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Conformational properties of pyrethroids*

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SUMMARY

X-ray database searches and theoretical potential-energy calculations indicate that the acid moieties of pyrethroid cyclopropanecarboxylate esters adopt a well-defined, relatively inflexible conformation. In contrast, the alcohol moieties can exist in many low-energy geometries. One of the least conformationally flexible pyrethroid alcohols is 4-phenylindan-2-ol. The approximate overall conformation adopted at the biological binding site by insecticidal esters of this alcohol can be deduced with reasonable confidence by molecular modelling. Graphics superposition of a variety of pyrethroid acids suggests the existence of a large but rather narrow pocket at the binding site, in which substituents at the 3-position of the cyclopropane ring can be accommodated. This pocket is asymmetric with respect to the plane of the cyclopropane ring, extending further on the side remote from the ester group. The effects of α-substitution on the insecticidal activity of pyrethroid esters may be due to the influence of substituents on the preferred conformations of the molecules. This hypothesis rationalises the paradoxical dependence on absolute stereochemistry of the activities of various allylbenzyl and cinnamyl alcohol derivatives.

INTRODUCTION

Pyrethroids (e.g. **1**–**6**) are synthetic analogues of the naturally occurring esters of chrysanthemic acid. They are commercially important insecticides. Their mode of action is not fully understood, but they are known to be nerve poisons which affect the permeability of neuronal membranes to sodium ions. This leads to repetitive neuronal activity, at high concentrations followed by permanent membrane depolarisation. Alternatively, it can lead to a steady depolarisation of the membrane resting potential, without repetitive activity. Depending on which of these effects is produced, pyrethroids are classified as Type I or II, respectively [1].

*Supplementary material available from the authors: Five pages with Cartesian coordinates of hypothesised active conformations of compounds **1**, **4**, **7**, **22**–**27**, **34**, **42** and **45**.

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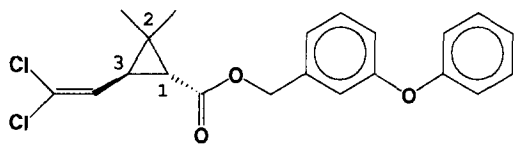
Pyrethroid insecticidal activity is highly dependent on stereochemistry. For example, only esters with the *R* configuration at C1 of the cyclopropane ring in **1–4** are insecticidal [2]. This high degree of stereoselectivity suggests that pyrethroids effect their biological activity by binding to a specific, chiral molecular-recognition site. (Presumably, there may be different sites for Type I and II pyrethroids. If so, these sites are probably closely related, since Type I and II molecules have strong structural similarities.)



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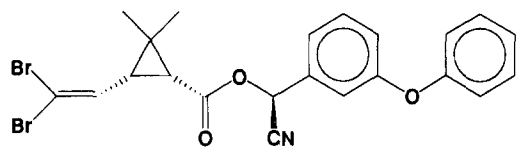

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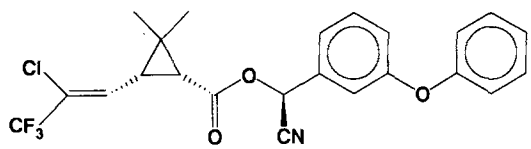

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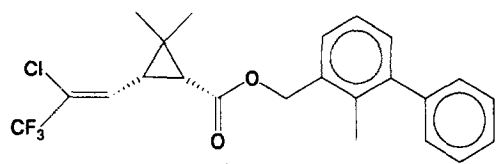

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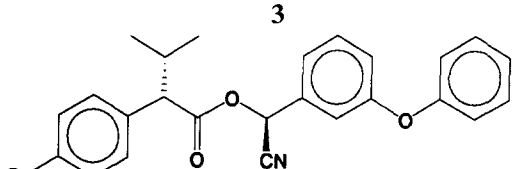

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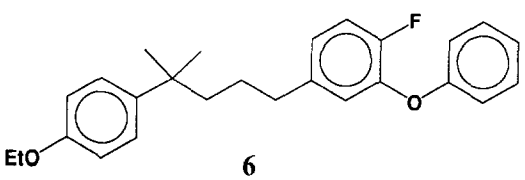

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Pyrethroid structure–activity relationships have been studied extensively [3,4]. However, the active conformation of pyrethroids (i.e., their conformation when bound to the receptor) is not known with certainty. The reason for this is that pyrethroids are very flexible molecules: excluding bonds to methyl groups, most pyrethroids have between six and eight single bonds about which torsional rotations can occur. Consequently, it is difficult to identify the active conformation amongst the many geometries that are theoretically attainable. In this study, we have investigated the conformational properties of several pyrethroids. Particular attention has been paid to molecules that show some degree of conformational restriction, or to pairs of stereoisomers, one of which is much more insecticidal than the other. The results give some insight into the steric requirements for pyrethroid activity and the probable active conformation of pyrethroids.

METHODS

Conformational preferences of pyrethroids and their component substructures were determined by the following techniques: (1) Analysis of crystallographic data taken from the Cambridge Structural Database (CSD) [5]. The database searches were first performed on the 1986–1987 versions of the CSD. However, the searches have been updated to 1992 where necessary (i.e., when the original search found few structures of relevance). (2) Ab initio molecular orbital (MO) calculations, using the RHF approximation at the STO-3G or 3-21G basis-set levels. These basis sets should give adequate equilibrium geometries for the types of molecules studied herein [6]. Calculations were performed with the GAUSSIAN82 [7] or GAMESS [8] packages. In geometry optimisations, all geometrical parameters were allowed to relax, unless otherwise stated. (3) Mol-

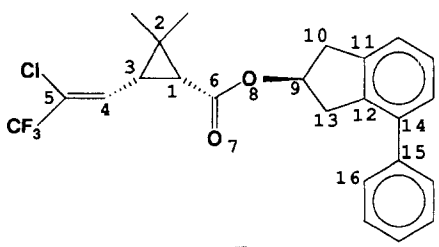
ecular mechanics calculations, using the program AESOP (Masek, B.B., unpublished results), which is an extension of BIGSTRN-3 [9], or MAXIMIN2 [10]. (4) Visual comparison of molecules on high-performance graphics devices (Evans and Sutherland MPS and PS390 terminals), using the packages VIKING (in-house molecular modelling program) and SYBYL [11]. Calculations were performed on VAX 11/750 and Silicon Graphics 4D/220 computers.

RESULTS

4-Phenylindanyl pyrethroids

Geometrical parameters

Compound **7** has insecticidal activity on Southern Armyworm, Mexican Bean Beetle, Boll Weevil and other species [12,13].



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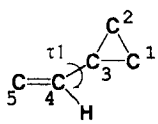

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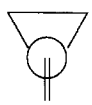

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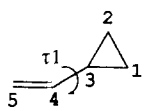

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It is particularly interesting because it has fewer degrees of conformational freedom than most other pyrethroids. We therefore chose to study this molecule in some detail. The geometry of **7** can be described by five parameters, viz. τ1, the improper torsion angle X–C3–C4–C5, where X is the midpoint of the C1-C2 bond; τ2, the improper torsion angle Y–C1–C6–O7, where Y is the midpoint of the C2-C3 bond; and τ3, τ4 and τ5, the torsion angles C1–C6–O8–C9, C6–O8–C9–C10 and C12–C14–C15–C16, respectively. The partially flexible five-membered indan ring represents a sixth degree of conformational freedom. Each of these parameters was considered in turn.

Torsion angle τ1 This parameter describes the orientation of the olefinic group relative to the cyclopropane ring. The CSD (1992 version) was searched for crystal structures containing substructure **8**, where the exocyclic C-C single bond is acyclic. Some 26 crystallographically independent observations of this fragment were found. The observed distribution of τ1 is summarised in Table 1. Apart from one outlier, all of the observations are within 20° of the

TABLE 1
CRYSTAL STRUCTURE GEOMETRIES OF VINYL-SUBSTITUTED CYCLOPROPANE

Range of |τ1| (degrees)	Number of observations
170–180	17
160–170	8
<160	1

τ1 = torsion angle X–C3–C4–C5, where X is the midpoint of the C1-C2 bond (see **8**). The sample comprised structures with CSD reference codes ALCHRB10, BIVZOV, BPVBCP, BRVCPC, BUWXIA, CEXVCP, CIXPAA, CLVCPCO1, CNPOVN, FAKCAV, FUWNOA, GEKVOH, GIDVEU, GIDVIY, GOJRAY, PXBVCP10, SEKNUR, SEKPAZ, SISYUO, TAGWED, TAGWIH, TCHRBA, VETLUB and VETMAI.

TABLE 2
AB INITIO MO CALCULATIONS ON CYCLOPROPYLETHENE

Calculation	τ1 (degrees)	Absolute energy (au)	Relative energy (kcal/mol)
1	0	−192.85177	2.6
2	−49	−192.85304	1.8
3	−90	−192.85189	2.5
4	−136	−192.85208	2.4
5	180	−192.85588	0.0

τ1 = torsion angle X–C3–C4–C5, where X is the midpoint of the C1-C2 bond (see **10**). Calculations were performed with GAMESS (3-21G basis set) with all geometrical parameters allowed to relax, except for τ1.

trans-bisecting conformation (τ1 = 180°), in which the olefinic group points away from the cyclopropane ring (Newman projection **9**, view down the C4-C3 bond). Over half of the crystal structures in this data set are pyrethroids or pyrethroid acids.

MO theory indicates that both the trans- and cis-bisecting (τ1 = 0°) conformations are stabilized by conjugation between the quasi π-orbitals located in the plane of the cyclopropane ring and the olefinic π-system [14]. The crystallographic data suggest that, of these two geometries, trans is preferred. We performed ab initio MO calculations (GAMESS, 3-21G basis set) on model compound **10** to confirm this. The results are summarised in Table 2, which gives the calculated energy of **10** as a function of τ1. As expected, τ1 = 180° is more stable than τ1 = 0°. If this is for steric reasons, as seems likely, the trans geometry should be even more favourable in molecules such as **7**, where the cyclopropane ring is substituted at C1 and C2.

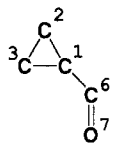
Torsion angle τ2 This parameter describes the orientation of the carbonyl group relative to the cyclopropane ring. As with τ1, MO theory indicates that the cis- and trans-bisecting geometries are stabilised by conjugation [14].

A preliminary search of the CSD (1986 version) found 47 crystallographically independent observations of substructure **11** with R-factors below 0.10. The observed values of τ2 indicated a marked preference for the cis-bisecting conformation (τ2 = 0°), in which the carbonyl group lies over the three-membered ring (Newman projection **12**, view down the C6-C1 bond). After detailed inspection of the crystal structures, 27 observations were eliminated because the compounds were judged to be poor models for **7** (e.g., they were sterically congested). The distribution of the remaining 20 observations is given in Table 3. It suggests an overwhelming preference for the cis-bisecting geometry.

TABLE 3
CRYSTAL STRUCTURE GEOMETRIES OF CARBONYL-SUBSTITUTED CYCLOPROPANES

Range of |τ2| (degrees)	Number of observations
0–10	12
10–20	5
20–30	2
150	1

τ2 = torsion angle Y–C1–C6–O7, where Y is the midpoint of the C2-C3 bond (see **11**). The sample comprised structures with CSD reference codes ALCHRB10, BAXTID, BEJVUH, BEKDAW, BEPTIZ, BRVCPC, BUBNER, BUWXIA, CEFWAL, CEGJIH, CLVCPC, CNPOVN, COMKIY, DMCPRC, MBCPCX, NPCPMK, PMCPRC10, PXBVCP10 and SDPPCX.



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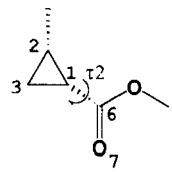

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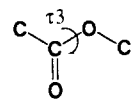

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This conclusion was supported by ab initio MO calculations (GAMESS, 3-21G basis set) on model compound **13**. Results are summarised in Table 4, which gives the energy of **13** as a function of $\tau 2$. The cis-bisecting arrangement is calculated to be the most favourable. The preference for cis rather than trans is perhaps a consequence of the C=O double bond being shorter than the C-O single bond, thus reducing steric interactions when the former rather than the latter lies over the three-membered ring.

Torsion angle $\tau 3$ This parameter describes the conformation of the ester linkage. The CSD (1986 version) was searched for crystal structures containing acyclic ester groups, substructure **14**. Some 2470 crystallographically independent observations were found with R-factors below 0.10. Of these, the vast majority (2361) has $|\tau 3| < 10°$, and only 13 structures were found with $|\tau 3| > 20°$. The crystallographic data therefore show an overwhelming preference for the coplanar arrangement with $\tau 3 \approx 0°$, i.e., with the carbonyl oxygen syn to the α-carbon of the alcohol [15].

Conformation of the five-membered ring The five-membered ring of the indanyl moiety is held in an envelope conformation by fusion to the aromatic ring, since the torsion angle C10–C11–C12–C13 is constrained to be close to zero. Two such envelope conformations exist, with the exocyclic oxygen atom either axial or equatorial (Fig. 1). The degree of nonplanarity of the ring can be measured by the two largest intra-annular torsion angles (C11–C10–C9–C13 and C10–C9–C13–C12), which, by symmetry, must be approximately equal in magnitude and opposite in sign. A search of the CSD (1992 version) found nine crystallographically independent observations of the indan ring system (CSD reference codes CPPHEN, CYPPCB, DEPDUX, DIWFAQ, FAMXUM, IPMIAC (two observations), JAZJUP and TAFZOP). With one exception (CYPPCB), the five-membered ring was invariably nonplanar, with the largest ring torsion angle falling in the range 10–30°; the average value was 20°.

TABLE 4
AB INITIO MO CALCULATIONS ON **13**

Calculation	$\tau 2$ (degrees)	Absolute energy (au)	Relative energy (kcal/mol)
1	−9	−380.60710	0.0
2	1	−380.60721	0.2
3	89	−380.59458	7.9
4	168	−380.60424	1.8
5	−179	−380.60378	2.1
6	−91	−380.59485	7.7

$\tau 2$ = torsion angle Y–C1–C6–O7, where Y is the midpoint of the C2-C3 bond (see **13**). Calculations were performed with GAMESS (3-21G basis set) with all geometrical parameters allowed to relax in calculations 1 and 4 and all geometrical parameters, except $\tau 2$, allowed to relax in the remaining calculations.

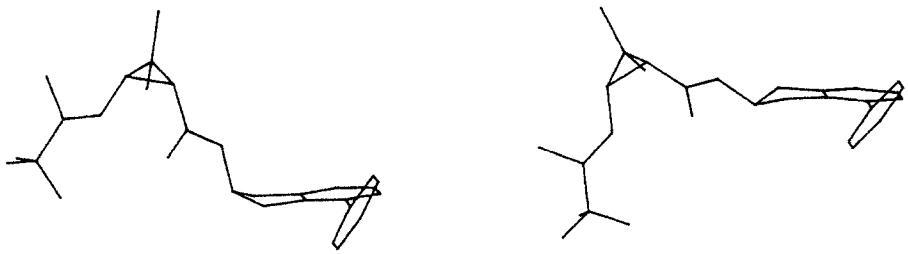
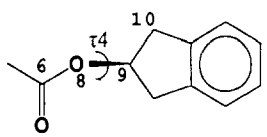


Fig. 1. Two possible envelope conformations of the five-membered ring in 7: oxygen axial (left) and equatorial (right).

It is difficult to say which of the two envelope conformations is favoured. Molecular mechanics calculations on model compound **15** indicated that the conformation with oxygen equatorial is favoured, but by only 0.7 kcal/mol; the corresponding value from ab initio MO calculations (GAMESS, STO-3G basis set) was 0.3 kcal/mol (Tables 5 and 6). Of the indan crystal structures retrieved from the CSD, only one (DIWFAQ [16], **16**) has an oxygen-linked substituent in the relevant position: the substituent is axial.



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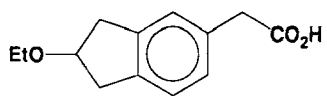

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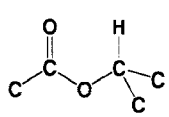
Torsion angle τ4 This parameter effectively describes the orientation of the 'acid end' of the molecule relative to the 'alcohol end'. A search of the CSD (1986 version) for substructure **17** (C-O single bonds acyclic) found 136 examples (R-factors below 0.10) and showed that the carbon atom of the carbonyl group is invariably within 60° of the position in which it eclipses the α-hydrogen atom. This corresponds to a preferred range of approximately 60 to 180° for τ4 in **7** (i.e., between Newman projections **18a** and **18b**, view down the O8-C9 bond).



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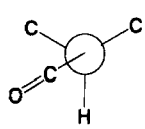

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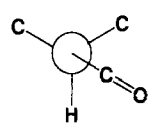


18b

The energy of model compound **15** was calculated as a function of τ4 by molecular mechanics. Results are given separately in Table 5 for the two different envelope conformations (oxygen axial or equatorial). They show that two isoenergetic potential-energy minima exist, at values consistent with the crystal structure data (τ4 ≈ 75 or 170°). Ab initio MO results (Table 6) are in good agreement with the molecular mechanics data.

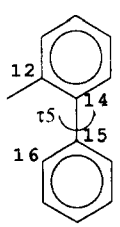
Torsion angle τ5 This parameter is the dihedral angle between the two aromatic rings. Ab initio MO calculations (GAMESS, STO-3G basis set) were used to predict the energy of model compound **19** as a function of τ5 (C12–C14–C15–C16). Two optimisations, starting from τ5 = 30 and 90°, both converged to the same minimum, with τ5 = 58° (absolute energy = −493.2288 au).

TABLE 5
MOLECULAR MECHANICS CALCULATIONS ON 2-INDANYL ACETATE[a]

Equatorial oxygen			Axial oxygen		
Calculation	τ4 (degrees)	Relative energy (kcal/mol)	Calculation	τ4 (degrees)	Relative energy (kcal/mol)
1	0	7.2	13	0	9.4
2	30	3.4	14	30	7.3
3	60	0.2	15	60	1.5
4	68	0.0	16	74	0.7
5	90	1.1	17	90	1.5
6	120	2.9	18	120	3.4
7	150	1.2	19	150	1.8
8	173	0.0	20	170	0.7
9	180	0.1	21	180	1.1
10	−150	3.5	22	−150	6.4
11	−120	7.4	23	−120	9.4
12	60	2.6			

[a] τ4 = torsion angle C6–O8–C9–C10 (see **15**). Program AESOP, all geometrical parameters were allowed to relax in calculations 4, 8, 16 and 20; all geometrical parameters, except τ4, were allowed to relax in the remaining calculations. Energies of axial conformations are given relative to those of the lowest energy equatorial conformers (calculations 4 and 8). Conformations with the ester group 'over' the indanyl ring system (i.e., τ4 between about −30 and −90°) and in the axial position flipped to the equatorial geometry on energy minimisation.

A search of the CSD (1992 version) for biphenyl derivatives with one ortho-substituent (**20**, R ≠ H) found 160 crystallographically independent observations. The observed distribution of τ5 (Table 7) is reasonably consistent with the MO calculations, the average value being 53°.



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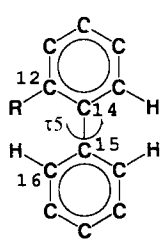

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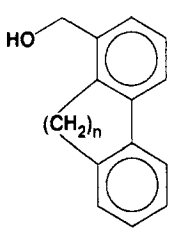

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This conclusion is supported by the observation that bridged biphenyl alcohols **21** give active pyrethroid esters when n = 3, but not when n = 2 or n = 4 [17]. A search of the CSD (1986 version) for relevant substructures showed that the dihedral angle between the rings falls in the range

TABLE 6
AB INITIO MO CALCULATIONS ON 2-INDANYL ACETATE[a]

	τ4 (degrees)	Absolute energy (au)	Relative energy (kcal/mol)
Equatorial oxygen	77	−566.16292	0.0
Axial oxygen	80	−566.16240	0.3

[a] Calculations were performed with GAMESS (STO-3G basis set), all geometrical parameters were allowed to relax. Starting geometries were taken from AESOP optimisations 4 and 16 above.

TABLE 7
CRYSTAL STRUCTURE GEOMETRIES OF ORTHO-SUBSTITUTED BIPHENYLS

Range of $\|\tau 5\|$ (degrees)	Number of observations	Range of $\|\tau 5\|$ (degrees)	Number of observations
<30	0	60–70	20
30–40	9	70–80	5
40–50	55	80–90	4
50–60	67		

$\tau 5$ = torsion angle C12–C14–C15–C16 (see **20**).

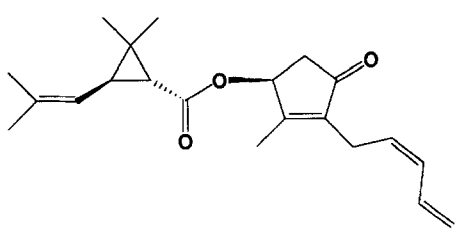
40–57° when n=3 (CSD reference codes BEWSOL, CAJCOF, CEYXAF, CUNSUZ, DMITCL10, HCMCHP, ISCHOL, MELOCH and NACCOL). Corresponding ranges for n=2 and n=4 are 13–20° (BOPHPH, DHBACN, HBZANT, HXNOPR and MBOPHP) and 70–71° (BHMNDC, BUBXUR and CETZUW), respectively.

Conformation of 7 at the pyrethroid binding site

Some conclusions may now be drawn about the conformation adopted by **7** at the pyrethroid binding site. The geometry of the acid moiety is relatively well defined. In particular, the preferences for $\tau 2$ and $\tau 3$ to be close to zero are so pronounced that these parameters are unlikely to be far from this value in the active conformation. $\tau 1$ is slightly more variable, but is likely to be within about 20° of 180°. Some additional evidence for this assumption is presented in the next section.

The alcohol moiety is more flexible. The five-membered ring must be in an envelope conformation, but can adopt either of the two alternatives (oxygen axial or equatorial) with almost equal facility. Molecular mechanics energy calculations (Table 5) indicate that the most likely values for $\tau 4$ are approximately 75° or 170°, but these two geometries are almost isoenergetic. The magnitude of $|\tau 5|$ should be about 50°, but the sign of the torsion angle is uncertain.

We were unable to resolve these ambiguities, but some speculative conclusions could be drawn by superimposing **7** on other insecticidally active pyrethroids on a graphics terminal. Firstly, this showed that **7** can best be superimposed on **4** [18] if the oxygen atom in **7** is axial (Fig. 2, top). Secondly, the overlay between **7** and the naturally occurring ester **22** [19] was judged visually to be marginally better with $\tau 5 = +50°$, rather than −50° (Fig. 2, bottom left). For this reason, $\tau 5 = +50°$ has been assumed in the remainder of this work, although we recognise that the evidence is flimsy and the opposite twist is almost equally likely. Finally, **7** was overlaid on the moderately active pyrethroid **23** [20]. In performing this overlay, it was assumed that: (a) the plane of the ethoxyphenyl substituent of **23** should be close to that of the olefinic group of **7**; (b) the trifluoromethyl group of **23** should be close to one or both of the methyl groups of **7**; (c) the



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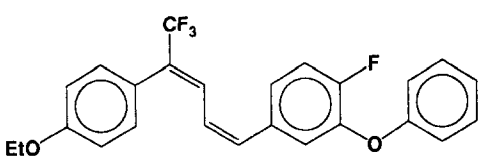

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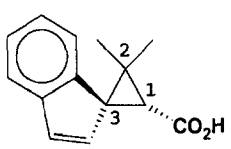
fluorophenyl group of **23** should be approximately coplanar with the indan system of **7**; (d) the terminal phenyl rings of **7** and **23** should be in close proximity. Given these constraints, a good overlay could be obtained if τ4 of **7** was set to approximately 75° (Fig. 2, bottom right), but not if τ4 ≈ 170°. Thus, with τ4 at 75°, the goodness of fit of the overlaid molecules was: (a) angle between planes = 9°; (b) distances between trifluoromethyl and methyl carbons = 0.8, 2.0 Å; (c) angle between planes = 10°; (d) rms distance between terminal phenyl rings = 1.0 Å. Corresponding figures for the overlay with τ4 at 170° were (a) 57°; (b) 2.1, 2.2 Å; (c) 11°; (d) 2.9 Å.

Steric properties of pyrethroid acids

The objective of the work described in this section was to determine the steric constraints on substitution at the acid end of pyrethroids.

Spiro-fused cyclopropane carboxylic acids

Pyrethroid acids **24**–**26** give insecticidal esters [21,22]. Crystallographic data from the CSD (reference codes CEMIND, COMZAF, COMZEJ, COVWOZ, MBINDL, MPINCX, MXMPIN and SINZIN) show that the indene ring system is approximately planar, though intra-annular torsion angles of up to about 10° are possible. Because of the spiro fusion, the indene system in **24** and **25** is forced to lie approximately in the plane bisecting the C1-C2 bond of the cyclopropane ring, i.e., the plane containing the olefinic group of **7** when τ1 = 180°. As we have seen, the indan ring system is nonplanar, because the five-membered ring adopts an envelope conformation. Consequently, the plane of the indan aromatic ring in **26** is inclined at an angle of about 20° to that of the indene ring system in **24** and **25**. Assuming that esters of **24**–**26** bind to the pyrethroid receptor in the same way as **7**, the activity of these esters therefore affords further evidence that τ1 = 180° ± 20° in the active conformation of **7**.



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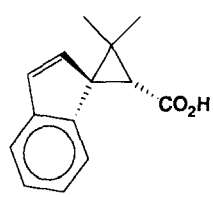

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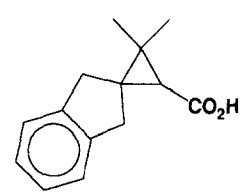

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Chlorostyryl-substituted cyclopropane carboxylic acids

The insecticidal activity of isomers **27** decreases in the order Z-trans > E-cis ≫ Z-cis ≈ E-trans [23]. The conformation of the 3-substituent on the cyclopropane ring can be described by two torsion angles, τa and τb (**27**). τa is identical to τ1 in **7**, which has already been shown to have an optimum value of 180°. τb is the torsion angle C4–C5–C6–C7, which describes the orientation of the aromatic ring plane relative to that of the olefinic group. Its optimum value depends on the stereochemistry of the double bond. We searched the CSD (1986 version) separately for the trans-substructure **28** and the cis-substructure **29**, finding 111 and 40 crystallographically independent observations, respectively. The observed distributions of τb are given in Table 8. About 80 percent of the τb values in **28** are smaller than 15°. In contrast, the majority of crystal structures containing **29** have τb > 45°, and those molecules with τb < 15° generally have small substituents

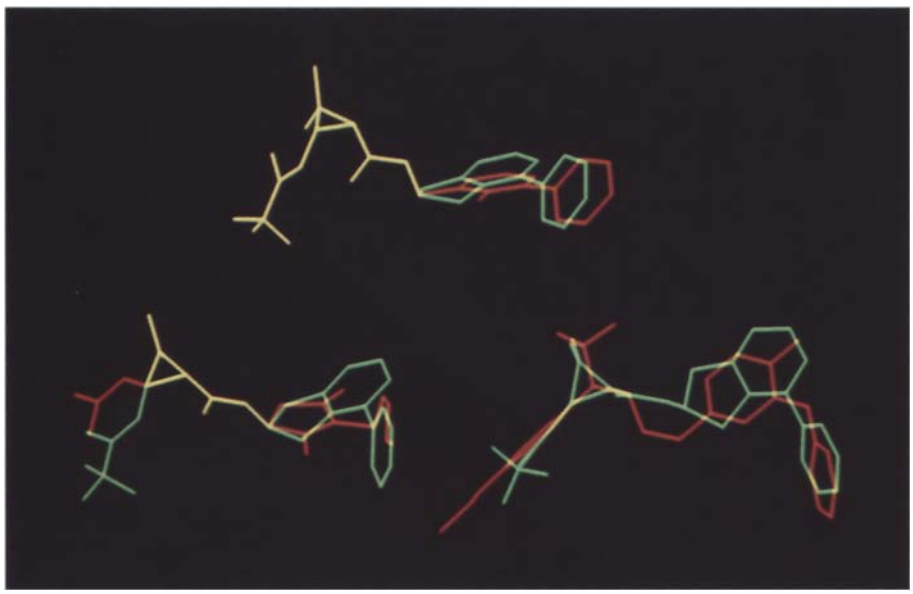
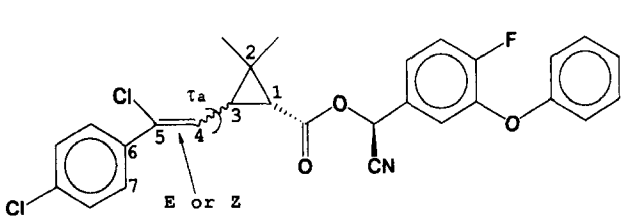


Fig. 2. Superposition of hypothesised active conformation of **7**, in green, on ester **4** (top), natural pyrethrin **22** (bottom left), and pyrethroid **23** (bottom right).

(e.g. Me, CN) cis to the aromatic ring. The τb values in the crystal structures of **30** and **31** – the closest analogues in the CSD of the acid component of **27** – are −12° and −63°, respectively (CSD reference codes CLTCIN and CLCCIN). Ab initio MO calculations (GAMESS, STO-3G basis set) on model compound **32** suggested that the optimum value of τb is 35° (absolute energy = −796.4238 au), but that τb = 0° is attainable, being less than 1 kcal/mol higher in energy. Molecular mechanics (AESOP) predicted an optimum τb value of 47°, with the τb = 0° geometry being some 2 kcal/mol higher in energy. Ab initio calculations on **33** indicated that the optimum value of τb is about 55° (absolute energy = −796.4215 au), the molecular mechanics prediction being 61°. We conclude that τa ≈ 180° in all isomers of **27**, τb ≈ 0–45° in the Z isomers, and τb ≈ 60°in the E isomers.



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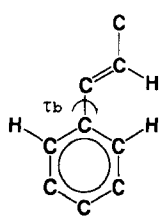

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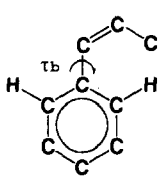

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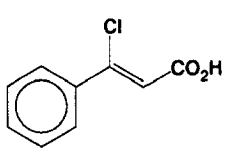

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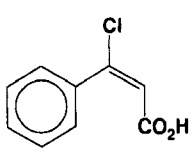

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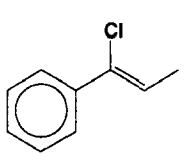

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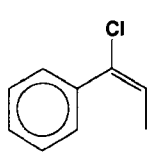

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TABLE 8
CRYSTAL STRUCTURE GEOMETRIES OF PHENYL-SUBSTITUTED OLEFINS

Trans-substructure **28**		Cis-substructure **29**	
Range of |τb| (degrees)	Number of observations	Range of |τb| (degrees)	Number of observations
0–15	89	0–15	7
15–30	15	15–30	3
30–45	5	30–45	3
45–60	1	45–60	13
> 60	1	60–75	10
		75–90	4

Oxime-substituted cyclopropane carboxylic acids

The insecticidal activity of the isomers of **34** decreases in the order Z-cis > E-trans ≫ Z-trans ≈ E-cis [23]. A search of the CSD (1992 version) found no examples of oxime-substituted cyclopropanes. Ab initio MO calculations on model compound **35** (GAMESS, 3-21G basis set) were therefore used to predict the optimum conformation around the C3-C4 bond (Table 9). As for **10**, the trans-bisecting arrangement appears to be preferred. A search of the CSD (1986 version) for the acyclic oxime substructure **36** found 31 crystallographically independent observations (R-factor below 0.10), inspection of which revealed a strong preference for the trans-coplanar arrangement (all observed values of the C–O–N=C torsion angle within 20° of 180°).

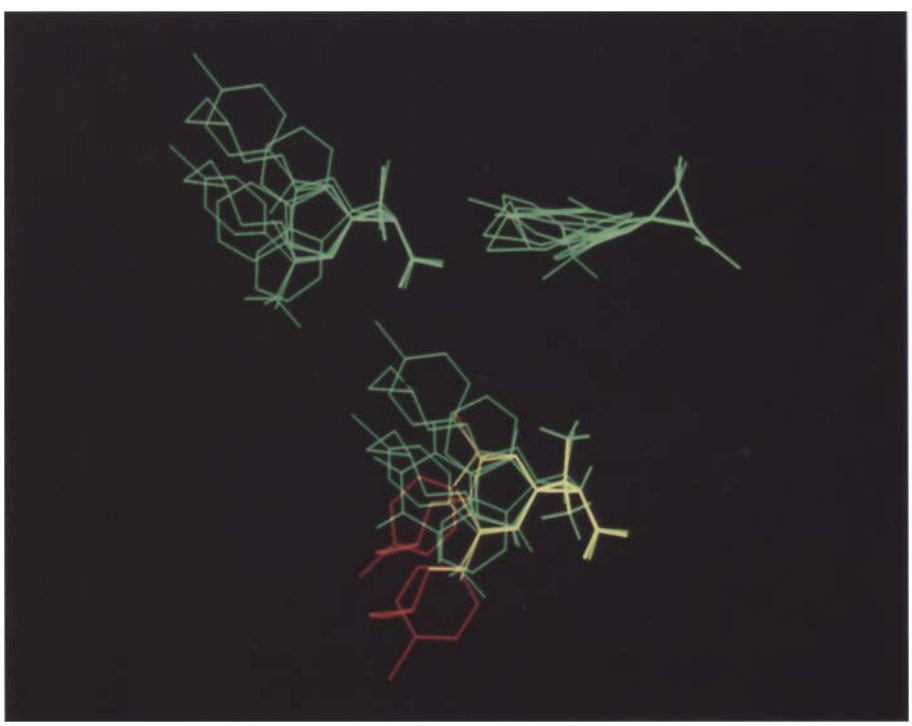
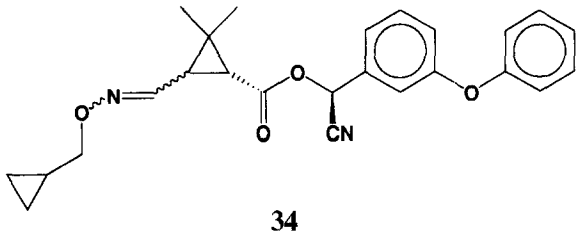


Fig. 3. Top: two views of a superposition of several pyrethroid acids. Bottom: active pyrethroid acids (green) superimposed on inactive acids (red). Yellow lines indicate where the active and inactive molecules are coincident.



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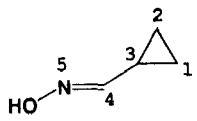

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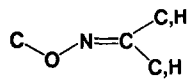

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Comparison of pyrethroid acids

Figure 3 (top) shows two views of a superposition of the acid moieties of the active esters **7**, **24**–**26**, Z-trans-**27**, E-cis-**27**, Z-cis-**34** and E-trans-**34**. The molecules are in the conformations suggested by the results presented above. Figure 3 (bottom) shows the same molecules, together with the acids of the inactive isomers of **27** and **34**. The superposition implies that the pyrethroid binding site has a large but rather narrow pocket which can accommodate substituents at the 3-position of the cyclopropane ring. This pocket extends further on one side of the ring (the side opposite the ester group) than on the other. The inactive isomers clearly extend beyond the accessible region defined by the active molecules.

Steric properties of pyrethroid alcohols

In this section, we describe the conformational preferences of some common pyrethroid alcohols. It is shown that these alcohols are sterically similar to the alcohol moiety of **7**.

3-Phenoxybenzyl alcohol

Several of the best known pyrethroids are esters of 3-phenoxybenzyl alcohol, e.g. permethrin, **1** [24]. A search of the CSD (1992 version) found 42 crystallographically independent observations of substructure **37**, including the crystal structures of several pyrethroids. Referring to **37**, the conformation about the C1-O bond can be defined by either of the torsion angles C2–C1–O–C4 or C3–C1–O–C4. One of these angles must be in the range −90 to +90° and the other in the range −180 to −90° or +90 to +180°. We chose to use the former of these angles (denoted τa). Similarly, the conformation about the C4-O bond can be defined by either of the torsion angles C5–C4–O–C1 or C6–C4–O–C1, and we chose whichever was in the range −90 to +90° (τb). This classification scheme is similar to that described by Van der Heijden et al. [25]. Defining $|\tau a| \leq |\tau b|$, examination of the crystallographic data (Fig. 4) showed that τa is typically in the range +10 to

TABLE 9
AB INITIO MO CALCULATIONS ON **35**

Calculation	τa (degrees)	Absolute energy (au)	Relative energy (kcal/mol)
1	0	−283.15671	0.1
2	−46	−283.15589	0.6
3	−89	−283.15162	3.3
4	−136	−283.15249	2.7
5	−180	−283.15681	0.0

τa = torsion angle X–C3–C4–N5, where X is the midpoint of the C1-C2 bond (see **35**). Calculations were performed with GAMESS (3-21G basis set) with all geometrical parameters, except τa, allowed to relax.

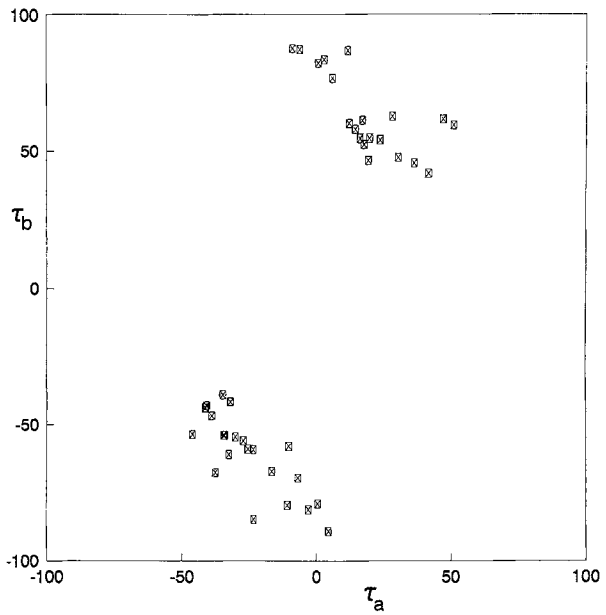
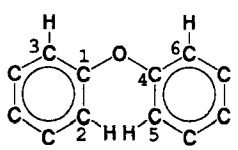


Fig. 4. Scatterplot of observed τa, τb values in crystallographic observations of substructure **37**.

+40° or −10 to −40°; τb is typically between +45 to +90° or −45 to −90°. Average values of |τa| and |τb| are 23° and 62°, respectively. In a given molecule, τa and τb invariably have the same sign, unless one is close to zero, as indicated by previous work [25]. The two torsion angles are negatively correlated.



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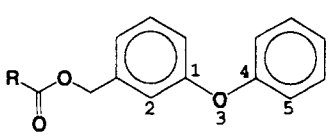

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These data suggest that the alcohol moiety of a pyrethroid such as **38** may be regarded, to a good degree of approximation, as having eight shallow and roughly isoenergetic potential-energy minima, centred at approximately the following values of torsion angles C2–C1–O3–C4 and C1–O3–C4–C5: +20,+60; −20,−60; +60,+20; −60,−20; +160,+120; −160,−120; +120,+160; −120,−160°.

Several insecticidally active derivatives of 4-fluoro-3-phenoxybenzyl alcohol are known, e.g.

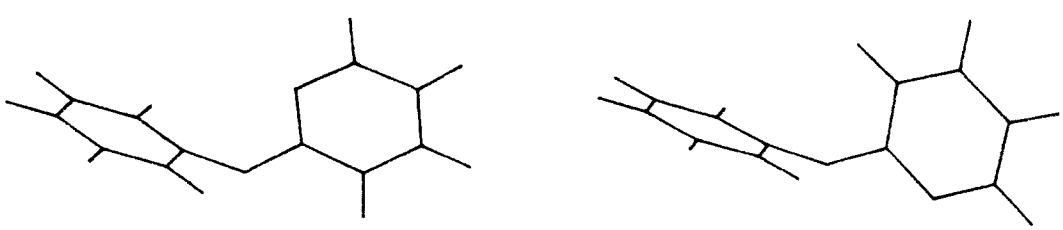


Fig. 5. Two alternative conformations of **41**.

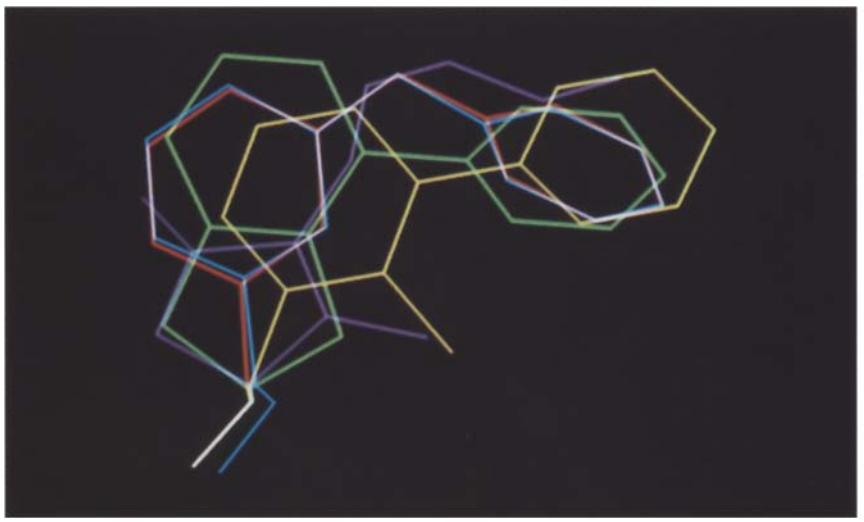
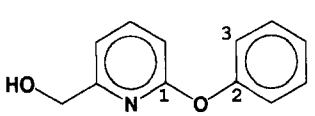


Fig. 6. Superposition of several pyrethroid alcohols in low-energy conformations.

27. There are no crystal structures in the CSD containing the relevant fluoro-substituted phenoxyphenyl substructure. However, ab initio MO calculations (GAUSSIAN82, STO-3G basis set) show that the fluoro-substituent has relatively little effect on the conformational preferences around the C-O bonds. The eight conformations listed in the preceding paragraph are no longer isoenergetic, but differences between them do not exceed about 1.0–1.5 kcal/mol.

Pyridyl alcohols

Insecticidal pyrethroid derivatives of **39** are known [26]. Only one relevant crystal structure was found in the CSD (DADFAP, **40**) [27]. The two halves of **40** are equivalent by crystallographic symmetry. The observed torsion angles around the C-O bonds are τ(N–C1–O–C2) = 1°, τ(C1–O–C2–C3) = 61°. Thus, the O-C2 bond lies approximately in the plane of the pyridine ring, with the nitrogen atom syn with respect to C2. This conformation is presumably stabilized both by conjugation and by an attractive dipolar interaction between the N-C1 and O-C2 bonds. Also, coplanarity can be achieved more easily than in **38**, because the absence of an ortho hydrogen on the pyridine nitrogen reduces steric repulsion between the two rings at small values of τ(N–C1–O–C2).



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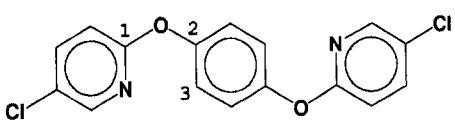

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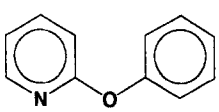

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Ab initio MO calculations on model compound **41** (GAMESS, STO-3G basis set) showed that the conformation in which the phenyl ring lies 'over' the pyridine nitrogen (Fig. 5, left) is lower in energy ($\Delta E \approx 3$ kcal/mol) than conformations in which the phenyl ring points in the other direction (Fig. 5, right; optimised energies of the two conformers were −544.2441 and −544.2381 au, respectively). We conclude that the optimum geometry of **39** has τ(N–C1–O–C2) close to 0° and τ(C1–O–C2–C3) $\approx \pm 60°$.

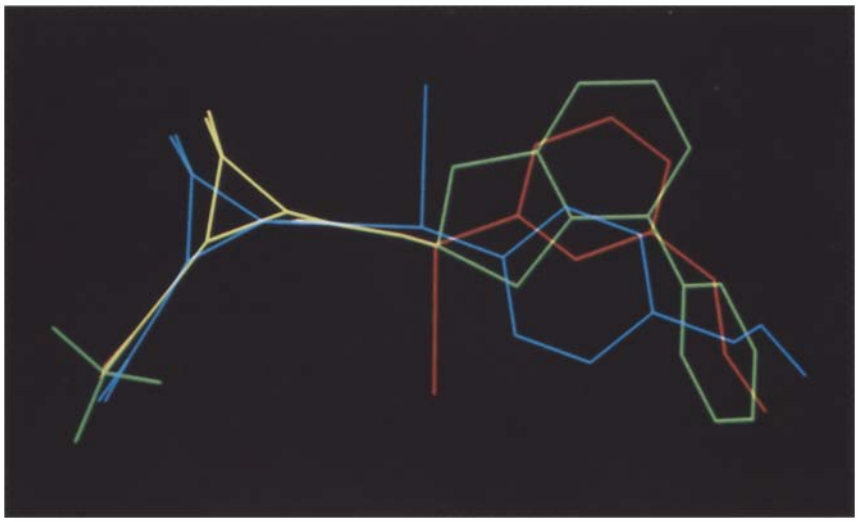


Fig. 7. Superposition of **42** (red) and **45** (blue) on the hypothesised active conformation of **7**.

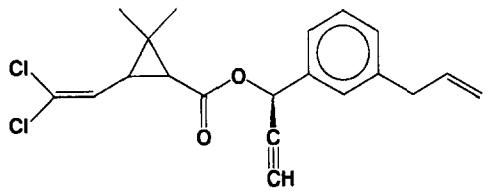
Graphics comparison of pyrethroid alcohols

Figure 6 shows the alcohol moiety of **7**, in its hypothesised active conformation, superimposed on 3-phenoxybenzyl alcohol and its pyridyl analogue **39**. The latter alcohols are both in conformations established above to be low in energy. Also included in the overlay are the alcohol moieties of **4** and **22**. The dihedral angle between the aromatic rings of the biphenyl alcohol is set to about 50°. Molecular mechanics calculations (program AESOP) indicate that the alcohol moiety of **22** is also in an energetically favourable geometry. The overlay shows that all five alcohols can adopt a similar shape.

α-Substituted alcohols

The insecticidal activity of many pyrethroid esters is increased by cyano substitution at the α-carbon atom of the alcohol; for example, **2** and **3** are potent insecticides. Importantly, the chirality at the α-carbon in these compounds must be *S*, the *R* isomers being much less active [28]. The reason for the efficacy of *S*-α-cyano substitution is unknown. Possibly, the cyano group forms a hydrogen bond with the receptor. However, this explanation is rendered less likely by the observation that α-ethynyl substitution can also lead to good insecticidal activity [29], since this group is not capable of strong hydrogen bonding. Alternatively, the α-substituent may fill an otherwise unoccupied pocket at the receptor, thus improving steric complementarity.

A further possibility is suggested by the intriguing structure–activity relationships of α-ethynyl-substituted allylbenzyl esters [29]. Compound **42** is more active than **43**, as expected by analogy with e.g. **2**. However, **44** is less active than **45**. We were only able to overlay **42** and **45** on the hypothesised active conformation of **7** by allowing the ethynyl groups to point in opposite directions (Fig. 7). This suggests that there is room for the ethynyl group on both sides of the receptor pocket, which appears to be incompatible with the observed dependence of activity on the stereochemistry at the α-carbon.



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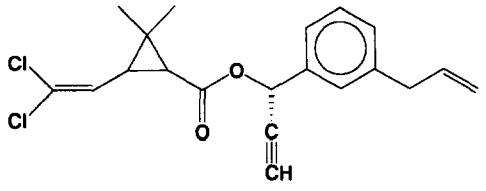

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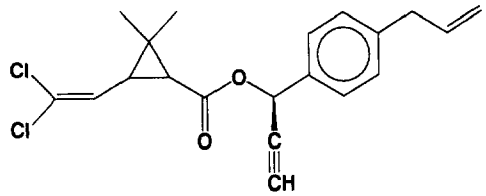

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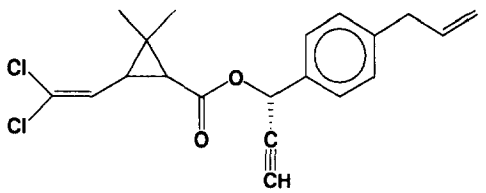
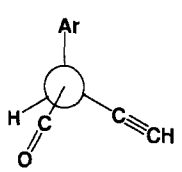


45

A possible explanation is that there is room at the binding site for α-substituents in either the *R* or *S* configuration, but that α-substitution affects activity by altering the preferred conformations of pyrethroids. In the overlay of Fig. 7, the conformations around the O-C bonds of **42** and **45** are as shown in Newman projections **46** and **47**, respectively. In each case, the carbonyl carbon is nearer to eclipsing the α-hydrogen atom than the ethynyl substituent. The orientation of the allylbenzyl groups relative to the acid moiety needs to be different in **42** and **45** in order to overlay the allyl chains on the terminal phenyl group of **7**.

Similarly, when **2** or **3** is overlaid on **7**, a good steric match requires the carbonyl carbon to eclipse, or nearly eclipse, the α-hydrogen (Newman projection **48**, view down the O-Cα bond).



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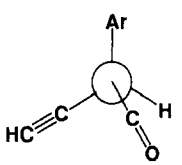

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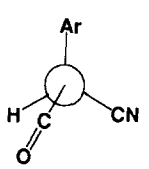

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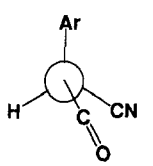

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TABLE 10
CRYSTAL STRUCTURE GEOMETRIES OF α-SUBSTITUTED BENZYL ESTERS

	Torsion angles (degrees)			Torsion angles (degrees)	
CSD reference code	C–O–Cα–H	C–O–Cα–X	CSD reference code	C–O–Cα–H	C–O–Cα–X
CNPOVN	44	74	PXBVCP10	11	134
FABHOF	27	91	SISYOU	33	81
FADGOG	21	97	TAGWED	35	71
FADGUM	18	100	TAGWIH	38	80
FADHAT	34	83	VAFDAH	36	83
PPANTR	46	162			

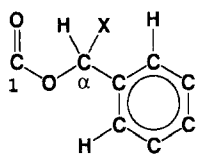
The torsion angles refer to compound **50**.

TABLE 11
AB INITIO MO CALCULATIONS ON α-CYANOBENZYL FORMATE

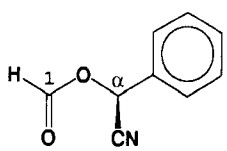
Calculation	τa (degrees)	Absolute energy (au)	Relative energy (kcal/mol)
1	−120	−542.08459	0.9
2	0	−542.07907	4.4
3	−73	−542.08605	0.0

τa = torsion angle C1–O–Cα–CN (see **51**). Calculations were performed with GAMESS (STO-3G basis set). All geometrical parameters, except τa, were allowed to relax in calculations 1 and 2. All geometrical parameters were allowed to relax in calculation 3 (the starting value of τa was −60°).

It seems likely that the conformations illustrated in **46**–**48** are more stable than the alternatives in which the cyano or ethynyl substituent is eclipsed, or nearly eclipsed, by the carbonyl carbon, e.g. **49**. In order to confirm this, we searched the CSD (1992 version) for substructure **50** (X = CN, Me or Et). Eleven relevant crystal structures were found; absolute values of the torsion angles C1–O–Cα–H and C1–O–Cα–X are tabulated in Table 10. In all 11 structures, the carbonyl carbon is nearer to eclipsing the α-hydrogen than the substituent X. Ab initio MO calculations (GAMESS, STO-3G basis set) on model compound **51** (Table 11) produced results consistent with the crystallographic data. Thus, the energy difference between the conformation with (C1–O–Cα–H) = 0° and that with (C1–O–Cα–CN) = 0° was predicted to be about 3.5 kcal/mol, and the optimum value of (C1–O–Cα–CN) was −73°.



50



51

We conclude that α-substitution favours the conformation in which the carbonyl carbon eclipses, or nearly eclipses, the α-hydrogen atom. In each of the compounds **2**, **3**, **42** and **45**, this conformation overlays particularly well with the hypothesised active conformation of **7**. This may be the reason for the stereospecific effect of α-substitution on insecticidal activity. A similar argument may be used to rationalise the absolute structure–activity relationships of various cinnamyl alcohol derivatives [29].

CONCLUSIONS

The work described in this paper shows that the conformation of the acid moiety of pyrethroids such as **1** and **7** is relatively well defined. This is mainly because of conjugation effects, which impose constraints on the geometry of the ester group and, to a lesser extent, on the cyclopropane-ester and cyclopropane-vinyl linkages. Because the acid geometry can be predicted with some certainty, it is possible to overlay confidently a variety of acids and thereby determine that a large, but rather narrow receptor pocket exists, in which substituents at the cyclopropane 3-position can be accommodated. In contrast, the alcohol moiety is very flexible. Analysis of the geometrical preferences of the alcohol group of **7**, together with molecular graphics work, enables

us to hypothesise what its conformation might be when **7** is bound to the receptor. Several other pyrethroid alcohols can adopt geometries that are sterically similar to this putative active conformation. Nevertheless, the hypothesis must be regarded as speculative. The effects of α-substitution on the insecticidal activity of pyrethroids may be due to the influence that the substituent has on the preferred conformation around the Cα-O bond.

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