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Towards an identification of the pyrethroid pharmacophore. A molecular modelling study of some pyrethroid esters

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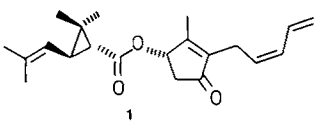
SUMMARY

A molecular modelling and computer graphics study of a series of pyrethroid insecticides has been carried out. The three-dimensional arrangement of the groups essential for the biological activity (pharmacophore) has been identified for the acid and the alcohol moieties, respectively. These pharmacophores are based on the relationship between molecular structure and biological activity for a number of pyrethroid esters. The pharmacophores, which describe the relative location in space of the unsaturated systems, the dimethyl groups and the ester moiety, may be useful in the design of novel compounds with pyrethroid activity.

INTRODUCTION

Pyrethroids are important insecticides. Originally they were derived from the naturally occurring esters of chrysanthemic acid, e.g. Pyrethrin I (**1**) [1,2], but during the last two decades extensive structure-activity studies have led to compounds with increased potency and with sufficient photostability for practical use. During these studies the original molecular framework present in Pyrethrin I has been heavily modified [1,2] and some of the compounds developed recently are even devoid of the ester group, e.g. MTI-500 (Ethofenprox, **2a**) [3], MTI-800 (**2b**) [4], and the ketone **2c** [5].



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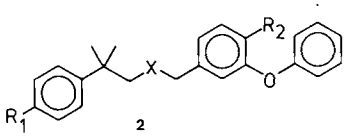
Pyrethrin I



2

a : X= O; R_1= OEt; R_2= H (MTI-500, Ethofenprox)
b : X= CH_2; R_1= OEt; R_2= F (MTI-800)
c : X= C=O; R_1= OEt; R_2= H or F

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The insect nervous system is the most important target site for the pyrethroids [6,7]. The biochemical mode of action of the pyrethroids involves interactions with a sodium channel in the nerve membrane in a highly stereospecific manner [8] indicating a receptor-mediated mechanism to be responsible for their biological activity. Detailed electrophysiological studies have revealed two fundamentally different types of effects leading to a classification of the pyrethroids into two groups: Type I and Type II pyrethroids. The characteristics of Type I effects are repetitive activity following a single stimulus and, for high doses, a permanent depolarisation of the membrane. Type II effects are characterized by a steady depolarisation of the membrane resting potential without repetitive activity [9–11].

The pyrethroids are very flexible molecules capable of adopting several conformations. A detailed conformational analysis of several representative pyrethroids has never been reported, although some conformationally restricted pyrethroids have been prepared [12–18] and a few pyrethroids have been studied by X-ray crystallographic [19–22] and/or computational methods [23–26]. However a considerable amount of information is available about the effects of substituents on the pyrethroid-framework from several quantitative structure-activity relationships (QSAR) studies [27–29].

In the present work, we describe a molecular modelling and computer graphics analysis of a series of Type I pyrethroids (**1** and **3–10**) containing structurally different, but representative pyrethroid frameworks. Based on these pyrethroids, three-dimensional models of the active conformations (pharmacophores) for the acid and the alcohol moieties, respectively, are established. From these pharmacophores, it is possible to derive the structural requirements necessary for biological activity of the pyrethroids.

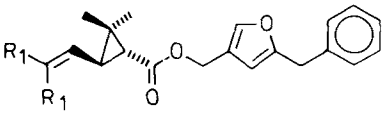
MATERIALS AND METHODS

Compounds

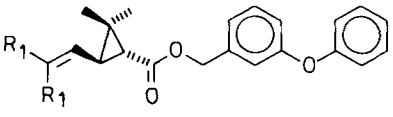
The pyrethroids included in this study (cf. Fig. 1) were selected in order to reflect the great diversity in the pyrethroid framework. Pyrethroids derived from both the *cis*-chrysanthemic acid (**5, 6** and **9**) and the *trans*-chrysanthemic acid (**1, 3** and **4**) as well as non-cyclopropane pyrethroids derived from phenyl-acetic acid (especially 2-phenyl-3-methyl-butanoic acid) (**7** and **8**) were included. Similarly, pyrethroids with different alcohol parts derived from substituted benzyl alcohols (**4, 6, 8** and **10**) and 3-furylmethyl alcohols (**3, 5** and **7**) were chosen to yield maximum information about the two π-systems and their relative location.

Toxicity data

All the pyrethroids depicted in Fig. 1 are potent insecticides against a broad range of insect species. Unfortunately, all the compounds have not been tested against the same insect, and/or the experimental conditions for the tests are not identical. Therefore a direct comparison of the toxicity data is difficult. In Table 1, we have collected some representative toxicities, preferably for house flies (*Musca domestica*) for the pyrethroids considered in this work [1,12,26,30–35]. Furthermore, the table illustrates the relative potency of the pyrethroids by successive filled boxes as originally described by Elliott [2]. The relative potencies have been estimated from the LD_{50}-values, although these have been determined by different test procedures for some of the compounds.



3 a : R_1= Me (Bioresmethrin)
b : R_1= Cl



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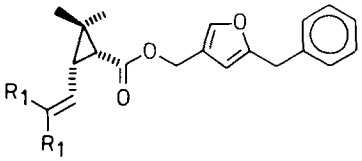
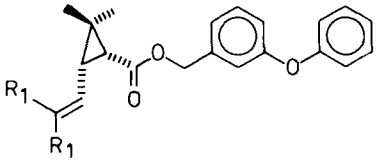
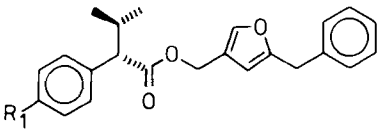
b : R_1= Cl (Biopermethrin)



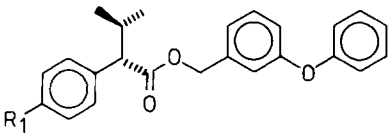
5 a : R_1= Me (Cismethrin)



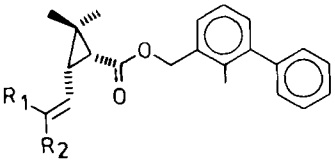
6 a : R_1= Me
b : R_1= Cl (Cispermethrin)



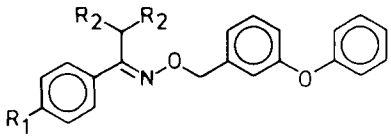
7 a : R_1= H
b : R_1= Cl



8 a : R_1= H
b : R_1= Cl



9 a : R_1= R_2= Me
b : R_1= CF_3; R_2= Cl (FMC-54800)
c : R_1= R_2= Cl



10 a : R_1= H; R_2= Cl
b : R_1= OEt; R_2= Cl
c : R_1= Cl; R_2= Me

Fig. 1. Pyrethroids considered in this work.

TABLE I

TOXICITY DATA FOR THE PYRETHROIDS SHOWN IN FIGURE 1. HF = HOUSEFLY (*MUSCA DOMESTICA*), SAW = SOUTHERN ARMY WORM (*SPODOPTERA ERIDANIA*), BF = AUSTRALIAN SHEEP BLOWFLY (*LUCILIA CUPRINA*), (±) CORRESPONDS TO THE LD_{50}-VALUE DETERMINED FOR THE RACEMIC MIXTURE OF **8b**. THE RELATIVE POTENCIES OF THE PYRETHROIDS ARE ILLUSTRATED BY SUCCESSIVE FILLED BOXES REPRESENTING TEN-FOLD CHANGES IN TOXICITY (SEE TEXT)

	Compound	LD_{50}	Relative Potency
1	(*S*)-(*Z*)-3-(Penta-2,4-dienyl)-2-methyl-4-oxo-cyclopent-2-enyl (1*R*, 3*R*)-chrysanthemate	0.33 μg/fly HF [31] 30 mg/kg HF [1]	
3a	5-benzyl-3-furylmethyl (1*R*,3*R*)-chrysanthemate	0.005 μg/fly HF [32] 0.25 mg/kg HF [32]	
3b	5-benzyl-3-furylmethyl (1*R*,3*R*)-2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarboxylate	0.003 μg/fly HF [33] 0.14 mg/kg HF [33]	
4a	3-phenoxy-benzyl (1*R*,3*R*)-chrysanthemate	0.022 μg/fly HF [32]	
4b	3-phenoxy-benzyl (1*R*,3*R*)-2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarboxylate	0.020 μg/fly HF [34]	
5a	5-benzyl-3-furylmethyl (1*R*,3*S*)-chrysanthemate	0.027 μg/fly HF [32] 0.7 mg/fly HF [32]	
6a	3-phenoxy-benzyl (1*R*,3*S*)-chrysanthemate	a	
6b	3-phenoxy-benzyl (1*R*,3*S*)-2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarboxylate	1.0 ppm SAW [12] 0.011 μg/fly HF [34]	
7b	5-benzyl-3-furylmethyl (*S*)-2-(4-chlor-phenyl)-3-methyl-butanoate	b	
8b	3-phenoxy-benzyl (*S*)-2-(4-chlor-phenyl)-3-methyl-butanoate	(±)0.09 μg/fly HF [35]	
9b	2-methyl-3-phenyl-benzyl (1*R*,3*S*)-2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropane-carboxylate	1.1 ppm SAW [12]	
9c	2-methyl-3-phenyl-benzyl (1*R*,3*S*)-2,2-dimethyl-3-(*Z*)-(2-chloro-3,3, 3-trifluoropropenyl)cyclopropanecarboxylate	2.9 ppm SAW [12]	
10b	(*Z*)-4-ethoxyphenyl-dichlormethyl-ketone-oxime *O*-(3-phenoxy-benzyl)-ether	0.4 mg/kg BF [26]	
10c	(*E*)-4-chlorophenyl-isopropyl-ketone-oxime *O*-(3-phenoxy-benzyl)-ether	0.20 μg/fly HF [35]	

[a] The toxicity against Mustard Beetle (*Phaedon Cochleariae*) of **6a** is approximately 2/9 of the toxicity measured for **3a** [1].
[b] The toxicity against HF of the racemic mixture of **7b** is approximately 1/10 of the toxicity measured for **3a** [1].

Computational details

All calculations were performed with the SYBYL molecular modelling system [36] using the standard SYBYL force field. Minimizations were carried out with the MAXIMIN program [37], which uses a simplex based minimization procedure. Charges were ignored during the minimization.

All molecules were constructed from standard molecular fragments and minimized with the MAXIMIN program. The conformational freedom of the acid and alcohol moieties, respectively,

TABLE 2
ACID MOIETIES **I–IV**. ENERGIES ASSOCIATED WITH ADOPTING THE PHARMACOPHORE CONFORMATIONS AND RMS VALUES FOR THE SUPERPOSITIONS

Acid moieties	ΔE^a	RMS[b]	ΔE^c
I	1.3	0.11	0.6
II	1.8	0.14	1.4
III	1.9	0.13	0.6
IV	5.0	0.13	2.5

[a] Energy difference (kcal/mol) between the pharmacophore conformation and the global minimum conformation.
[b] Root-mean-square values (Å).
[c] Energy difference (kcal/mol) between the relaxed pharmacophore conformations (cf. Fig. 3) and the global minimum energy conformations.

were carefully explored in order to determine the global minimum energy conformation (cf. Tables 2 and 3).

The flexible fits were performed with the MAXIMIN program, which allows parts of a molecule to be handled as a fixed fragment (e.g. the aromatic rings) or as a flexible/rotable bond (simultaneously variation of the torsional angles and minimization of bond lengths and bond angles). The flexible fit option in SYBYL minimizes the sum of the square deviations (root-mean-square, RMS) between selected points (atoms or eventually dummy atoms) in each of the molecules and the corresponding average points common for all the molecules in the flexible fit. The actual intermolecular spring constants may be chosen individually, and in this way different parts of the molecules can be differently weighted.

The different superpositions were evaluated by considering: (1) the root-mean-square (RMS) values; (2) the energy difference (ΔE) between the global minimum and the pharmacophore conformation of the molecules, i.e. the energy associated with adopting the biologically active conformation; and (3) a visual inspection of the superpositions since a priori no limits can be set up for the RMS- and ΔE-values.

TABLE 3
ALCOHOL MOIETIES **A-D**. ENERGIES ASSOCIATED WITH ADOPTING THE PHARMACOPHORE CONFORMATIONS AND RMS VALUES FOR THE SUPERPOSITIONS

Alcohol moieties	ΔE^a	RMS[b]	ΔE^c
A	2.7	0.22	1.0
B	3.9	0.36	1.8
C	3.4	0.19	1.9
D	14.7	0.25	4.1

[a] Energy difference (kcal/mol) between the pharmacophore conformation and the global minimum conformation.
[b] Root-mean-square values (Å).
[c] Energy difference (kcal/mol) between the relaxed pharmacophore conformations (cf. Fig. 7) and the global minimum energy conformations.

The calculations were performed on a VAX 11/750 minicomputer and structures were displayed and manipulated on an Evans & Sutherland PS330 system.

RESULTS

Pharmacophore mapping

For receptor-mediated reactions, it is generally well accepted that the activity of a drug, insecticide, etc. is caused by the presence of certain functional groups or key atoms. Originally, Ehrlich [38] named such essential groups a 'pharmacophore', and later a pharmacophore has been defined as the three-dimensional arrangement of the groups essential for recognition and activation [39,40]. The concept of pharmacophore mapping has been applied to a variety of problems in medicinal chemistry and has proven very useful in the determination of the 'active conformation' of a given molecule or a series of molecules [39,40].

Different approaches exist for mapping of the pharmacophore. If some conformationally restricted and potent compounds are known one may use these as templates for superposition of the more flexible compounds. For systems with considerable conformational flexibility, it has proven useful to explore the conformational space by rigid rotation about the flexible bonds and subsequent analysis of the obtained conformations based on energy and/or distance criteria [41]. The pyrethroids shown in Fig. 1 contain 6–8 flexible bonds and a systematic generation of all possible conformations around each of the flexible bonds in steps as big as 30° leads to a very large number of conformations, which are difficult to analyze with the methods available to us.

In this work, we decided to consider the pyrethroids as composed of two separate parts, an acid and an alcohol part, with independent conformational characteristics. The validity of this approach is based on the strong tendency of non-cyclic aliphatic esters to adopt an antiperiplanar (*ap*) conformation in crystal structures [42]. Not only do the esters prefer an *ap* arrangement of the alkyl groups, but deviations from planarity are very small, i.e. normally less than 10° [42].

In the following, we will discuss the acid and alcohol parts of the pyrethroids separately. The combination of the acid and alcohol pharmacophores, the determination of their relative orientations, and an evaluation of the conformational characteristics of the complete pyrethroid molecules will be presented in a future paper.

The acid moieties

During the extensive structure-activity optimization which followed the discovery of the original pyrethroids, it soon became evident that esters of both the *cis*- and *trans*-chrysanthemic acid as well as some derivatives of these led to potent insecticides [1,2].

The stereochemistry has proven to be of ultimate importance. An *R*-configuration at the position 1 in the chrysanthemic acid derivatives (cf. Fig. 2) is a necessity for high biological activity. An *S*-configuration normally leads to a complete loss of activity [30]. The *cis*-(1*R*,3*S*)- and *trans*-(1*R*,3*R*)-arrangements have been shown to represent the biologically active configurations of chrysanthemic acid (cf. Fig. 2).

A very promising candidate for the acid moiety appeared to be the (normally *para*-substituted) 2-phenyl-3-methylbutanoic acid (present in **7** and **8**, as well as in the potent and widely used Type

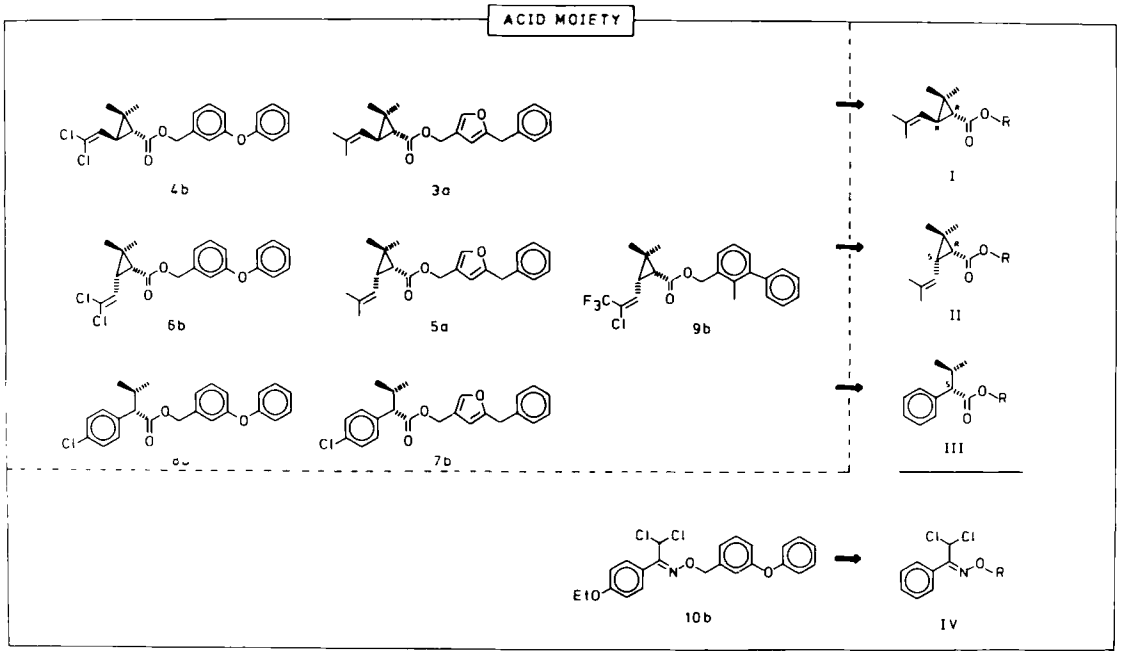


Fig. 2. Decomposition of the pyrethroids in their basic acid moieties (**I–III**), as well as the decomposition of the *O*-alkyl-oxime into its *O*-methyl-oxime (**IV**).

II pyrethroid insecticide Fenvalerate [43], which is a cyano-substituted derivative of **8**). Also for this class of compounds, the stereochemistry of the acid moiety is very important with an *S*-configuration at position 2 (cf. Fig. 2) leading to pyrethroids one or two orders of magnitude more potent than the corresponding *R*-isomers.

A common feature for these three types of compounds is the presence of an unsaturated system (an alkene or an aromatic ring) as well as two geminally placed methyl groups. Both molecular features seem to be necessary. Removal of the π-system leads to compounds with very low or without any pyrethroid-like activity [30]. Removal of one or both methyl groups in either of the above types of compounds results in a marked decrease in activity [44,45].

Whereas the structural requirements of the basic framework seem to be rather strict, a large variety of substituents on either the alkene-moiety or the phenyl-ring is allowed. For both the cyclopropane-derivatives (**1, 3–6** and **9**) and the 2-phenyl-butanoates (**7** and **8**), different patterns of substituents result in comparable biological activities [30,32,35].

In this work we have carried out calculations on the acid moieties **I, II** and **III** (cf. Fig. 2), i.e., the 2,2-dimethylvinyl substituted cyclopropane derivatives (**I** and **II**) and the unsubstituted phenyl-derivative (**III**). These acid moieties contain the molecular features, which are essential for a description of the conformational characteristics.

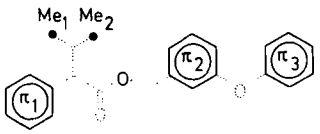
One more compound, the *O*-methyl-oxime **IV**, has been included in our study in order to yield indirect information about the arrangement around the Cα–CO bond in the acid moieties **I–III.** The dichloro-substituted *O*-alkyl-oxime (**10b**), the corresponding isopropyl (**10c**) and several other related analogs are all potent insecticides [26,35] with a built-in conformational restriction.

Oximes normally adopt a planar arrangement of the oxime moiety, and by including the *O*-methyl-oxime **IV** in our study we were able to limit the number of conformations possible for the acid moieties **I–III** considerably.

The acid pharmacophore

The actual mapping of the acid pharmacophore was carried out on the methyl-esters of the acids (**I–IV**, R = Me) to avoid any interference from the acidic hydrogens of the carboxylic acid groups, and to mimic the framework in the pyrethroid esters **1** and **3–10**.

In order to get the essential groups of the molecules (**I–IV**) superpositioned we decided to fit the unsaturated system (π), the two methyl groups (Me_1 and Me_2), and the ether oxygen atom of the ester group to each other (cf. **11** and **12** for a designation of the key groups).



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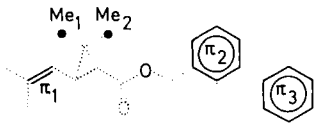

12

Several trial superpositions of the acids (**I–III**) and the oxime (**IV**) were performed. It turned out to be rather problematic to get the unsaturated part of the molecules superpositioned satisfactorily. The problem was overcome by using an approach similar to the one described by Andrews et al. [46,47] in their analysis of a series of CNS-active drugs, but here extended to other unsaturated systems than a phenyl group.

For both the 2,2-dimethylvinyl cyclopropanes (**I** and **II**) and the phenyl-derivatives (**III** and **IV**) the π-systems were described by a vector orthogonal to the plane of the π-system through its center. The vector was fixed at 3.5 Å on each side of the π-system, which resembles the distance between parallel stacked aromatic π-systems [48], and thus reflects the thickness of a π-system. In **I** and **II**, the centers of the π-systems were defined as the centroid made by the two carbon atoms next to the double bond and *cis* to each other, and in **III** and **IV** as the centroid made by the six aromatic carbon atoms of the phenyl ring. This description of the unsaturated systems is not only determined by practical reasons (it is now possible to fit the position as well as the orientation of the π-systems without considering atom-to-atom alignments), but it also reflects the possible location of hydrophobic contacts between the π-system and the receptor.

First the three acid derivatives **I–III** were fitted to each other by a flexible fit. The π–system and each of the two methyl groups were weighted equally, whereas the ether oxygen of the ester groups was given half the weight. Next the *O*-methyl oxime IV was included and all four molecules were fitted to each other. This time the molecules **I–III** were kept fixed in the conformations obtained in the original fit except for the ester moieties, which were adjusted to fit the *O*-methyl oxime conformation. The *O*-methyl oxime IV was not restricted at all.

This resulted in the pharmacophore conformations depicted in Fig. 3. Reasonable ΔE [49] and RMS values were observed (cf. Table 2). By a subsequent minimization the ΔE values dropped (cf. Table 2) without affecting the quality of the fit, i.e., only small adjustments in bond angles were observed. Stereo representations of all four molecules are shown in Fig. 4.

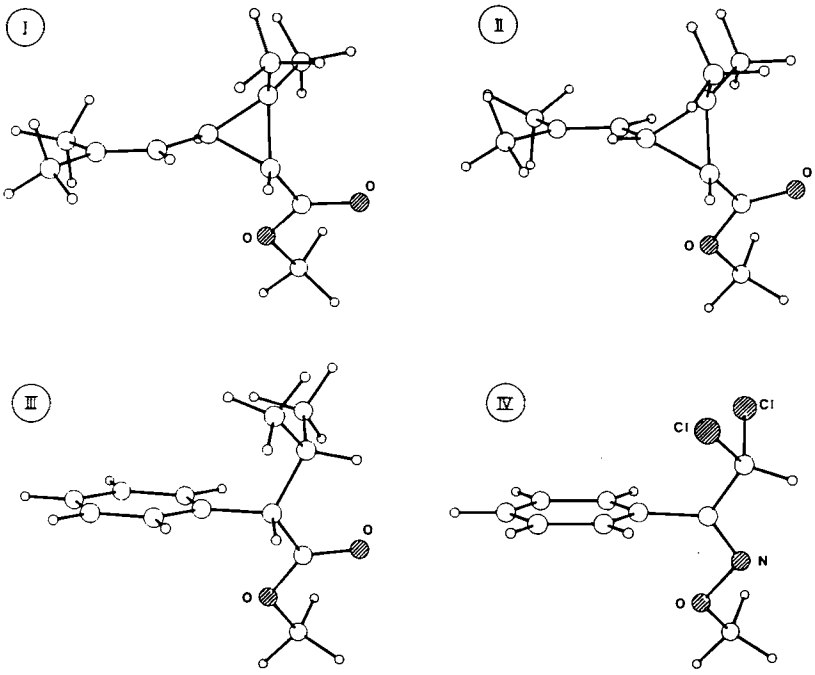

Fig. 3. Three-dimensional representations of the acid moieties (**I–IV**) in their pharmacophore conformations.

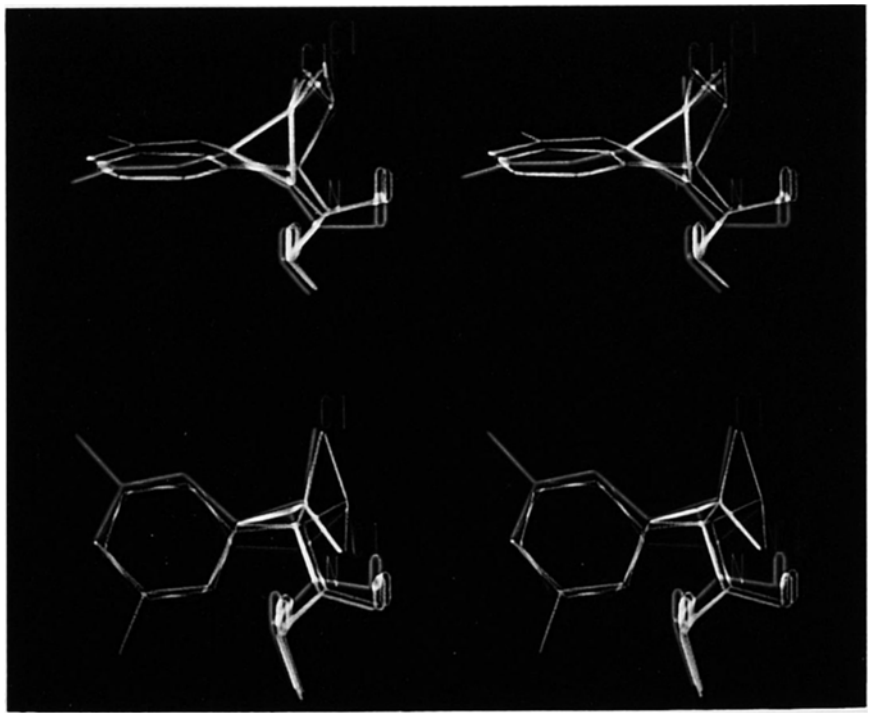

Fig. 4. Stereo representations of the acid pharmacophore. (Two different views. Hydrogen atoms have been omitted for clarity. Colour coded as **I** red, **II** green, **III** cyan, and **IV** purple.)

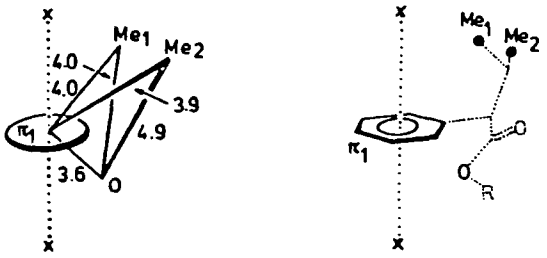

Fig. 5. Schematic representation of the key-points of the acid pharmacophore model. (All distances are in Å.)

In Fig. 5, a schematic representation of the pharmacophore is presented. It is important to point out that the pharmacophore reflects the stereospecificity of the pyrethroids with the two methyl groups placed in an asymmetrical manner with respect to the the π-system and the ether oxygen atom.

The alcohol moieties

Although the variations of the alcohol part of the pyrethroids have been extensively explored only a limited number of conformationally restricted alcohols have been studied. Most work has been concerned with the effects of the nature and the location of the substituents on the aromatic systems. During these modifications, the 5-benzyl-3-furylmethyl alcohol moiety present in **3, 5**

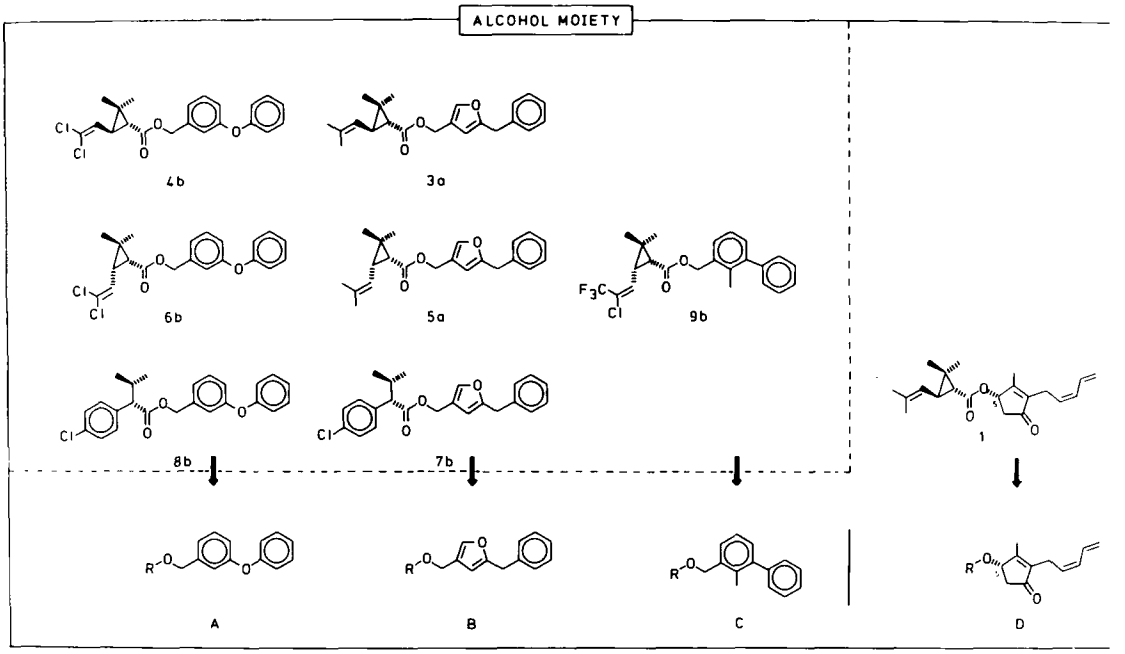

Fig. 6. Decomposition of the pyrethroids in their basic alcohol moieties (**A-D**).

and **7** turned out to yield highly active, but photolabile pyrethroids. Later the 3-phenoxy-benzyl alcohol moiety present in **4, 6, 8** and **10** proved to be one of the best alcohols because it combines high activity with low mammalian toxicity and good photostability. Several modifications of this alcohol have been tested, but without considerable success. The 3-phenyl-benzyl alcohol present in **9** marked a breakthrough, showing that it was possible to design novel alcohols which could mimic the effect of the efficient 3-phenoxy-benzyl alcohol.

This led us to the selection of the three structurally different alcohols **A-C** (cf. Fig. 6). In addition, the (*S*)-pyrethrolone **D** present in Pyrethrin I (**1**) was included.

The alcohol pharmacophore

The alcohol pharmacophore was constructed in a two-step procedure. In the first step, the three acetylated alcohols **A-C** were fitted to each other by a flexible fit to determine the conformation of the two unsaturated systems π_2 and π_3 (cf. **11** and **12**). In the second step, the conformations of **A-C** obtained in the first step were adjusted in order to fit the pyrethrolone **D** with its *S*-configuration at position 1 (cf. Fig. 6). This approach was chosen to utilize the structural information present in **D** about the conformation around the C1(pyrethrolone)–O bond without letting the flexible side chain of **D** influence the conformation of the two unsaturated systems.

The π-systems were not fitted directly by an atom-to-atom alignment due to the different nature of the compounds. Analogously to the mapping of the acid pharmacophore, both π-systems were described by a vector orthogonal to and through the center of each π-system. In order to facilitate

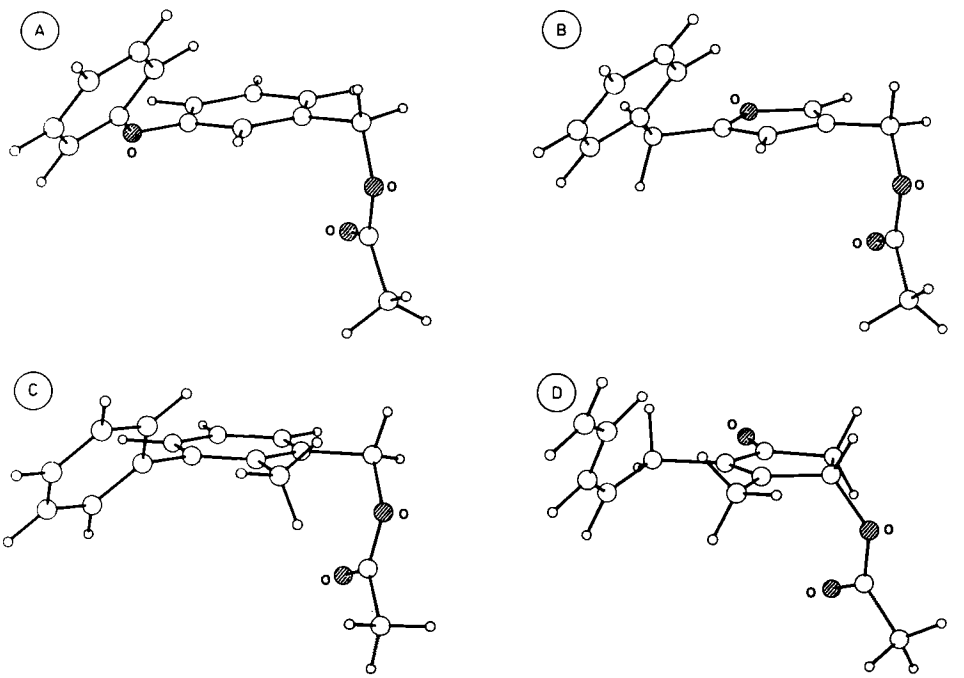

Fig. 7. Three-dimensional representations of the alcohol moieties (**A-D**) in their pharmacophore conformations.

a later combination of the acid and alcohol pharmacophores the ether oxygen of the ester group (acetylated alcohols) were included in the flexible fit. The points describing the π_2 system were given twice the weight than the points describing the π_3 system reflecting the relative importance of these two π-systems for the biological activity. The oxygen atom was given same weight as the π_3 system. After the initial flexible fit of **A-C**, the pyrethrolone **D** was included, and the molecules **A-C** were fixed in the conformations obtained in the original fit except for the acetylated alcohol part of the molecules. The orientation around the bond between the ether oxygen atom and the carbon placed alpha to the oxygen atom in the alcohol side chain was not restricted either, since the purpose of this second fit was to fit the conformation around this bond in **A-C** to the (*S*)-pyrethrolone **D**.

The conformations thus obtained from the flexible fit were considerably more strained than the minimum energy conformations (cf. Table 3). Especially, the pyrethrolone **D** with a $\triangle$E of 14.7 kcal/mol was too strained to be accepted. The geometries of all four compounds were then refined by another minimization with MAXIMIN. These minimizations led to more reasonable $\triangle$E values [49] and were only associated with insignificant changes in the overall shape of the molecules.

The pharmacophore conformations of the alcohols **A-D** are depicted in Fig. 7, and stereo representations of the four alcohols in their pharmacophore conformations are shown in Fig. 8. The average distance between the center of the aromatic systems amounts to 4.5 Å with the π_3 system rotated approximately 54° in a clockwise direction. The direction of this rotation reflects the stereospecificity of the pharmacophore model. Plummer et al. [13] have recently found a similar angle between the π-systems. A schematic representation of the key-points of the pharmacophore is shown in Fig. 9.

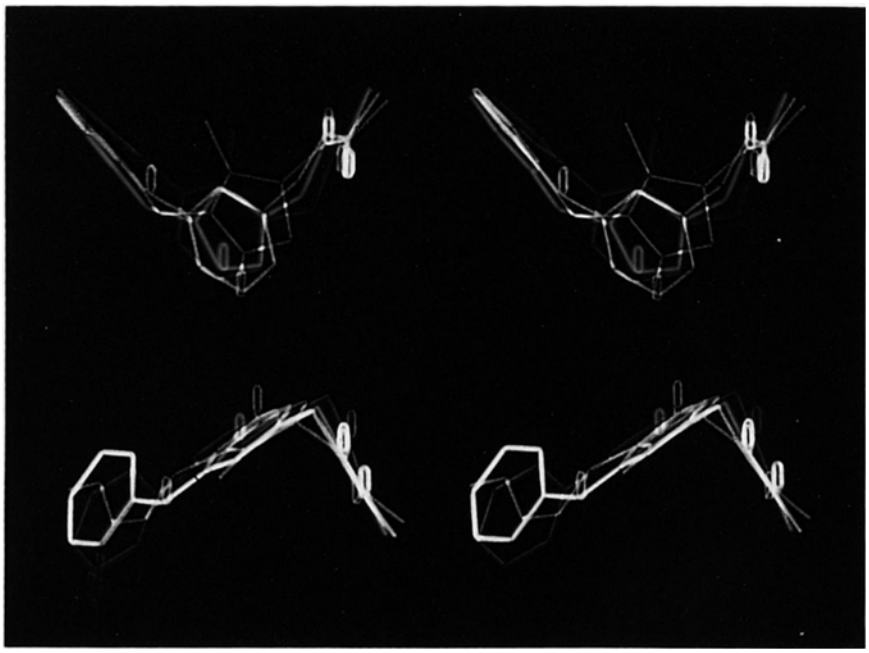

Fig. 8. Stereo representations of the alcohol pharmacophore. (Two different views. Hydrogen atoms have been omitted for clarity. Colour coded as **A** green, **B** red, **C** purple, and **D** cyan.)

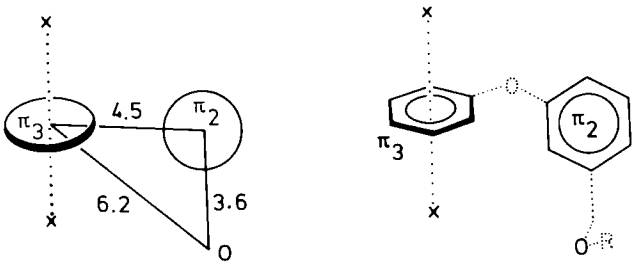

Fig. 9. Schematic representation of the key points of the alcohol pharmacophore model. (All distances are in Å.)

CONCLUSION

The joint molecular modelling and computer graphics study of the pyrethroid insecticides **1** and **3–10** (cf. Fig. 1) reported here show that it is possible to explain the activity of these structurally different compounds by a common pharmacophore model.

The acid and alcohol moieties of the compounds have been treated separately, and the three-dimensional arrangement of the groups being essential for activity has been mapped.

The pharmacophore model (Fig. 5) for the acid moiety consists of a π-system (an aromatic ring or an alkene) in addition to two methyl groups. Furthermore, the ether oxygen of the ester group has been included in the pharmacophore model in order to make it stereospecific and to enable a later combination with the alcohol pharmacophore. The acid pharmacophore allows an explanation for both the *cis*- (**5, 6** and **9**) and the *trans*- (**3** and **4**) chrysanthemic acid derivatives being active. Furthermore, it illustrates the similarity between these compounds and the pyrethroids derived from an isopropyl-substituted phenylacetic acid (**7** and **8**) with respect to their capability to place the geminal methyl groups at the same positions in space.

Analogously, the pharmacophore model for the alcohol moiety (Fig. 9) consists of two π-systems (aromatic systems, except for Pyrethrin I (**1**) with the pentadiene side chain), and the ether oxygen of the ester group, which has been included for consistency. The alcohol pharmacophore nicely reveals the similarity between the diphenylether moiety present in **4, 6, 8** and **10**, the benzylfuryl moiety present in **3, 5,** and **7** and the biphenyl moiety present in **9**, the nearly identical location of the methyl groups in **1** and **9**, as well as illustrates the overall shape of the alcohol part of the pyrethroids.

The identification of the acid and alcohol pharmacophores, respectively, is the first step towards a complete description of the structural characteristics necessary for pyrethroid activity. At the moment, work is in progress to combine the two pharmacophore models into one pharmacophore, i.e., determine the relative orientations of the acid and alcohol pharmacophores. A common pharmacophore for the whole pyrethroid unit may allow one to deduce important information about the active conformation of the pyrethroids and obtain information about the interactions between the pyrethroids and the receptor, and eventually enable design of novel compounds with pyrethroid activity.

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