Original Article

Insecticidal Activity of Pyrethroids Containing a Heterocycle against *Musca domestica* and Their Structure-Activity Relationship

Tadashi OHSUMI, Chiyoza TAKAYAMA, Takao MOTOKI,
Toshihiko YANO, Masachika HIRANO and Nobushige ITAYA

Pesticides Research Laboratory, Takarazuka Research Center,
Sumitomo Chemical Co., Ltd., Takatsukasa, Takarazuka 665, Japan

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Various kinds of pyrethroids containing a heterocycle in their alcohol moiety were synthesized and their insecticidal activity against *Musca domestica*, the housefly was determined by the filter paper contact method. The activity was greatly influenced by the kinds of heterocycles introduced in the alcohol moiety. The stable conformations of these pyrethroids were calculated by the MNDO molecular orbital method and their steric resemblance was studied in the stable conformations. The hydrophobicity of these pyrethroids was also measured by reversed phase HPLC and expressed in terms of $\log k' [= \log (t_R - t_0)/t_0]$, t_R : retention time of the *trans* isomer of the test compound, t_0 : retention time of formamide]. The analysis of the structure-activity relationship by the use of physicochemical parameters and regression analysis showed the importance of molecular shape and hydrophobicity to the insecticidal activity.

INTRODUCTION

Our previous paper¹⁾ reported that 3-benzylpyrrol-1-ylmethyl 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylate (**II**) was a potent insecticide, being two times as active as resmethrin²⁾ against *Musca domestica*, the housefly. The discovery of the new pyrethroid having a pyrrole ring in the alcohol moiety led us to synthesize a series of pyrethroids containing a pyrazole, oxazole or thiazole ring instead of a pyrrole ring and to find that their insecticidal activity was greatly influenced by the kinds of heterocycles and their bonding positions.

Since pyrethroids are a class of insecticides in which the whole molecular shape is crucial for the insecticidal activity, our interest was in examining whether or not the pyrethroids with various kinds of heterocycles in the alcohol moiety could have the same molecular shape.

Tosi *et al.*³⁾ showed that fitness to a receptor

is closely associated with conformational stability. This finding prompted us to calculate the stable conformation for these pyrethroids by the MNDO molecular orbital method^{4,5)} and to examine their steric resemblance in stable conformations.

Here we would like to report on the relationship between chemical structure and insecticidal activity by means of physicochemical parameters and regression analysis.

MATERIALS AND METHODS

1. Syntheses of Compounds

Compounds **I-VII** were prepared by reaction of 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarbonyl chloride with appropriate alcohols by the conventional method. 2-Benzyl-4-furylmethanol was prepared according to the method²⁾ previously described. 2-Benzylloxazole-4-methanol and 5-benzylloxazole-2-methanol were obtained by sodium borohydride reduction of 2-benzylloxazole-4-carboxaldehyde.

hyde⁶⁾ and ethyl 5-benzylloxazole-2-carboxylate,^{7,8)} respectively. 1-Benzylpyrazole-3-methanol was synthesized by benzylation of ethyl pyrazole-3-carboxylate,⁹⁾ followed by lithium aluminum hydride reduction.

4-Benzylthiazole-2-methanol

2-Hydroxythioacetamide tetrahydropyranylether (3.50 g, 0.02 mol) and 1-bromo-3-phenyl-2-propanone¹⁰⁾ (4.26 g, 0.02 mol) were dissolved in tetrahydrofuran with stirring overnight at room temperature. Precipitated salt was filtered and dissolved in dimethylformamide. Anhydrous potassium carbonate (2.76 g, 0.02 mol) was added to the resulting solution and the mixture was stirred at 140°C for 4 hr. The reaction mixture was poured into water and extracted with ethyl acetate. After evaporating the solvent, the residue was dissolved in methanol containing a few drops of concentrated hydrochloric acid. The resulting solution was mixed with water and extracted with ethyl acetate. The extracts were concentrated and purified with column chromatography (silica gel, *n*-hexane: ethyl acetate=1:1, v/v) to give 2.72 g of the alcohol.

The structure of the compounds was confirmed by PMR spectroscopy and their isomer ratios were determined by reversed phase high performance liquid chromatographic analysis in the same condition as described in 3.1. The prepared pyrethroids are listed below with their physical data.

2-Benzyl-4-furylmethyl 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylate (I) PMR(CDCl₃) δ ppm: 7.17 (1 H, s), 7.07 (5 H, s), 5.86 (1 H, s), 6.12, 5.47 (1 H in total, doublet in each, $J=8.0, 8.0$ Hz), 4.78 (2 H, s), 3.86 (2 H, s), 2.3–1.5 (2 H, m), 1.4–1.1 (6 H, m). *cis/trans*=43/57.

3-Benzylpyrrol-1-ylmethyl 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylate (II) PMR(CDCl₃) δ ppm: 7.03 (5 H, s), 6.7–6.5 (1 H, m), 6.4–6.3 (1 H, m), 6.0–5.8 (1 H, m), 6.08, 5.47 (1 H in total, doublet in each, $J=8.0, 8.0$ Hz), 5.58 (2 H, s), 3.69 (2 H, s), 2.4–1.4 (2 H, m), 1.4–1.0 (6 H, m). n_D^{25} =1.5533. *cis/trans*=45/55.

2-Benzylloxazol-4-ylmethyl 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylate (III) PMR(CDCl₃) δ ppm: 7.36 (1 H, s), 7.11 (5 H, s), 6.12, 5.47 (1 H in total, doublet in each, $J=$

8.0, 8.6 Hz), 4.87 (2 H, s), 3.99 (2 H, s), 2.3–1.5 (2 H, m), 1.4–1.0 (6 H, m). $n_D^{16.0}$ =1.5340. *cis/trans*=43/57.

1-Benzylpyrazol-4-ylmethyl 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylate (IV) PMR(CDCl₃) δ ppm: 7.29 (1 H, s), 7.18 (1 H, s), 7.4–6.9 (5 H, m), 6.2–5.4 (1 H in total, doublet in each, $J=8.0, 8.0$ Hz), 5.3 (2 H, s), 4.83 (2 H, s), 2.4–1.4 (2 H, m), 1.4–1.1 (6 H, m). $n_D^{20.0}$ =1.5503. *cis/trans*=43/57.

4-Benzylthiazol-2-ylmethyl 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylate (V) PMR(CDCl₃) δ ppm: 7.08 (5 H, s), 6.58 (1 H, s), 6.12, 5.48 (1 H in total, doublet in each, $J=7.8, 8.0$ Hz), 5.20 (2 H, s), 3.98 (2 H, s), 2.4–1.5 (2 H, m), 1.5–1.1 (6 H, m). $n_D^{20.0}$ =1.5641. *cis/trans*=40/60.

1-Benzylpyrazol-3-ylmethyl 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylate (VI) PMR(CDCl₃) δ ppm: 7.4–6.9 (6 H, m), 6.11 (1 H, d, $J=2.4$ Hz), 6.21, 5.47 (1 H in total, doublet in each, $J=8.4, 8.4$ Hz), 5.10 (2 H, s), 4.98 (2 H, s), 2.5–1.5 (2 H, m), 1.4–1.0 (6 H, m). $n_D^{19.5}$ =1.5561. *cis/trans*=44/56.

5-Benzylloxazol-2-ylmethyl 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylate (VII) PMR(CDCl₃) δ ppm: 7.09 (5 H, s), 6.50 (1 H, s), 6.11, 5.46 (1 H in total, doublet in each, $J=8.0, 8.0$ Hz), 4.93 (2 H, s), 3.88 (2 H, s), 2.4–1.5 (2 H, m), 1.4–1.0 (6 H, m). $n_D^{21.0}$ =1.5440. *cis/trans*=40/60.

2. Biological Activity

Ten milligrams of the test compound (isomeric mixture) was dissolved in 0.1 ml of xylene–dimethylformamide (1:1 v/v) containing Sorpol 3005X (35 mg). The resulting solution was added to deionized water to give an aqueous solution of predetermined concentration. The solution (0.7 ml) was dropped on the filter paper (5.5 cm in diameter) placed in a plastic cup with sucrose (30 mg). Ten female adult houseflies were released in the plastic cup and their mortality was assessed 48 hr later. The insecticidal activity was expressed as the pLC₅₀, negative logarithm of the molar concentration required for the 50% mortality.

3. Physicochemical Parameter

According to Burt *et al.*¹¹⁾ ($\pm$)-*trans* and *cis* isomers of **I** are almost equal in insecticidal

activity against *M. domestica* and their ratio is 100:94 (=trans:cis). Since compounds **I–VII** are isomeric mixtures having almost the same trans:cis ratio (=3:2) and the activity of trans and cis isomers in each of **I–VII** is supposed to be not much different from the activity of **I–VII**, physicochemical parameters could be calculated against the trans isomer to analyze the structure-activity correlation by Hansch-Fujita's method.¹²⁾

3.1 Hydrophobicity

Hydrophobicity of compounds **I–VII** was measured by reversed phase high performance liquid chromatographic analysis [column: YMC Pack AM 303 (ODS S-5, 4.5 mm × 25 cm) purchased from Sumika Chemical Analysis Service Ltd., head pressure: 80 kg/cm², column temp.: 40°C, analytical wavelength: 215 nm, mobile phase: water-acetonitrile (20:80 v/v), non-retained substance: formamide]. It is expressed in terms of log *k'*¹³⁾ [=log (*t_R* - *t₀*)/*t₀*, *t_R*: retention time of the trans isomer of the test compound, *t₀*: retention time of formamide].

3.2 Steric resemblance

In this study compound **I** was selected as a reference molecule to be matched with compounds **II–VII** because of its highest insecticidal activity. Since all compounds (**I–VII**) have a 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxyl group, this group was held in the trans form and kept fixed in the conformation based on the results of X-ray analysis¹⁴⁾ obtained for an allethrin derivative. The initial shapes for heterocycles of compounds **I–VII** were based on X-ray analysis data^{15,16)} and their initial conformations for optimization were chosen using the Dreiding model to give the minimum number of contacts between nonbonded atoms. Optimization was done by the use of the MNDO method for the part of the reference molecule (**I**) listed in Table 1. The same part of the others was optimized for calculating their stable conformations. Steric resemblance was measured by superimposing **I** on the other compounds (**II–VII**) in stable conformations. Superimposition was done to bring the compounds as close as possible to the guidance of the reference atoms shown in Fig. 1. Root-mean-square (RMS) deviation of distances was calculated by extracting the square

Table 1 Optimization of the bond length, and bond and torsion angles of compound **I**.

Defining atoms		
Bond length	Bond angle	Torsion angle
C4–C12	C4–C12–H13	C3–C4–C12–H13
C12–C15	C4–C12–H14	C3–C4–C12–H14
C15–O16	C4–C12–C15	C3–C4–C12–C15
O16–C17	C12–C15–O16	C4–C12–C15–O16
C17–C18	C15–O16–C17	C12–C15–O16–C17
C18–C19	O16–C17–C18	C15–O16–C17–C18
C17–H20	C17–C18–C19	O16–C17–C18–C19
C19–H21	O16–C17–H20	C15–O16–C17–H20
C18–C22	C18–C19–H21	C17–C18–C19–H21
C22–H23	C17–C18–C22	O16–C17–C18–C22
C22–H24	C18–C22–H23	C17–C18–C22–H23
C22–O25	C18–C22–H24	C17–C18–C22–H24
	C18–C22–O25	C17–C18–C22–O25

Fig. 1 The reference molecule for superimposition.

Reference atoms for matching are denoted by arrows.

root of mean from the square of the inter-atomic distances in the matched features. Steric resemblance was expressed by the RMS value.

All computation was done on an ACACS¹⁷⁾ (Advanced Computer-Aided Chemistry System) developed by Sumitomo Chemical Co., Ltd., Sumitomo Pharmaceuticals Co., Ltd. and NEC Co., Ltd.

RESULTS AND DISCUSSION

RMS and log *k'* values of compounds **I–VII** are listed in Table 2 with their insecticidal

Table 2 Physicochemical parameters of compounds **I–VII** and their insecticidal activity against *M. domestica*.

Compd.	Structure	RMS value (Å)	log <i>k'</i>	<i>M. domestica</i> pLC ₅₀
I		0.00	0.38	5.10
II		0.16	0.36	5.10
III		0.15	0.07	4.32
IV		0.15	-0.01	3.93
V		0.36	0.26	3.52
VI		0.29	0.03	3.46
VII		0.62	-0.07	3.32

activity, pLC₅₀. The examination on the relationship between the RMS and pLC₅₀ values produced Eq. (1).

$$\text{pLC}_{50} = -3.007 \text{ RMS} + 4.850 \quad (1)$$

(2.687) (0.827)

$$n=7, s=0.508, r=0.790, F_{1,5}=8.3$$

In this and the following equations, *n* is the number of data points used in the correlation, *s* the standard deviation, *r* the correlation coefficient, *F*_{*v*₁*v*₂} the *F*-value of the correlation (*v*₁=*m* and *v*₂=*n*-*m*-1; *m* is the number of independent variables used in the correlation) and the figures in parentheses the 95% confidence limits. Parameter terms and intercept are justified at levels between 97.5 and 95% and above 99.5% by the *t*-test respectively. Equation (1) indicates that the compounds with the three-dimensional structure similar to the reference molecule are expected to have high insecticidal activity, which is in good accordance with the empirical knowledge that the whole molecular shape plays a very im-

portant role for the insecticidal activity of pyrethroids.

Recent studies^{18,19)} on structure-activity relationships of pyrethroids have shown that their insecticidal activity is closely related to their hydrophobicity. In our study on the relationship between the hydrophobicity and insecticidal activity of **I–VII**, Eq. (2) also shows that the hydrophobicity determines the insecticidal activity. The insecticidal activity increases with the hydrophobicity of compounds.

$$\text{pLC}_{50} = 3.160 \log k' + 3.650 \quad (2)$$

(3.055) (0.681)

$$n=7, s=0.533, r=0.765, F_{1,5}=7.1$$

Since the squared correlation coefficient between the log *k'* and RMS is rather small (0.325), they could be taken as independent parameters. The coefficients of the log *k'* and RMS terms in the equations are nearly the same with a different sign. The pLC₅₀ values of **I–VII** were plotted against (log *k'* - RMS) values

Fig. 2 The relationship between insecticidal activity and $\log k' - \text{RMS}$ values.

to give Fig. 2, which indicates that the activity is linearly related to the $\log k' - \text{RMS}$ value.

It is noteworthy that $\log k'$ and RMS values could be adopted to the analysis of structure-activity correlation of pyrethroids with various kinds of heterocycles in the alcohol moiety. The insecticidal activity of structural isomers (III and VII, IV and VI) with the same heterocycle in the alcohol moiety could be conveniently analyzed by this regression analysis technique.

The reason why compound II was most active among compounds II–VII is that it has not only the structure similar to the reference molecule (I) but also higher hydrophobicity than the others (III–VII).

The above findings provide the conclusion that both the molecular shape and hydrophobicity are the two factors which must be taken into consideration in order to design new pyrethroids efficiently.

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要 約

イエバエに対する含複素環ピレスロイドの殺虫活性およびその構造活性相関

大住忠司, 高山千代蔵, 本木隆夫, 矢野俊彦
平野雅親, 板谷信重

種々のヘテロ環をアルコール成分に有するピレスロイドを合成し, イエバエに対する殺虫活性を測定した。その結果, 活性は, 導入されるヘテロ環の種類に著しく影

響を受けることが明らかとなった。これらピレスロイドの安定コンフォメーションを MNDO 法を用いて計算し, 2-ベンジル-4-フリルメチル 2,2-ジメチル-3-(2,2-ジクロロビニル)シクロプロパンカルボキシレートに対照分子として立体類似性 (RMS 値) を算出した。RMS 値および逆相液体クロマトグラフィーを用いて測定した $\log k'$ 値は殺虫活性と相関性を示し, ピレスロイドの殺虫活性における立体形状と疎水性の重要性が示唆された。