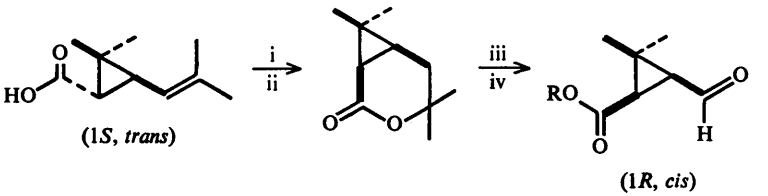
Many of the structural variations for segment G were first introduced[128] (*cf.* ref. 129) by Wittig synthesis with an aldehydoester. A simple ester (*e.g.* R = Me) is normally the best intermediate but for side chains labile in base, the acid (15, R = H) is obtained easily by using the t-butyl ester and pyrolysing the Wittig product (15, R = Bu^t) (Scheme 5). Thence, many analogues with well-defined stereochemistry could be synthesized.



Reagents: i, O_3; ii, $R^1R^2C{=}PPh_3$

Scheme 5

Commercial resolution of (±)-*trans*-chrysanthemic acid[130] gives the (1*R*,*trans*) acid, and thence by ozonolysis the *trans* aldehyde. The (1*S*,*trans*) acid, which gives esters of much diminished potency, can be converted *via* the (1*R*,*cis*) acid to the *cis* aldehyde as shown in Scheme 6.[131] As discussed below, this aldehyde is very significant commercially in addition to providing variations for structure–activity studies.



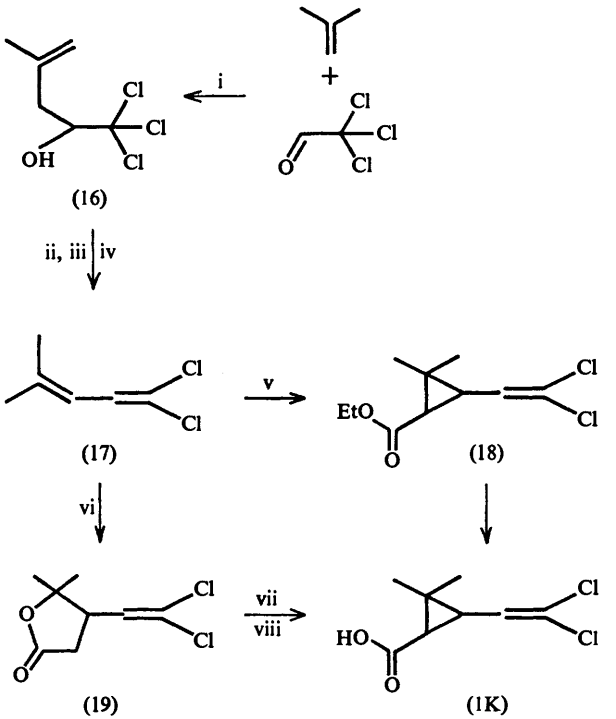
Reagents: i, H_3O^+; ii, KOBu^t; iii, $MgBr_2{,}6H_2O$; pyridine; iv, O_3

Scheme 6

[124] T. Aratani, Y. Yoneyoshi, and T. Nagase, *Tetrahedron Letters*, 1975, 1707; Jap. Kokai 74 14448, 102650. 75 137955.
[125] T. Aratani, Y Yoneyoshi, and T. Nagase, *Tetrahedron Letters*, 1977, 2599.
[126] B.P. 1359968/1972; 1369519/1972; 1369730/1972; F. Horiuchi and M. Matsui, *Agric. Biol. Chem.*, 1973, **37**, 1713: Ger. Offen. 2356702/1974; Jap. P. 75 34019.
[127] Ger. Offen. 2453639/1975.
[128] M. Elliott, N. F. Janes, and D. A. Pulman, *J.C.S. Perkin I*, 1974, 2470.
[129] (*a*) L. Crombie, C. F. Doherty, and G. Pattenden, *J. Chem. Soc.* (*C*), 1970, 1076; (*b*) Fr. P. 1580474—6/1969; Jap. P. 75 33050.
[130] F. P. 1536458/1966.
[131] Belg. P. 746726/1969.

Dihalovinyl Acids. The (±)-*cis,trans*-dichlorovinyl analogue (1K) of chrysanthemic acid, esterified in permethrin (10K) and cypermethrin (11K) was synthesized following Farkas *et al.*[132]

The potential commercial importance of these products has stimulated the search for alternative syntheses. The dichlorodiene (17) can be made by electrolytic reduction of the acetate of (16),[133] by dehydrocoupling of isobutylene and vinylidene chloride with palladous acetate,[134] or by dehydration of hydroxy intermediates (Scheme 7).[135] The final stage can be operated continuously[136] or alternatively the 2-carbon unit is added using manganic acetate[137] and the lac-



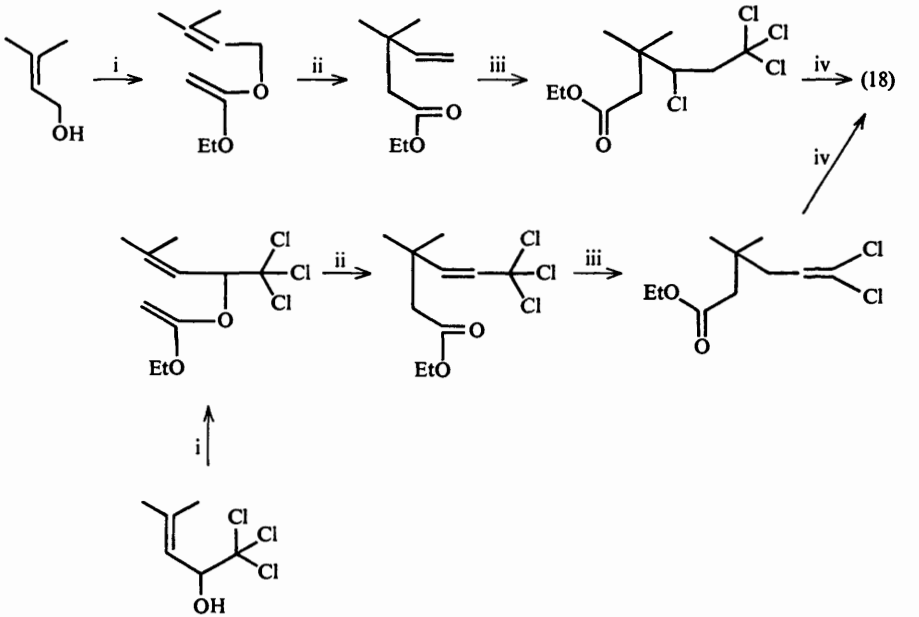
Reagents: i, $AlCl_3$; ii, Ac_2O; iii, Et_2O; iv, toluene-4-sulphonic acid; v, CHN_2CO_2Et + Cu; vi, $Mn(OAc)_3$; vii, $SOCl_2$, EtOH; viii, base

Scheme 7

[132] J. Farkas, P. Kourim, and F. Sorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 2230; J. Collonge and A. Perrot, *Bull. Soc. chim. France*, 1957, 204.
[133] M. Alvarez and M. L Fishman, in ref. 12.
[134] D. Holland, D. J. Milner, and H. W. B. Reed, *J. Organometallic Chem.*, 1977, **136**, 111.
[135] B.P. 1493228; 1494817/1977.
[136] B.P. 1459285/1976.
[137] Fr. Demande 36424—5/1976; *cf.* Ger. Offen. 2707104/1977.

tonic product (19) converted with thionyl chloride into the required acid derivative.[138]

The synthesis Kondo developed from an earlier route[139] and later modified[140] uses the simple, though not readily accessible, starting materials dimethylallyl alcohol and ethyl orthoacetate, and proceeds *via* a Claisen rearrangement, which is also an essential step in a related route[141] from the trichloroethane derived from (16) as shown in Scheme 8.



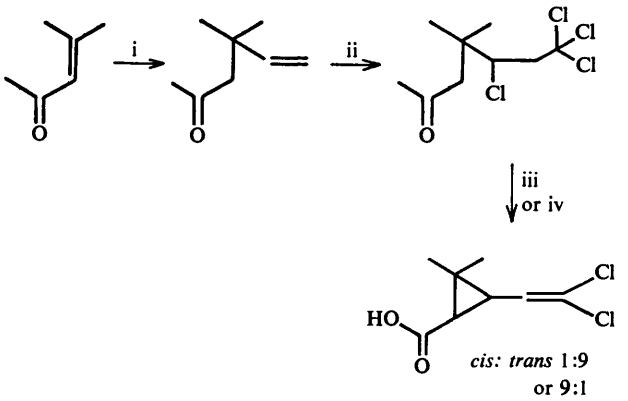
Reagents: i, $CH_3C(OEt)_3$; ii, heat; iii, CCl_4, *hν*; iv, base

Scheme 8

Another approach is based on 4,4-dimethylhex-5-en-2-one, available from a variety of reactions including catalysed addition of vinyl magnesium chloride to mesityl oxide. Thence, carbon tetrachloride addition, cyclization, and dehydrohalogenation give the required product (Scheme 9).[138] The sequence of the two last steps determines the *cis*/*trans* ratio of the product.

The *cis* and *trans* isomers of the acid (1K) give insecticidal esters of different potency, species specificity, and mammalian toxicity; controlling their ratio in

[138] N. Itaya, T. Matsuo, N. Ohno, T. Mizutani, F. Fujita, and H. Yoshoika, in ref. 12.
[139] K. Kondo, K. Matsui, and Y. Takahatake, *Tetrahedron Letters*, 1976, 4359; Belg. P. 833 278/1976.
[140] Ger. Offen. 2547510/1976.
[141] Ger. Offen. 2542377/1976.

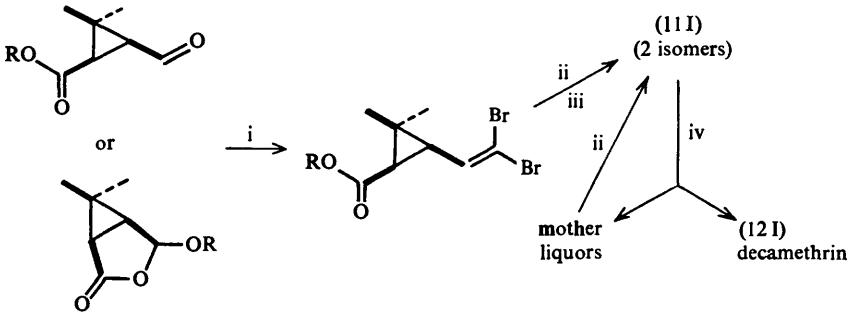


Reagents: i, CH_2=CHMgCl; ii, CCl_4, $h\nu$; iii, NaOH, then NaOCl; iv, NaOCl, then NaOH

Scheme 9

the product is therefore valuable. The *cis*-rich products from any synthesis can be equilibrated at the acid chloride stage of ester preparation to a 22:78 mixture.[142] Although under practical conditions the ethyl diazoacetate route gives a constant 45:55 *cis*:*trans* ratio, that from the Kondo[139] and Kuraray[141] routes can be adjusted within limits; the Sumitomo synthesis[138] is even more flexible. The biologically active 1*R*,*trans* esters are available by resolution of the (±)-*trans* acid.[73]

The outstanding insecticidal activity (see Table 1) of decamethrin (NRDC 161; 121) stimulated interest in commercial production of this single stereoisomer (of eight possible). This is feasible using a practical and extremely elegant route developed by Martel and shown in Scheme 10.[131] The (1*S*,*trans*) chrysanthemic



Reagents: i, PPh_3, CBr_4; ii, base; iii, acid chloride; iv, hexane

Scheme 10

acid available after resolution of the (±)-*trans* form to provide the 1*R* acidic component for bioallethrin, *S*-bioallethrin, and bioresmethrin is used as a

[143] M. Elliott. N. F. Janes. D. A. Pulman, L. C. Gaughan, T. Unai, and J. E. Casida, *J. Agric. Food Chem.*, 1976, **24**, 270. Ger. Offen. 2621830/1976. *cf.* Jap. Kokai. 75 160242.

convenient source of the required (1*R*,*cis*)-caronaldehyde as described above. This, or a bicyclic equivalent[129b] gives with carbon tetrabromide in a Wittig reaction the (1*R*,*cis*)-dibromovinyl acid (11) used as summarized above to synthesize the insecticidal ester.

2-(4-*Chlorophenyl*)-3-*methylbutyric Acid.* Isopropyl halides alkylate *p*-chlorobenzyl cyanide in dimethyl formamide or in a phase transfer system,[143] then hydrolysis provides the acidic component of fenvalerate.

6 Photochemistry

A. Introduction.—The stability of pyrethroids in the presence of air and light has profoundly influenced their development as commercially important insecticides. Rapid decomposition after application of the natural pyrethrins and all commercial synthetic analogues developed before 1973 limited them to situations where only immediate kill is necessary. The recent more stable pyrethroids represent a major advance in insect control because their favourable combination of properties renders them appropriate for a much wider range of uses, especially in agriculture. Consequently, interest in synthetic pyrethroids has greatly increased, and the photochemistry of both unstable and stable compounds has been studied intensively (for a recent detailed review see ref. 144).

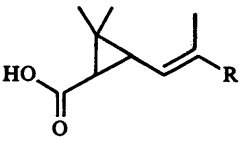
B. Unstable Compounds.—Both oxygen and light are necessary for rapid polymerization of the natural pyrethrins;[4] pyrethrins I and II (and pyrethrolone acetate) with dienic side chains polymerize more rapidly than the mono-enic constituents.[145] The intractibility of the photodecomposition products formed by attack on the alcoholic components of the natural pyrethrins has obstructed detailed study of the rapid reactions by which they are formed.[4,146]

Photo-oxidative attack on the acid (chrysanthemate) component involves stepwise oxidation at the *trans*-methyl group in the side chain [compounds (20)—(22) isolated] for pyrethrin I, allethrin, and tetramethrin, and epoxidation of the olefinic group for resmethrin.[146,147]

The products of photo-oxidative attack on the alcohol component of resmethrin[146] suggest an intermediate cyclic peroxide (23) (Scheme 11). The bicyclic products decompose further to simple benzene derivatives, including phenylacetic acid.

The above reactions are rapid, and predominate when both air and light are present, but if oxygen is excluded, as in many laboratory u.v. irradiation studies, other reactions of these unstable compounds are observed.[148]

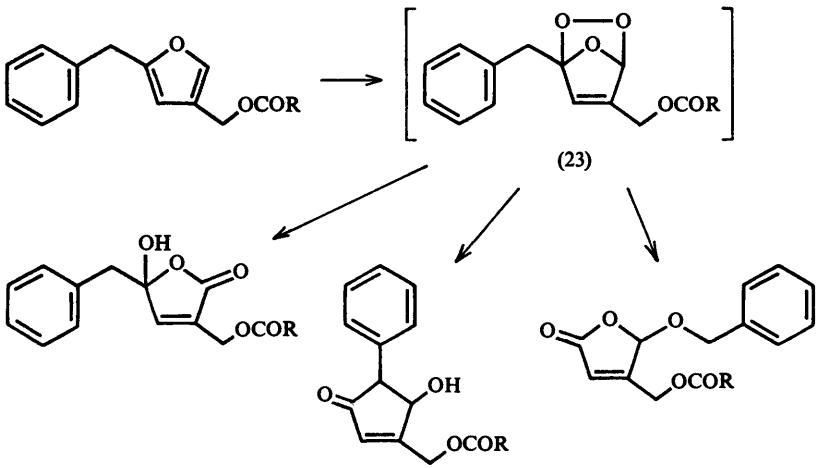
[143] Jap. Kokai 76 63 145.
[144] R. L. Holmstead, J. E. Casida, and L. O. Ruzo, in ref. 12.
[145] M. Elliott, *J. Chem. Soc.*, 1964, 5225; Y. Abe, K. Tsuda, and Y. Fujita, *Botyu-Kagaku*, 1972, **37**, 102.
[146] Y.-L. Chen and J. E. Casida, *J. Agric. Food Chem.*, 1969, **17**, 208.
[147] K. Ueda, L. C. Gaughan, and J. E. Casida, *J. Agric. Food Chem.*, 1974, **22**, 212.
[148] M. J. Bullivant and G. Pattenden, *Pesticide Sci.*, 1976, **7**, 231.



(20) R = CH_2OH

(21) R = CHO

(22) R = CO_2H



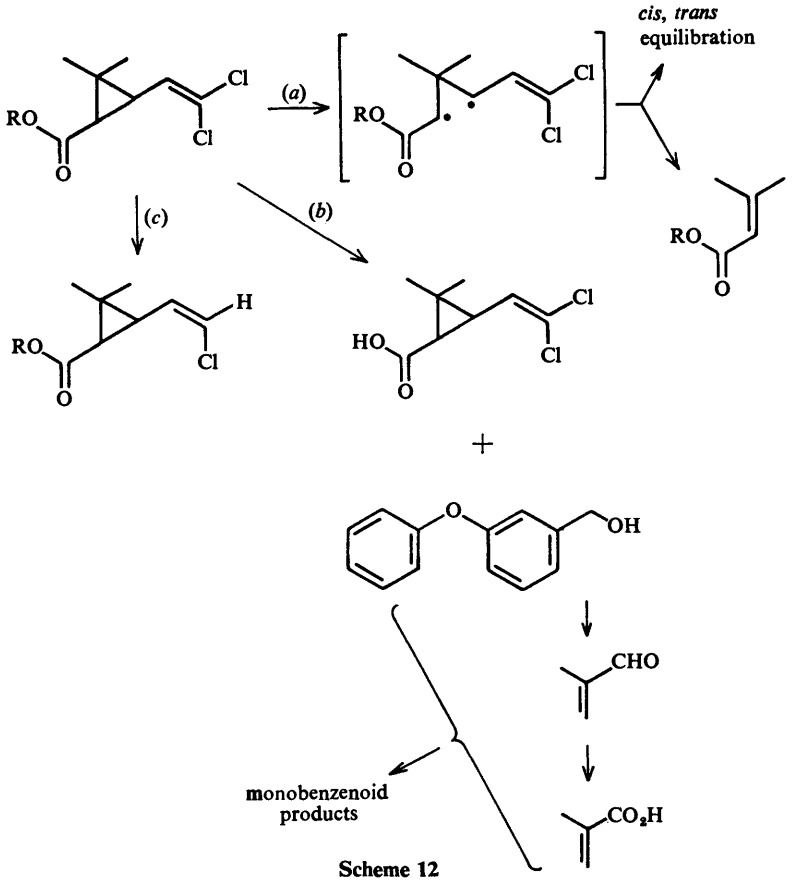
(23)

Scheme 11

C. Stable Compounds.—In the synthetic pyrethroids developed since 1973, with properties suitable for outdoor applications, the major photo-oxidative routes described above cannot occur. On the acid side, the isobutenyl side chain in chrysanthemates is replaced; similarly, no sites equivalent to those in rethrolones or furan alcohols, vulnerable to oxidative attack, are present in the benzenoid alcohols on which these important esters are based. Even one photosensitive component, in either part of the molecule, induces fast photodecomposition, but if both alcohol and acid are photostable, deposits persist substantially longer.[26b]

Consequently, the photoproducts formed from the more stable compounds are not analogous to those from photolabile esters. The pattern for permethrin in solvents (and incidentally in soil)[149] involves (see Scheme 12) (*a*) a diradical intermediate similar to that proposed for chrysanthemates,[148] leading to epimers, or by decomposition to 3-phenoxybenzyl dimethylacrylate, (*b*) loss of halogen from the dichlorovinyl side chain, and hydrogen capture to form the mono-

[149] R. L Holmstead, J. E. Casida, L. O. Ruzo, and D. G. Fullmer, *J. Agric. Food Chem.*, 1976 **26**, 590.



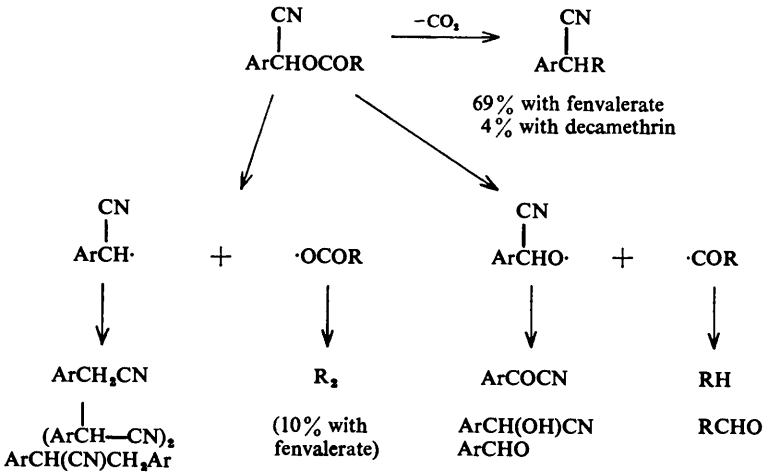
Scheme 12

chlorovinyl analogue (a minor metabolite), and (*c*) hydrolysis, followed by further oxidation or decomposition of the alcohol components.

Photolysis products[143,150] from two stable α-cyano-substituted pyrethroids, decamethrin and fenvalerate, suggest that reaction pathways for permethrin (especially monodehalogenation) apply also to decamethrin, but that the major breakdown pathways on irradiation in solution involve cleavage of bonds at the ester group (Scheme 13).

Although much work remains to be done, the important principle is already established that the photolabile pyrethroids decompose in light by pathways which involve oxygen, whereas the more stable compounds undergo alternative types of reaction.

[150] R. L. Holmstead and D. G. Fullmer, *J. Agric. Food Chem.*, 1977, **25**, 56; L. O. Ruzo, R. L. Holmstead, and J. E. Casida, *ibid.*, p. 1385: R. L. Holmstead, D. G. Fullmer, and L. O. Ruzo, *ibid.*, 1978, **26**, 954.



Scheme 13

7 Structure–Toxicity Relationships of Pyrethroids in Vertebrates

In practice, insecticides can at present be applied only relatively inefficiently;[151] much of the dose does not reach the target and is potentially available to contaminate the environment or affect unintended recipients. An important property of the new compounds is therefore their selectivity between target and non-target organisms, the distinction between insect and mammal being especially important. Averaged selectivity factors (Table 2) for four groups of insecticides indicate the relative safety of pyrethroids. Within this class, relative toxicities (see Table 3) are

Table 2 *Comparison of toxicities of classes of insecticides*[a]

	Insects/mg kg^{-1}	*Rats*/mg kg^{-1}	*Selectivity factor*
Carbamates	2.8	45	16
Organophosphates	2.0	67	33
Organochlorines	2.6	230	91
Pyrethroids	0.45	2000	4500

[a]Values given are geometric means of LD_{50}'s obtained for a series of representative members of each class, against four species of insect, and against rats.

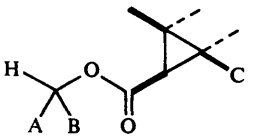
Condensed with permission from a table published in 'Synthetic Pyrethroids', see ref. 12)

related to the ease with which the compounds are metabolized in mammals. The reactions involved, classified as ester-cleavage, oxidation (mostly hydroxylation), and conjugation, are described below.[152]

[151] I. J. Graham-Bryce, *Chem. and Ind.*, 1976, 545.

[152] For more extensive information, see: J. E. Casida, K. Ueda, L. C. Gaughan, L. T. Jao, and D. M. Soderlund, *Arch. Environ. Contam. Toxicol.*, 1975/6, **3**, 491; J. Miyamoto, *Env. Health Persp.*, 1976, **14**, 15; L. O. Ruzo and J. E. Casida, *Env. Health Persp.*, 1977, **21**, 285; L. O. Ruzo, T. Unai, and J. E. Casida, *J. Agric. Food Chem.*, 1978, **26**, 918.

Microsomal esterases, predominantly in the liver, cleave a wide range of pyrethroids at rates[153] related to the degree of hindrance at the ester link. Studies with an isolated enzyme system indicate that esters of secondary alcohols (24; A, B ≠ H) (cyclopentenolones; α-cyanobenzyl alcohols) are cleaved more slowly than those of primary alcohols, and 2,2-dimethyl-cyclopropanecarboxylates with a substituent at C-3 *cis* to the ester group (24; C ≠ H) [*e.g.* cismethrin (9F); NRDC 108 (9L)] are hydrolysed less readily than *trans*-only substituted compounds. 2-Methyl-3-phenylbutyrates (M) react at rates intermediate between those of the *cis* and *trans* cyclopropane analogues.



(24)

Oxidation at the *trans* methyl group (*cf.* photochemical reaction Section 6) of the isobutenyl side chain ($CH_3 \rightarrow CH_2OH \rightarrow CHO \rightarrow CO_2H$) dominates other mechanisms in all chrysanthemates; epimerization at C-3 in some compounds during this process probably involves the aldehyde intermediate.[154] The cyclopropyl methyl groups are attacked ($CH_3 \rightarrow CH_2OH$) when pathways to alternative products are suppressed (for example in the dichlorovinyl analogues of chrysanthemates). Furylmethyl and benzyl alcohols liberated by hydrolysis are oxidized to the corresponding acids ($CH_2OH \rightarrow CO_2H$). 5-Benzoyl-3-furoic acid is formed from resmethrin ($CH_2 \rightarrow CHOH \rightarrow CO$)[155] and a secondary alcohol derivative [$CH_2{=}CHCH_2 \rightarrow CH_2{=}CHCH(OH){-}$] produced by attack on the side chain of allethrin.[156] The double bonds in the side chains of allethrin and pyrethrins I and II give diols,[156] probably *via* epoxide intermediates. Phenoxy rings are hydroxylated at the 4′, and less at the 2′, positions.

The alcohols, phenols, and carboxylic acids formed by these hydrolyses and oxidations may be conjugated with glycine, glucuronic acid, sulphate, and other groups. The water solubilities of pyrethroid metabolities are thereby increased, facilitating their excretion.

The low mammalian toxicity traditionally associated with the natural pyrethrins extends to some, but by no means to all, synthetic pyrethroids, as indicated by oral toxicities (Table 3). The ease with which pyrethrins I and II are oxidized on the diene side chain and pyrethrin II is cleaved at the methoxy-carbonyl group is associated with their low oral toxicities. *S*-Bioallethrin, with a less reactive monoene side chain, is more toxic. The central ester bond is not hydrolysed

[153] D. M. Soderlund and J. E. Casida, in ref. 12, p. 162.
[154] K. Ueda, L. C. Gaughan, and J. E. Casida, *J. Agric. Food Chem.*, 1975, **23**, 106.
[155] J. Miyamoto, T. Nishida, and K. Ueda, *Pesticide Biochem. Physiol.*, 1971, **1**, 293.
[156] M. Elliott, N. F. Janes, E. C. Kimmel, and J. E. Casida, *J. Agric. Food Chem.*, 1972, **20**, 300.

Table 3 *Mammalian toxicities of synthetic pyrethroids*[a]

Compound	*Formula*	*LD_{50} to rats*/mg kg^{-1}		*Selectivity factor*[d]
		Oral	*Intravenous*	
Pyrethrin I	See Fig. 1	900[b]	2—5	72
Pyrethrin II	See Fig. 1		0.4—1	
S-Bioallethrin	(3B)	680	4[c]	270
Bioresmethrin	(9B)	8000	340	30000
Biophenothrin	(10B)	10000	—	24000
Cismethrin	(9F)	100	6—7	170
NRDC 108	(9L)	140	4—5	410
RU 11679	(9N)	63	5—10	400
NRDC 132	(9O)	900	111—130	5400
NRDC 133	(9P)	800	90—130	5000
NRDC 140	(±)(9D)	400	26—33	1600
NRDC 141	(±)(9H)	18	1.4—2.8	68
NRDC 173	(9C)	130	2.0	2000
NRDC 174	(9G)	14	0.5	150
permethrin	(10K)	2000	450	4800
cypermethrin	(11K)	500	50	4200
decamethrin	(12I)	70—140	2—3	~6000
fenvalerate	(11Q)	450	75	900

[a]Much of this table reproduced, with permission, from the 'Annual Review of Entomology', Volume 23, © 1978 by Annual Reviews Inc. The remainder is from results (some previously unpublished) by Dr. J. M. Barnes and colleagues, Medical Research Council, Carshalton, Surrey. The data have been collected and averaged for these comparative purposes only, and should not be quoted out of context; [b]Natural pyrethrins; [c]bioallethrin; [d]calculated as LD_{50} to rats (oral)/LD_{50} to houseflies (topical), each in mg kg^{-1}

significantly in these three compounds, but bioresmethrin and phenothrin, easily cleaved primary esters of a *trans*-substituted cyclopropane acid with an isobutenyl side chain also susceptible to attack are outstanding in their low toxicity; they are among the safest known insecticides. NRDC 108 and cismethrin, esters of acids with *cis*-substituents, are more toxic. In NRDC 132 and 133, absence of the *trans*-methyl group of the chrysanthemates leads to moderate toxicity, not so great, however, as that of RU 11679, where extreme lipophilicity may be significant. Transition from isobutenyl to dihalovinyl at C-3 increases toxicity to mammals (NRDC 140 and 141 compared with bioresmethrin and cismethrin) especially with the difluoro compounds NRDC 173 and 174, but these changes are offset by replacing 5-benzyl-3-furylmethyl (9) by 3-phenoxybenzyl (10), giving esters somewhat less active as insecticides but also more susceptible to mammalian detoxification by hydroxylation. The greater insecticidal activity produced by introducing the α-cyano group (cypermethrin and decamethrin) amply compensates for the increased mammalian toxicity of the compounds associated with hindrance of esterase activity and diminished rate of oxidation.[153]

Although intravenous toxicities (Table 3) bear little relation to the practical

application of pyrethroids they provide valuable information for correlation of structure with activity especially where the toxicities *per os* found for many pyrethroids are too low to permit significant deductions. They may provide evidence of intrinsic toxicity at the site of action in mammalian nervous systems, where few comparisons are yet reported. In one study, White *et al.*[157] measured a six-fold difference in brain levels of cismethrin and bioresmethrin in rats just showing lethal symptoms.

The pyrethroids so far examined have very low toxicities to birds, but are lethal to fish at low concentrations (for a discussion and references see ref. 10).

8 Other Aspects of Biological Activity

A. The Influence of Polarity.—Correlation of biological activity with measured or estimated polarity (expressed, in the Hansch approach[158] as P, the octanol/water partition coefficient) has been attempted in many systems. With pyrethroids, only a broad generalization that potent compounds have log P values near 6 was possible; the measured activity of pyrethroids is necessarily influenced by many factors, such as rate of penetration, detoxification, and potency at the site of action, dependent upon the chemical and physical properties of the compounds. Pyrethroidal activity depends closely on the overall shape of the molecule[22] and may respond to small changes in conformational preference,[93] properties which are not easily expressed quantitatively; no useful correlations with other parameters have been reported.

Nevertheless, typical log P values of pyrethroids and of other insecticides relate well with many aspects of their behaviour.[85] Like the organochlorine compounds, *e.g.* dieldrin and DDT(log P also *ca.* 6) they partition preferentially into the lipoid rather than the aqueous tissues of complex organisms. However, unlike the organochlorine compounds, pyrethroids are readily metabolized (see above) and do not accumulate. Many organophosphate and carbamate insecticides have log P values below 4 and act systemically in plants, which implies some affinity for the moving aqueous phase. In contrast, the known pyrethroids, being extremely lipophilic, show no systemic, nor even translaminar, action.

B. Knockdown.—Some pyrethroids paralyse insects remarkably rapidly. If followed by recovery, the effect is recognized as knockdown rather than kill.[159] The two actions appear to be associated with different properties:[160] knockdown with the more polar pyrethroids, perhaps because they penetrate more rapidly (but see also ref. 21) and the more prolonged effects that eventually kill the insect[85] with greater lipophilicity. Those pyrethroids with more powerful knockdown action

[157] I. N. H. White, R. D. Verschoyle, M. H. Moradian, and J. M. Barnes, *Pesticide Biochem. Physiol.*, 1976, **6**, 491.
[158] C. Hansch, in 'Drug Design', ed. E. J. Ariens, Academic Press, New York, 1971, vol. 1, p. 271.
[159] R. M. Sawicki, *J. Sci. Food Agric.*, 1962, **13**, 283.
[160] G. G. Briggs, M. Elliott, A. W. Farnham, and N. F. Janes, *Pesticide Sci.*, 1974, **5**, 643.

(indicated by 'KD' in Table 1) are mostly less effective killing agents; of the compounds listed, only NRDC 173 (9C) combines the two actions strongly.

Knockdown agents are incorporated in many domestic aerosol insect sprays and are therefore significant commercially; they are less important for agricultural applications, where formulations for residual contact are most appropriate.

C. Synergism.—Most commercial formulations of the natural pyrethrins include a synergist (usually piperonyl butoxide in 8—10-fold excess). Potency is thereby increased up to 10-fold, despite the inactivity of the additive alone. In such preparations, the natural compounds, though expensive, compete with less well synergized synthetic alternatives.

For research, synergism is most rationally investigated by applying a constant large dose of synergist (*e.g.*, 2 μg per housefly) before the insecticide; otherwise, at fixed toxicant:synergist ratios, relatively little additive would be administered with the more potent compounds. Few formulations with synergists are therefore anticipated for the more stable, active compounds suitable for agricultural applications. The mode of action of synergists is not yet adequately understood, but may involve suppression of oxidative and esteratic detoxification[161] or other mechanisms.[162] Methylenedioxyphenyl synergists, such as piperonyl butoxide, are thought to suppress primarily oxidative detoxification within the insect; the high factor of 300 with pyrethrin I[163] is consistent with the many biologically oxidizable sites recognized in this compound.[156] However, synergists do not appreciably increase the activities of pyrethroids in all insects. Later synthetic pyrethroids, not well synergized even in the housefly,[163] may be less susceptible to detoxification by insects, especially by oxidative routes.

9 Summary and Conclusions: The Present and Future Importance of Synthetic Pyrethroids

This survey has indicated the diverse range of insecticidally active compounds related to the prototype, pyrethrin I. Pyrethroids are lipophilic compounds, very active as contact insecticides and possibly as stomach poisons against a wide range of insect species; some members of the group also have useful repellent action. The exceptional potency of some of the compounds discovered shows how well an active natural product (particularly a chiral one) can serve as the parent structure for examining the relationship between biological activity and chemical structure.

The first synthetic compounds, although very active and relatively safe, were too unstable for many applications, but development of more persistent compounds with many of the favourable characteristics of the earlier esters greatly increased the scope of the group. In addition to understanding of insecticidal

[161] J. E. Casida, *Ann. Rev. Biochemistry*, 1973, **42**, 259.
[162] A. W. Farnham and R. M. Sawicki, unpublished results.
[163] P. E. Burt, M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, and J. H. Stevenson, in 'Crop Protection Agents—Their Biological Evaluation', ed. N. R. McFarlane, Academic Press, London, 1977, p. 384.

activity, knowledge is now accumulating of the influence of structure on toxicity to mammals, birds, and fish and on stability in light and in soils. All implications of the anticipated widespread use of the more stable synthetic pyrethroids must be considered. In many respects they have more favourable properties than other groups of lipophilic insecticides such as the organochlorine compounds because, although they persist adequately on crop surfaces, their physical properties restrict migration in solution and as vapour, and they are rapidly decomposed when exposed to metabolizing systems, such as soil micro-organisms.

The potential for developing new compounds with properties especially appropriate for many different individual applications or specifically active against particular pests is great. The many types of biological activity against invertebrates (for example repellency and antifeeding action in addition to kill) latent in the structures of the natural compounds have almost certainly not yet been fully exploited. The further development of synthetic pesticides related to the natural pyrethrins is therefore a challenging area for practical application of many aspects of organic chemistry.

We acknowledge help, discussion, and disclosure of unpublished results from colleagues at Rothamsted Experimental Station, Harpenden; Medical Research Council Toxicology Unit, Carshalton; and numerous industrial organizations, and support from the National Research Development Corporation.