The Pyrethrins and Related Compounds. Part 21.[1] Carbon-13 Nuclear Magnetic Resonance Spectra of Synthetic Pyrethroids

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The ^{13}C n.m.r. spectra of a range of synthetic pyrethroids are assigned. Spectra of esters are generally similar to the combined spectra of the component acids and alcohols, and shifts show consistent trends with changes in substituent and stereochemistry, modified in some cases by small through-space effects between distant groups.

THE recent development of very active and relatively photostable synthetic pyrethroids[2-4] retaining the favourable toxicological properties of the earlier known esters[1] has greatly increased their potential for use in insect control, including many applications for which other established groups of insecticides, especially the organochlorine derivatives, are now employed. The biological activity of pyrethroids, examined by systematic modification of the structure of the natural esters,[5] is closely related to the shape of the molecule.[6,7] Therefore ^{13}C n.m.r. spectroscopy, which confirms structure and stereochemistry directly, could be especially valuable in pyrethroid studies. In addition, the assignment of individual peaks to particular carbon atoms is essential for interpreting T_1 data, which may provide information on conformations and molecular motions in solution. In the present paper, the ^{13}C spectra of a range of synthetic compounds are analysed, to complement the study[8] of the six natural esters of pyrethrum.

Like the natural constituents[9] [prototype pyrethrin 1(3C)] all the synthetic compounds are esters, and their ^{13}C spectra are essentially additive combinations of signals from the acidic and the alcoholic components, except for small shifts due to interactions across the ester bond, discussed later.

Table 1 gives values assigned to the carbon atoms in the alcoholic components of synthetic pyrethroids. Assignments for allethronyl (2—) and benzylnorthronyl (4—) esters follow directly from earlier work.[8] Those for 5-benzyl-3-furylmethanol (5A) and its esters (5—) are derived from those for furan (C_α 143.0, C_β 109.7 p.p.m.[10]) and methyl 3-furoate (9). δ Values are consistent for each signal in the spectra of these 15 esters, the variations ranging from 0.8 p.p.m. (for C-1), nearest the ester group) to 0.3 p.p.m. or less (for distant carbon atoms). Similarly, differences between the alcohol and its esters are largest for the carbon atoms near the hydroxy-group.

Assignments for esters of 3-benzylbenzyl alcohol (6A) can be deduced by comparison with diphenylmethane (10), but in these compounds the aromatic signals are closely grouped, and complete analysis is difficult. Analogous use of diphenyl ether (11) for comparisons with the 3-phenoxybenzyl group (7) leaves only one ambiguity (C-5 and -7), tentatively resolved as shown. This assignment is based on the result of esterification of the alcohol (7A), which consistently produces a *ca.* 1 p.p.m. shift difference for the signals assigned to C-3 and C-7, but only a 0.5 p.p.m. shift for that assigned to C-5. Shift differences in the alcoholic part of the molecule on esterification are then generally related to distance from the hydroxy-group (C-1 > C-2 > C-3,C-7 > remainder), as in the furan series. A cyano-group introduced at C-1 [(8A) and its esters] produces an orderly series of changes: C-1, —3 p.p.m.; C-2, +5; C-3 and C-7, —0.5; C-4 and C-6, +0.7; C-5, +2; C-9, —1.2, which are independent of the nature of the esterifying acid.

The ranges of shifts recorded (Table 1) for cyclopentenone-, furan-, and benzene-based esters are therefore all small, permitting definite recognition of alcoholic components, and, in most cases, unequivocal assignment of all their carbon atoms.

Acidic components (Table 2) considered here are analogues of *cis*- and *trans*-chrysanthemic acid, examined by Crombie *et al.*,[8,11] whose analysis leads to consistent assignments for the synthetic components. In both *cis*- and *trans*-3-(2,2-dihalogenovinyl) analogues of the chrysanthemic acids, there are regular changes along the series F, Cl, Br at C-6, -7, and -8 (large), -2 and -3 (medium), and -1, -4, and -5 (small or zero). These are related to their distance from, and the size of, the halogen. For esters of the two difluoro-acids [(—D), (—H)], couplings are seen for C-8 (290, 290 Hz) > C-7 (*ca.* 18, 27 Hz) > C-6 (6 Hz). In all the spectra examined, the only signal showing diminished nuclear Overhauser enhancement was from C-8 in esters of the dibromovinyl acids [(—F), (—J)], where the scalar mechanism of relaxation must be important solely for this centre.

Differences between the *cis*- and *trans*-series of acids are explained by the increased steric compression in the *cis*-compounds. Thus, one of the methyl groups (C-4) is now close to two substituents, and resonates well upfield, whereas the signal of the other is shifted down-

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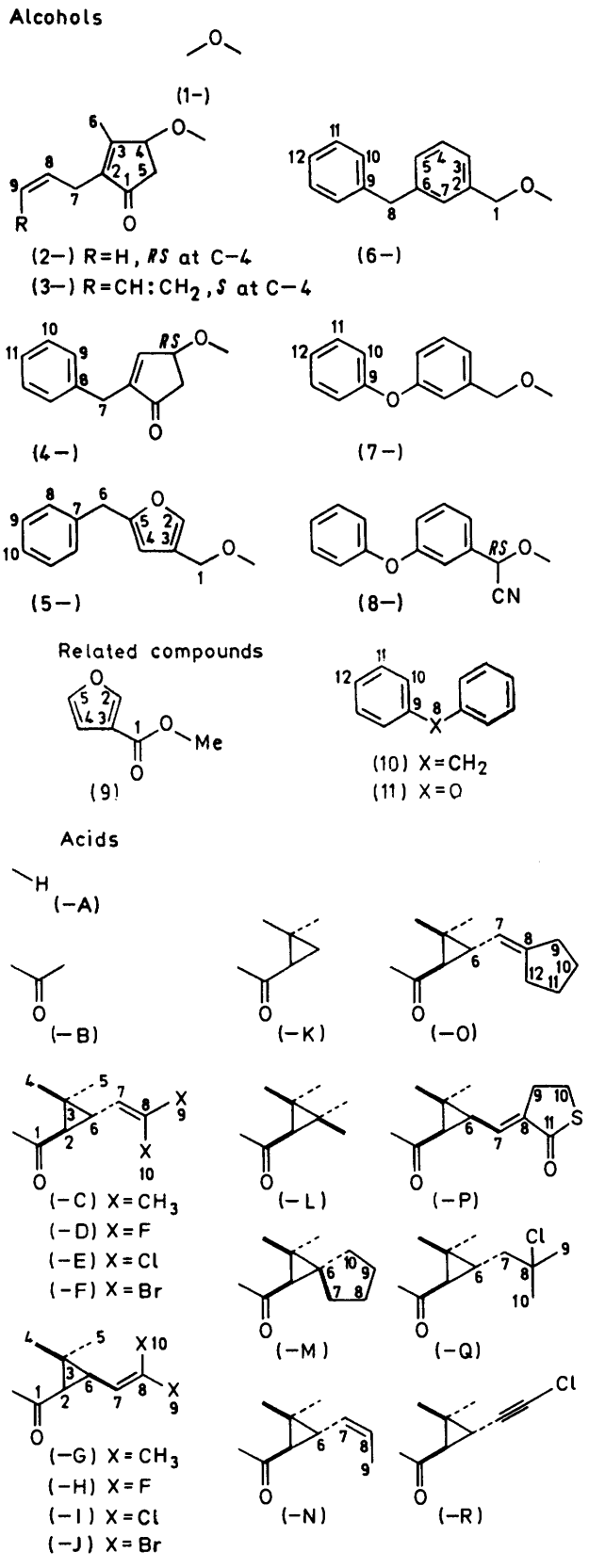


FIGURE 1 Structures and numbering schemes for esters examined; esters are referred to in the text by a number–letter combination to designate the alcoholic and acidic components, respectively

field (*cf.* ref. 11). All the other peaks (notably that of the carboxylic carbon atom) are consistently up to 4 p.p.m. further upfield in the *cis*-compounds. Such differences should facilitate structural determination and semiquantitative analysis of *cis–trans*-mixtures of pyrethroids in all but the most difficult cases.

The shifts for C-1 to C-6 in other cyclopropane acids (Table 2) of synthetic pyrethroids are similar to those in chrysanthemates, with additional contributions from relief (—K) or enhancement [(—L), (—M)] of steric compression, but with little change from cyclisation (—O), saturation (—Q) or dehydrochlorination (—R) of the side-chain. The side-chain carbon atoms in esters with cyclic C_5 substituents [(—M), (—O)] cannot yet be fully assigned.

Variations on one side of the ester bond do not substantially affect the shifts for the component on the other side, except in the case of esters of α-cyano-3-phenoxybenzyl alcohol (8—). Table 2 lists the shifts for the acid components of these esters separately, and Figure 2 summarises the differences. They are similar

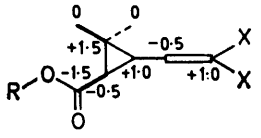
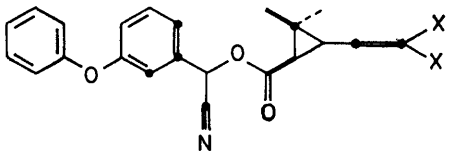


FIGURE 2 Differences (in p.p.m.) induced by changing esterifying alcohol to (8A)



	Alcohol				Acid		
	C-2	C-3	C-7	C≡N	C-3	C-7	C-8
S-Isomer of (8J) (decamethrin)	133.7	121.9	117.5	115.7	28.6	132.3	90.9
R-Isomer of (8J)	133.5	122.0	117.6	115.8	28.7	132.4	90.7

FIGURE 3 Carbon atoms showing differences when configuration at C-1 is inverted, and their assignments for one pair of isomers

for the *cis*- and *trans*-substituted acids, and for the symmetrical 2,2,3,3-tetramethylcyclopropanecarboxylic ester (—L), and indicate that the large diamagnetic anisotropy of the nitrile group exerts a strong effect through space, even to the distant atoms, C-7 and -8, with increasing magnitude through the series X = F, Cl, Br. The overall consistency of these shift differences allows a previous ambiguity concerning C-2 and C-6 in *cis*-chrysanthemic esters (—G) [11] to be resolved.*

Related differences, also due to the interaction of alcoholic and acidic components of esters, are detected in the spectra of diastereoisomeric pairs, formed by esterifying (±)-α-cyano-3-phenoxybenzyl alcohol (8A) with a single isomeric form of the acid. Differences between the two isomers for *cis*- and *trans*-acids, and for several side chains, affected signals from carbons in

* A study of the shift differences induced by ionisation of the acids leads to the same assignments (E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gasic, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and P. M. Wovkulich, *Topics* ^{13}C *N.M.R. Spectroscopy*, 1976, **2**, 81).

TABLE 1

^{13}C N.m.r. data for the alcoholic components of synthetic pyrethroids and related compounds (shifts in p.p.m. from Me_4Si)

Cyclopentenones	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	Others
(2 C, D, H, K)	72.7—73.2	41.6—41.8	203.1—203.4	141.2—141.5	165.4—165.6	13.8—14.0	27.1—27.2	133.6—133.7	115.8—115.9				
(4 C, K)	70.1	41.7—41.9	203.7—203.9	148.9—149.0	153.1—153.3		31.1	137.6	128.5—128.6 [a]	128.8—128.9 [a]	126.4—126.5		
Furans													
(9)	163.5	147.8	119.5	109.9	143.9								51.4(CH_3)
(5 A)	56.1	138.5	125.8	106.5	155.3	34.5	137.8	128.4 [a]	128.6 [a]	126.4			
(5 B, C, D, E, G, H, I, J, L, M, N, O, P, Q, R)	57.2—58.0	140.1—140.5	121.0—121.7	107.1—107.3	155.4—155.8	34.3—34.7	137.7—137.9	128.3—128.6 [a]	128.5—128.8 [a]	126.3—126.6			
Benzenes													
(10)								41.9	141.0	128.9 [a]	128.4 [a]	126.0	
(6 C, I)	66.0—66.2	136.2—136.6	125.9—126.0 [b]	128.6—128.9 [a]	127.9—128.4 [a]	140.8 [c]	128.4—128.9	41.8—41.9	141.3—141.5 [c]	128.9 [a]	128.5—128.6 [a]	126.1 [b]	
(11)									157.6	119.0	129.8	123.2	
(7 A)	64.3	142.9	121.5	129.7	117.6	157.3 [a]	117.1		157.5 [a]	118.8	129.7	123.2	
(7 D, E, F, H, I, J, Q, R)	65.5—66.0	137.8—138.4	122.5—122.7	129.6—129.8	118.1—118.4 [a]	156.8—157.1	118.1—118.3 [a]		157.4—157.6	118.9—119.1	129.6—129.8	123.3—123.4	
(8 A)	62.9	137.3	121.0	130.4	119.6	157.9 [a]	116.7		156.4 [a]	119.3	129.9	123.9	118.9(CN)
(8 C, D, E, F, G, H, I, J, K, L, R)	61.8—62.7	133.4—134.3	121.9—122.1	130.4—130.6	119.9—120.1	157.9—158.2 [a]	117.5—117.8		156.0—156.5	119.2—119.4	129.8—130.0	123.9—124.1	115.7—116.2(CN

[a,b,c] Assignments may be transposed.

TABLE 2

^{13}C N.m.r. data for the acid components of synthetic pyrethroids and related compounds (shifts in p.p.m. from Me_4Si)

trans-Di-X-vinyl		C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
X = Me	(1, 2, 4, 5, 6, 8 C)	171.8—172.1 (170.4) [c]	34.4—34.8 (34.0)	28.5—28.9 (30.3)	20.3—20.5	22.0—22.1	32.7—33.1 (34.0)	120.9—121.2 (120.3)	135.3—135.8 (136.3)	18.4—18.5	25.4—25.5	
F	(2,5,7,8 D)	171.1—171.5 (169.6)	33.5—33.7 (32.8)	27.4—28.0 (29.1)	19.8—19.9	21.9—22.1	26.2—26.5 (27.4)	76.2—76.3 (75.8)	157.4—157.7	C-6 (d, *J ca.* 6 Hz) C-7 (dd, *J ca.* 19 and 26 Hz) C-8 (t, *ca.* 290 Hz)		
Cl	(5, 7, 8 E)	170.6—170.8 (169.1)	34.5—34.8 (33.7)	28.6—28.9 (30.2)	19.9—20.1	22.3—22.5	32.6—32.8 (33.7)	126.9—127.0 (126.0)	121.9—122.0 (122.8)			
Br	(5, 7, 8, F)	170.4—170.5 (168.9)	35.8—35.9 (33.4)	28.7—28.9 (29.9)	19.8—19.9	22.3—22.5	34.3—34.4 (36.7)	135.3—135.4 (134.4)	90.6—90.8 (91.8)			
cis-Di-X-vinyl												
X = Me	(1, 5, 8 G)	170.7—171.3 (168.8)	31.1—31.2 (30.6)	26.1—26.3 (27.7)	14.7—14.9	28.6—28.8	32.3 (33.4)	118.1—118.4 (117.3)	134.5—134.6 (136.2)	18.2—18.3	25.7	
F	(2, 5, 7, 8 H)	170.3—170.5 (168.7)	29.9—30.1 (29.4)	25.9—26.4 (27.6)	14.4—14.7	28.0—28.3	26.5—26.8 (27.6)	73.3—73.9	157.1—157.3	C-6 (*J ca.* 6 Hz) C-7 (dd, *J ca.* 17 and 28 Hz) C-8 (t, *J ca.* 290 Hz)		
Cl	(5, 6, 7, 8, I)	170.0—170.2 (168.4)	31.7—31.8 (31.0)	27.4—27.5 (28.9)	14.7—14.9	28.0—28.3	32.5—32.6 (33.4)	124.7—124.8 (124.0)	120.6—120.8 (121.8)			
Br	(5, 7, 8 J)	169.4—170.1 (168.3)	31.4—31.7 (31.1)	27.4—27.8 (28.5)	14.9—15.0	28.0—28.3	35.6—35.7 (36.3)	133.1—133.4 (132.4)	89.3—89.6 (90.9)			
Other acids												
	(1, 2, 4, 8 K)	172.0—172.7 (170.7)	26.7—27.1 (26.1)	22.8—23.5	18.6—18.8	26.5—27.1	22.0—22.4 (23.2)					
	(5, 8 L)	171.6 (169.6)	35.7 (35.0)	30.0 (31.8)	16.6 (16.4)	23.5 (23.3)						
	(5 M)	171.7	36.4	28.9	16.9	24.5	42.1	33.4 [a]	26.7 [a]	26.4 [a]	26.0 [a]	
	(5 N)	171.9	34.9	28.6	20.3	22.1	31.6	127.1	127.1	13.3		
	(5 O)	172.1	34.6	28.6	20.4	22.2	33.7	116.5	140.8	34.8,[a] 34.2,[a]	26.4,[a] 29.3 [a]	
	(5 P)	169.7	34.5 [a]	29.2	15.0	28.6	33.4 [a]	130.4	137.3	34.0 [b]	27.7 [b]	197.4
	(5, 7 Q)	171.9—172.0	32.9	26.9—27.1	20.5—20.6	21.6	29.9—30.1	44.2	69.7	32.3		
	(5, 7, 8 R)	170.0—170.2 (168.6)	34.5—34.6 (33.8)	28.7 (30.3)	18.9	22.8—22.9	22.1—22.2 (23.3)	67.6 (66.7)	57.3—57.4 (58.3)			

[a,b] Assignments may be transposed. [c] The figures in parentheses refer to esters of (8A), where the values fall outside the normal range (see text).

both the alcoholic and acidic components (see Figure 3). In the special case of the ester (8J), one isomer (decamethrin, NRDC 161 [3]) has been separated and purified by crystallisation. From the absolute configuration, established by *X*-ray crystallography,[12] each peak can be assigned to either the *R*- or the *S*-isomer (Figure 3). The shift differences are very small, so to avoid ambiguity from differences between samples the assignments were based on a spectrum of a mixture richer in one component. Differences for diastereoisomers of the natural esters, and for the synthetic ester bioallethrin (1C) have been observed previously in both ^{13}C (ref. 8) and ^{1}H (ref. 13) n.m.r. spectra.

The two effects summarised above (Figures 2 and 3), one for the changes on introducing cyano at C-1 in the alcohol component, the other for inverting its configuration, both appear at C-7 and C-8, which would not be expected if the molecule remained fully extended, as in the crystal.[12] The two groups (cyano and acid sidechain) must therefore spend a significant proportion of time closer together than in the crystal; the importance of this interaction in terms of preferred conformation and its possible influence on biological activity has been discussed.[14]

The foregoing results show that the ^{13}C n.m.r. spectra of pyrethroids conform to a consistent pattern, so that ester spectra can be predicted and interpreted with confidence. Even small deviations due to interactions between alcohol and acid components are significant. ^{13}C N.m.r. spectroscopy is particularly powerful in examining those aspects of stereochemistry and conformation which have proved important in determining biological activity of pyrethroids.

EXPERIMENTAL

The esters were available from previous work at Rothamsted (see refs. 15—17 and references therein), or were gifts

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from Roussel-Uclaf [(4O) and (4P)]. The spectrum of each compound (50—300 mg) in deuteriochloroform (0.6 ml) (10 mm tube) was recorded at *ca.* 25 °C with tetramethylsilane as internal standard. The spectrometer (JEOL PFT-100) was operated at 25.15 MHz, with an 8 μs (30°) pulse every 3.0 s (100—5 000 scans) and with 10 W of wideband r.f. for ^{1}H decoupling. It was connected to an EC-100 computer using 8 191 data points for 6 250 Hz. Where appropriate, assignments were confirmed by off-resonance decoupling or selective decoupling experiments.

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