■■■■■■■■■■
Note
■■■■■■■■■■

Structure-Activity Relationship of Insecticidal α -Cyanobenzylcyclopropanecarboxylates

Makoto HATAKOSHI, Noritada MATSUO and Isamu NAKAYAMA

*Research Department, Pesticides Division, Sumitomo Chemical Co., Ltd.,
Takatsukasa, Takarazuka, Hyogo 665, Japan*

(Received August 1, 1982)

The structure-activity relationships of insecticidal 3-substituted- α -cyanobenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylates have been analyzed by the Hansch method against housefly, *Musca domestica*. The variation of the activity was shown to be mainly related to the variation of the hydrophobicity of the 3-substituent. The activity of the compounds whose 3-substituent has either π electrons or a lone pair at the β -position was about 2 times higher than the other compounds.

INTRODUCTION

There are a few reports about the quantitative structure-activity study of pyrethroids. Many α -cyanobenzylcyclopropanecarboxylates such as cyphenothrin¹⁾ and cypermethrin²⁾ have been found to possess high insecticidal activities, but their structural requirements for such high activity have not yet been clarified. We have synthesized a number of compounds and tested their insecticidal activity against the housefly. In this paper, we describe the relationship between the chemical structure of 3-substituted- α -cyanobenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylates and its insecticidal activity against housefly.

MATERIALS AND METHODS

1. Chemicals

All chemicals were prepared from the reaction of the corresponding benzaldehydes, 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarbonyl chloride and sodium cyanide in the presence of the phase transfer catalyst in *n*-heptane and water. The structure of compounds was confirmed by IR and NMR spectroscopy. A typical example is shown below.

α -cyano-3-(2-methyl-2-propenyloxy)benzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecar-

boxylate

To the mixture of 3-(1-propenyloxy)benzaldehyde (1.62 g) and 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarbonyl chloride (2.27 g) in *n*-heptane (15 ml), was added sodium cyanide (0.64 g) in water (1 ml) and this was stirred overnight at room temperature. The resulting mixture was poured into water (50 ml), extracted with ethyl acetate and the organic layer was washed with a saturated aqueous sodium chloride solution and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the residue (3.6 g) was chromatographed over silica gel (60 g) and eluted with *n*-hexane/ethylacetate (20 : 1) to give the desired compound (2.89 g). $n_D^{20}=1.5416$.

2. Insecticidal Activity

A filter paper was seated at the bottom of a plastic cup (5.5 cm in diameter, 115 ml in volume) and 25 mg of sucrose was put into the cup as a diet. All compounds were formulated as the 20% emulsifiable concentrate by weight with *N,N*-dimethylformamide (20%), xylene (20%) and an emulsifier, Sorpol SM100P (Toho Chemical Co., Ltd.) (40%), and diluted with distilled water to the desired concentration. Then 0.7 ml of the test emulsion was dropped onto the filter paper and ten four-day-

Table 1 Insecticidal activity of 3-substituted- α -cyanobenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylates.

No.	Substituent ^{a)}	$n_D(^{\circ}\text{C})$	π	F_{π}	Activity	
					Obs. ^{b)}	Calc. ^{c)}
1	H	1.5408 (19)	0.00	0	3.09	3.20
2	F	1.5290 (21)	0.14	0	3.30	3.27
3	Cl	1.5479 (20.5)	0.71	0	3.57	3.59
4	Br	1.5580 (26)	0.86	0	3.85	3.67
5	C ₆ H ₅	1.5341 (21.5)	1.02	0	4.17	3.76
6	CH ₂ CH=CH ₂	1.5348 (21.5)	1.10	1	4.04	4.17
7	CH ₂ OCH ₃	1.5343 (23.5)	-0.78	1	2.99	3.14
8	CH ₂ OC ₂ H ₅	1.5315 (25)	-0.24	1	3.40	3.43
9	CH ₂ OCH ₂ CH=CH ₂	1.5358 (19.5)	0.13	1	3.63	3.63
10	CH ₂ OCH ₂ C $\equiv$ CH	1.5410 (20)	-0.33	1	3.61	3.38
11	OCH ₃	1.5440 (18)	-0.02	0	2.77	3.19
12	OC ₂ H ₅	1.5378 (19.5)	0.38	0	3.16	3.41
13	OC ₄ H ₇ (<i>i</i>)	1.5322 (18)	0.85	0	3.78	3.66
14	OC ₄ H ₉ (<i>s</i>)	1.5291 (21)	1.42	0	3.97	3.98
15	OCH=CH ₂	1.5428 (22.5)	-0.08	1	3.70	3.52
16	OCH=CHCH ₃	1.5427 (23.5)	0.71	1	4.05	3.95
17	OCH ₂ C(CH ₃)=CH ₂	1.5416 (17)	0.99	0	3.78	3.74
18	OC(CH ₃) ₂ C $\equiv$ CH	1.5225 (27)	0.56	0	3.53	3.51
19	CH ₂ C ₆ H ₅	1.5590 (30)	2.01	1	4.37	4.46
20	OC ₆ H ₅	1.5642 (19)	2.08	1	5.08	4.70
21	OC ₆ H ₄ Cl(<i>p</i>)	1.5700 (20)	2.79	1	4.82	5.09

^{a)} *i*, *s* and *p* denote *iso*, *secondary* and *para*, respectively.^{b)} Observed.^{c)} Calculated by Eq. (2).

old female houseflies, *Musca domestica* per cup were released. The mortality of the flies was expressed as the LC₅₀ value, the molar concentration in the test emulsion required for 50% lethality of the housefly and listed in Table 1.

RESULTS AND DISCUSSION

The insecticidal activity of 3-substituted- α -cyanobenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylates considerably varies with the variation of the 3-substituent as shown in Table 1. The structure-activity relationship has been analyzed quantitatively by the method developed by Hansch and Fujita³⁾ by means of physicochemical substituent parameters and regression analysis.

The structure-activity correlation is fairly represented by Eq. (1) with a single parameter, the hydrophobic π .⁴⁾

$$-\log \text{LC}_{50} = 3.363 + 0.563\pi \quad (1)$$

$$(\pm 0.169) (\pm 0.155)$$

$$n=21, s=0.290, r=0.868, F=58.0$$

In this and the following equation, n is the number of compounds, s is the standard deviation, r is the correlation coefficient and F is the F -value of the correlation.

The figures in parentheses are 95% confidential intervals of the corresponding constants. Substituting π by van der Waals volume, V_w ,⁵⁾ molar refractivity, MR,⁶⁾ or adding the π^2 singly or together with V_w , MR, electronic $\sigma^7)$ and steric E_s ⁸⁾ to Eq. (1) does not give a significant reduction in the standard deviation. Nakada *et al.*⁹⁾ reported the relationship between the insecticidal activity against American cockroach and the chemical properties of 4-substituted 1-indanyl chrysanthemates and showed that the existence of the unsaturated bond in allyl derivatives was important for high activity.

As shown in Fig. 1, the activity of the compounds having π electrons or a lone pair at β -position of the 3-substituent is higher than

Fig. 1 Insecticidal activity and the π value of 3-substituted- α -cyanoderivatives.

- : Having π electrons or a lone pair at β -position of the 3-substituent,
 □: Not having π electrons or a lone pair at β -position of the 3-substituent.

that of the others. Thus, the variation in activity is expected to be determined not only by the hydrophobicity but also by the (extra) effect of the 3-substituent. We have found that this effect is best correlated with the indicator variable, F_π , which takes 1 for the compounds having π electrons or a lone pair at β -position and 0 for the others. Adding indicator variable F_π to Eq. (1) gives improved Eq. (2).

$$-\log LC_{50} = 3.198 + 0.549\pi + 0.366F_\pi$$

$$(\pm 0.161) (\pm 0.120) (\pm 0.206)$$

(2)

$$n=21, s=0.244, r=0.928, F=55.6$$

Fujimoto *et al.*¹⁰⁾ reported that the oxygen atom attached to the benzene ring increased the activity. However, no significant improvement was obtained by adding the indicator variable, which takes 1 for the compounds having an oxygen atom at α -position of the 3-substituent and 0 for the others, to Eq. (1).

Equation 2 shows that the insecticidal activity is really related to the hydrophobicity of the 3-substituent, the more the hydrophobicity, the higher the activity. As the activity was determined by the filter paper method, this result indicates that penetration

of the compound to the critical site in the insect body might be important for the activity. Briggs *et al.*^{11,12)} showed the importance of hydrophobicity on insecticidal activity. The fact that the coefficient of the F_π term in Eq. (2) is 0.366 means that the activity of the derivatives whose 3-substituent has π electrons or a lone pair at β -position is about 2.3 times higher than that of the others. Ford¹³⁾ examined the relationships between the insecticidal activity and the chemical properties of methylsubstituted-benzyl chrysanthemates and showed that the electronic property was important for high activity against the housefly. He emphasized that the aromatic ring of the alcohol moiety of methylsubstituted-benzyl chrysanthemates made the charge-transfer complex at the site of action. The π electrons or a lone pair at β -position which is modified to higher activity may be related to the electronic interaction with the critical site for the activity.

ACKNOWLEDGMENTS

We wish to express our thanks to Prof. Dr. T. Fujita, Kyoto University, for his invaluable suggestions. We also thank Dr. O. Kirino for his fruitful discussions.

REFERENCES

- 1) T. Matsuo, N. Itaya, T. Mizutani, N. Ohno, K. Fujimoto, Y. Okuno & H. Yoshioka: *Agric. Biol. Chem.* **40**, 247 (1976)
- 2) M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham & D. A. Pulman: *Nature* **248**, 710 (1974)
- 3) C. Hansch & T. Fujita: *J. Am. Chem. Soc.* **86**, 1616 (1964)
- 4) C. Hansch & A. Leo: "Substituent Constants for Correlation Analysis in Chemistry and Biology," John Wiley & Sons, Inc., New York, p. 18, 1979
- 5) A. Bondi: *J. Phys. Chem.* **68**, 441 (1964)
- 6) C. Hansch, A. Leo, S. H. Unger, K. -H. Kim, D. Nikaitani & E. J. Lien: *J. Med. Chem.* **16**, 441 (1973)
- 7) C. Hansch, S. D. Rockwell, P. Y. C. Jow, A. Leo & E. E. Steller: *J. Med. Chem.* **20**, 304 (1977)
- 8) S. H. Unger & C. Hansch: *Proc. Phys. Org. Chem.* **12**, 91 (1976)
- 9) Y. Nakada, S. Ohno, M. Yoshino & Y. Yura: *Agric. Biol. Chem.* **42**, 1365 (1978)

- 10) K. Fujimoto, N. Itaya, Y. Okuno, T. Kadota & T. Yamaguchi: *Agric. Biol. Chem.* **37**, 2681 (1973)
- 11) G. G. Briggs, M. Elliott, A. W. Farnham & N. F. Janes: *Pestic. Sci.* **5**, 643 (1974)
- 12) G. G. Briggs, M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, D. A. Pulman & S. R. Young: *Pestic. Sci.* **7**, 236 (1976)
- 13) M. G. Ford: *Pestic. Sci.* **10**, 39 (1979)

要 約

殺虫剤 α -シアノシクロプロパンカルボキシレート の構造活性相関

波多腰 信, 松尾憲忠, 中山 勇

3-置換 α -シアノベンジル 3-(2,2-ジクロロビニル)-2, 2-ジメチルシクロプロパンカルボキシレートのイエバエに対する殺虫活性の構造活性相関を Hansch 法で解析した。活性の変化はおもに 3 位置換基の疎水性と関係づけられた。さらに, 3 位の置換基が β 位に π 電子または孤立電子対をもつと, 化合物の活性は他の化合物の約 2 倍上昇した。