

Studies on the Syntheses of the Pyrethrin Analogues and their Biological Activities. (I)*

Allethronyl Esters of Cyclopropanecarboxylic Acids

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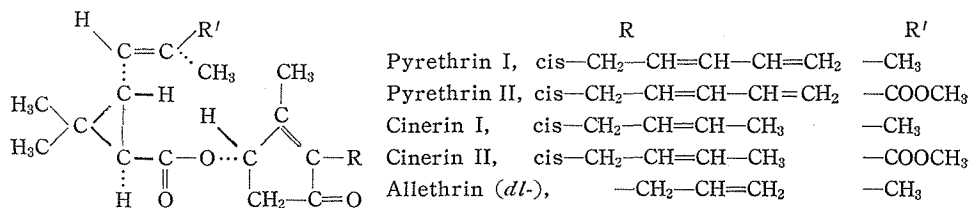
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Some new allethronyl esters of cyclopropanecarboxylic acids were prepared, and their insecticidal activities were tested against common house fly. Allethronyl esters of cyclopropanecarboxylic acids having 3,4-methylenedioxyphenyl group on the cyclopropane ring were more or less toxic. Among them, allethronyl 2,2-dimethyl-3-(3',4'-methylenedioxyphenyl)-cyclopropane-1-carboxylate was found to be more toxic than α -*dl*-trans-allethrin, and the calculated relative effectiveness were 1.48 and 1.21 on the mortality and knock-down activity respectively as compared with α -*dl*-trans-allethrin.

The active principles of pyrethrum flower are known to be a mixture of four keto-esters, generally referred to as the "Pyrethrins". Four naturally occurring pyrethrins are recognized to be represented by the following general formulae :



The elucidation of their structures and subsequent success in the syntheses thereof led, as a matter of course, to the preparation of many homologous "rethrins".

In search for a more active analogues, many attempts have been made on modifications in cyclopropanecarboxylic acid as well as cyclopentenolone-moieties. It has been chiefly in the modification in the alcoholic part that successful results were obtained. Thus, allethrin has been introduced as an effective analogue which can compete with the natural pyrethrins in insecticidal activity and is now commercially produced for domestic uses.

On the other hand, the modifications in acid part of the rethrins had not

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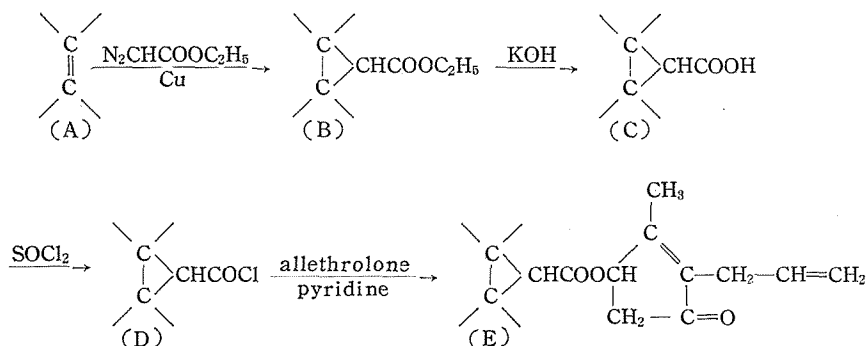
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been realized.

In the view mentioned above, the authors attempted to synthesize such cyclopropanecarboxylic acids as to give more effective esters with allethrolone. Some new allethronyl esters of cyclopropanecarboxylic acids were prepared and their insecticidal activities were tested against common house fly*. Most of these esters showed little activities, but allethronyl esters of substituted-phenyl-cyclopropanecarboxylic acids were more or less toxic. Thereupon, the authors synthesized such cyclopropanecarboxylic acids as to have some substituted-phenyl groups attached to the cyclopropane ring, and tested their insecticidal activities to clarify the relationship between the toxicity and the substitution on the cyclopropane ring.

Many synthetic methods for cyclopropane ring have been known, in which the most common one consists in the addition of diazo-compounds to olefinic compounds. In order to obtain the cyclopropanecarboxylic acids, the authors added ethyl diazoacetate to unsaturated hydrocarbons (A) and ethyl cyclopro-



panecarboxylates (B) were subsequently saponified to the expected acids (C). Allethronyl esters of these acids were prepared by the usual method through the acid chlorides (D), and were purified by chromatography on alumina column. The insecticidal activities of these allethronyl esters (E) were tested against common house fly, *Musca domestica vicina* Macq.

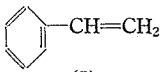
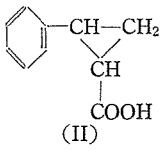
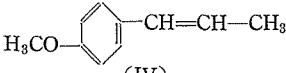
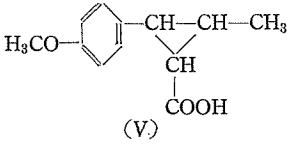
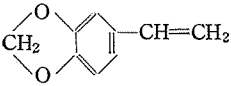
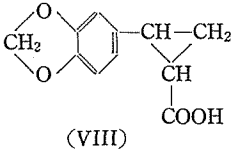
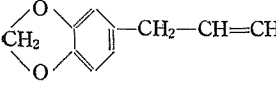
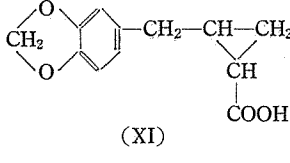
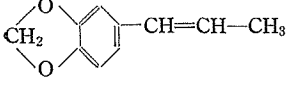
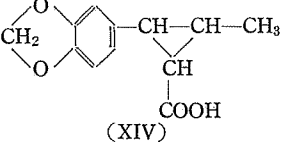
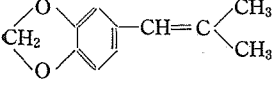
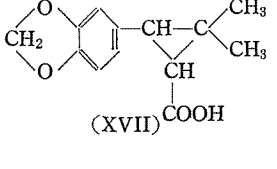
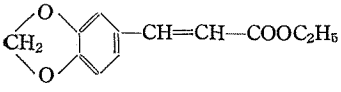
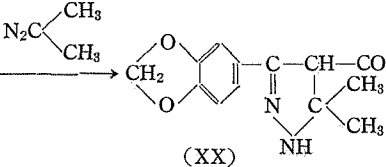
The chemical structures of these acids and the results of bioassay were listed in Table 1.

As is apparent from Table 1, allethronyl 2-phenylcyclopropane-1-carboxylate(III) and 2-methyl-3-(3'-methoxyphenyl)-cyclopropane-1-carboxylate(VI) which have no methylenedioxy group on the phenyl, showed a little insecticidal activities. Moreover allethronyl 2-piperonylcyclopropane-1-carboxylate(XII) was nontoxic, but allethronyl 2-methyl-3-(3', 4'-methylenedioxyphenyl)-cyclopropane-1-carboxylate(XV) showed remarkable activities, and the relative effectiveness was calculated as 0.18 on mortality, and 0.49 on knock-down activity as compared with *α-dl-trans*-allethrin.

From these results, the authors concluded that the insecticidal activities of these allethronyl esters depend to some extent on the existence of 3, 4-methylenedioxyphenyl group as one of the substituents on the cyclopropane

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Table 1.

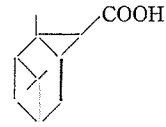
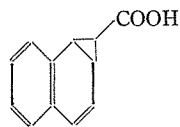
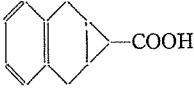
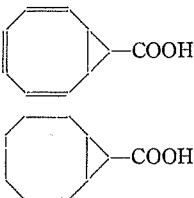
Unsaturated compounds Structure & Code	Cyclopropane carboxylic acids Structure & Code	Allethronyl cyclopropanecarboxylates		
		Code	Insecticidal activity	
			Knock-down % after 30 mins.	Mortality after 24 hrs.
 (I)	 (II)	(III)	0.0	—
 (IV)	 (V)	(VI)	0.0	+
 (VII)	 (VIII)	(IX) a b	67.9 0.0	+++ +
 (X)	 (XI)	(XII)	0.0	+
 (XIII)	 (XIV)	(XV)	100.0	++++
 (XVI)	 (XVII)	(XVIII) a b	100.0 100.0	++++ +++++
<i>α-dl-trans-allthrin</i>			100.0	+++++
 (XIX)	 (XX)			
			$\xrightarrow[\text{KOH}]{\text{Cu}}$	(XVII)

ring, and attempted to synthesize such cyclopropanecarboxylic acids.

As the simplest cyclopropanecarboxylic acid containing 3, 4-methylenedioxyphenyl group on the cyclopropane ring, 2-(3', 4'-methylenedioxyphenyl)-cyclopropane-1-carboxylic acid(VIII) was synthesized by the addition of ethyl diazoacetate to 1-vinyl-3,4-methylenedioxybenzene(VIII)¹⁾, and two isomeric acids were obtained by fractional crystallization (VIIIa, m.p. 144-5°; VIIIb, m.p. 121-2°). Both of their allethronyl esters (IXa, IXb) were less toxic than previously synthesized allethronyl 2-methyl-3-(3',4'-methylenedioxyphenyl)-cyclopropane-1-carboxylate(XV). The fact that allethronyl 2-(3', 4'-methylenedioxyphenyl)-cyclopropane-1-carboxylates(IX) were less toxic than allethronyl 2-methyl-3-(3', 4'-methylenedioxyphenyl)-cyclopropane-1-carboxylate (XV), suggests that the insecticidal activities of such allethronyl esters may be affected by the existence of methyl group on the cyclopropane ring.

The suggestion mentioned above led that allethronyl 2, 2-dimethyl-3-(3', 4'-methylenedioxyphenyl)-cyclopropane-1-carboxylate might be more toxic. Piperonal was treated with isopropylmagnesiumbromide, and following dehydration of the resulting 1-methyl-2-(3', 4'-methylenedioxyphenyl)-propanol, 1-(isobut-1-enyl)-3, 4-methylenedioxybenzene(XVI) (b.p. 94.5-95.5°/2 mm.) was obtained. This aralkenyl compound (XVI) was treated with ethyl diazoacetate in the

* They are shown in the following Table, and they did not show the insecticidal activities on the bioassay.

Unsaturated compounds	Cyclopropanecarboxylic acids				Allethronyl esters n_D
	Structure	m. p.	Analysis		
			Found	Calcd.	
α -Pinene		158-9°	C: 73.86 H: 9.16	C: 74.19 H: 9.34	n_D^{20} 1.5175
		121-2°	C: 74.31 H: 9.54	C: 74.19 H: 9.34	n_D^{20} 1.5220
3,4-Dihydronaphthalene		160-1°	C: 76.90 H: 6.45	C: 76.75 H: 6.43	n_D^{20} 1.5658
1,4-Dihydronaphthalene		157-8°	C: 76.74 H: 6.64	C: 76.75 H: 6.43	n_D^{20} 1.5630
Cyclo-octatetraene		163-4° ^a			n_D^{21} 1.5382
		111-2° ^a			n_D^{25} 1.5199

^a S. Akiyoshi and T. Matsuda, *J. Am. Chem. Soc.*, 77, 2476 (1955).

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usual way. After the saponification of the resulting ester, the acid (XVII) was fractionally crystallized to give two isomeric acids (XVIIa, m.p. 171-2°; XVIIb, m.p. 134-5°). The allethronyl esters of these acids (XVIIIa, XVIIIb) was the most toxic among allethronyl esters previously synthesized by the authors, and its relative toxicities were calculated as 1.48 times more active on the mortality and 1.21 times on the knock-down activity than α -*dl*-trans-allethrin as the standard.

Afterwards, the authors obtained the same acid (XVIIb) by the other route, *i.e.* the addition of dimethyldiazomethane to ethyl piperonylideneacetate (XIX) to yield a pyrazoline ester (XX) (m.p. 142-3°). This pyrazoline ester (XX) was submitted to thermal decomposition, and the subsequent hydrolysis of the resulting ester yielded an acid m.p. 134-5° exclusively. This acid was shown to be identical with previously synthesized acid (XVIIb) (m.p. 134-5°) by the other route using ethyl diazoacetate, by the mixed melting point comparison as well as by the complete identity of IR-spectra.

EXPERIMENTAL

The general procedure for the preparation of cyclopropanecarboxylic acids using ethyl diazoacetate and for the esterification with allethrolone, and the insecticidal tests were carried out as exemplified in the following :

a) Preparation of cyclopropanecarboxylic acid. The unsaturated hydrocarbon (A) was heated to 110° in ligroin (b.p. 110-120°) and in the presence of copper powder (5 g./1 mole. of A). To the mixture, was added ethyl diazoacetate (0.8-1 mole./1 mole. of A) dropwise within 2 hrs. so as to keep the reaction temperature at 110-120°. After the evolution of nitrogen was over, the reaction mixture was cooled and copper powder was filtered off. From the filtrate, unreacted original compound (A) and ligroin were recovered. Since the resulting ethyl cyclopropanecarboxylate (B) has high boiling points in general, the residue of the evaporation was directly hydrolyzed by refluxing with 10% alcoholic KOH on a water bath. The acid (C) was isolated in the usual manners and was purified by fractional crystallizations.

b) Esterification with allethrolone. The acid (C) dissolved in chloroform containing thionylchloride (1.2 mole./1 mole. of C), was set aside for 1 day or was refluxed on a water bath for 3 hrs. After the duration, chloroform and the excessive thionylchloride were completely removed *in vacuo*, the remaining acid chloride (D) was enough pure for further use.

The acid chloride (D) in dry benzene was added to the solution of allethrolone (0.8 mole./1 mole. of C) in benzene and dry pyridine. The reaction mixture was kept at room temperature for 24 hrs., then the neutral product containing the ester (E) and unreacted allethrolone was extracted with ether. The extract was separated by elution chromatography using Al₂O₃ for the absorbant and eluted with petroleumether-ether (3:1). These esters were characterized by the absence of the OH band in the IR-spectra.

c) Bioassay. The common house fly, *Musca domestica vicina* Macq., was

reared with culture medium, and 3 or 4 days individuals after emergence were used. For the insecticidal test of the ester (E), two methods were employed. The one is the settling mist apparatus method in 1% refined kerosene solution to examine the knock-down effect after 30 mins., and the other is the topical application method by microsyringe in 1% acetone to examine the mortality after 24 hrs. The relative effectiveness of these esters were calculated from their median knock-down doses and median lethal doses.

2-Phenylcyclopropane-1-carboxylic acid (II). m.p. 146-7°, Yield 37%, (*Anal.* Found : C, 74.13, H, 6.33; Calcd. for $C_{10}H_{10}O_2$: C, 74.05, H, 6.22).

Allethronyl 2-phenylcyclopropane-1-carboxylate (III). n_D^{20} 1.5518.

2-Methyl-3-(4'-methoxyphenyl)-cyclopropane-1-carboxylic acid (V). m.p. 121-2°, Yield 24%, (*Anal.* Found : C, 69.78, H, 6.93; Calcd. for $C_{12}H_{14}O_3$: C, 69.88, H, 6.84).

Allethronyl 2-methyl-3-(4'-methoxyphenyl)-cyclopropane-1-carboxylate (VI). n_D^{18} 1.5455.

2-(3', 4'-Methylenedioxyphenyl)-cyclopropane-1-carboxylic acid (VIII). An acid (VIIIa) of m.p. 144-5° which dissolved more easily in methanol than in chloroform, and an acid (VIIIb) of m.p. 121-2° which dissolved more easily in chloroform, were obtained by fractional recrystallization. (VIIIa) Yield 9.5%, (*Anal.* Found : C, 64.11, H, 4.81; Calcd. for $C_{11}H_{10}O_4$: C, 64.07, H, 4.89), and (VIIIb) Yield 9.5%, (*Anal.* Found : C, 64.32, H, 5.05; Calcd. for $C_{11}H_{10}O_4$: C, 64.07, H, 4.89).

Allethronyl 2-(3', 4'-methylenedioxyphenyl)-cyclopropane-1-carboxylate (IX). The acids (VIIIa, VIIIb) were esterified with allethrolone respectively. (IXa) n_D^{23} 1.5642, (IXb) n_D^{23} 1.5410.

2-Piperonylcyclopropane-1-carboxylic acid (XI). m.p. 128-9°, Yield 5%, (*Anal.* Found : C, 65.30, H, 5.94; Calcd. for $C_{12}H_{12}O_4$: C, 65.44, H, 5.49).

Allethronyl 2-piperonylcyclopropane-1-carboxylate (XII) n_D^{20} 1.5470.

2-Methyl-3-(3', 4'-methylenedioxyphenyl)-cyclopropane-1-carboxylic acid (XI-V). m.p. 134-5°, Yield 11%, (*Anal.* Found : C, 65.3), H, 5.66; Calcd. for $C_{12}H_{12}O_4$: C, 65.44, H, 5.49).

Allethronyl 2-methyl-3-(3', 4'-methylenedioxyphenyl)-cyclopropane-1-carboxylate (XV). n_D^{23} 1.5482.

2, 2-Dimethyl-3-(3', 4'-methylenedioxyphenyl)-cyclopropane-1-carboxylic acid (XVII). a) Piperonal (30 g., 0.2mole.) in 200 ml. of ether was added to the Grignard reagent which was prepared from magnesium (4.9 g., 0.2 mole.) and isopropylbromide (28 g., 0.2 mole.) at room temperature. After hydrolysis with cold 10% H_2SO_4 , the organic layer was separated and the aqueous layer was extracted with ether. After the solvent was distilled off, the extract containing 1-(3', 4'-methylenedioxyphenyl)-2-methylpropanol was diluted with 200 ml. of dry benzene and refluxed with P_2O_5 on a water bath for 3 hrs. The reaction mixture was poured into water to decompose the excessive P_2O_5 . 1-(Isobut-1'-enyl)-3, 4-methylenedioxybenzene (XVI) was isolated in the usual way. b.p. 94.5-95.5°/2 mm., n_D^{20} 1.5605, Yield 32 g. (91%).

The compound (XVI) was treated with ethyl diazoacetate following the

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general procedure, and the acid (XVII) was separated into two isomers by fractional recrystallization from methanol. (XVIIa) m.p. 170-1°, Yield 6.4%, (*Anal.* Found: C, 66.50, H, 5.90; Calcd. for $C_{13}H_{14}O_4$: C, 66.65, H, 6.20) and (XVIIb) m.p. 134-5°, Yield 19%, (*Anal.* Found: C, 66.37, H, 6.11; Calcd. for $C_{13}H_{14}O_4$: C, 66.65, H, 6.20).

b) Dimethyldiazomethane²⁾ (*ca.* 3 g., 0.14 mole.) was added to ethyl pi-peronylideneacetate (XIX) (2.9 g., 0.14 mole.) in chilled (-10 ~ -20°) xylene solution and the reaction temperature was kept at -10 ~ -20° for 3 hrs, and then at room temperature for 24 hrs. After removal of xylene, a crystalline pyrazoline ester (XX), m.p. 142-3°, (*Anal.* Found: C, 62.02, H, 6.31, N, 9.65; Calcd. for $C_{15}H_{18}O_4N_2$: C, 62.05, H, 6.25, N, 9.65) was isolated.

The thermal decomposition of the pyrazoline ester (XX) in the presence of copper powder took place at an elevated temperature (170-190°) under evolution of nitrogen, and subsequent distillation *in vacuo* of the residue gave the expected ester, b.p. 130-1°/2 mm., n_D^{18} 1.5340, Yield 1.5 g., (13% based on dimethyldiazomethane). This ester was hydrolysed with 10% alcoholic KOH, and the acid of m.p. 134-5° was obtained. This acid was shown to be identical with the acid (XVIIb) previously synthesized by the other route using ethyl diazoacetate, by the mixed melting point comparison as well as by the complete identity of IR-spectra.

Allethronyl 2, 2-dimethyl-3-(3', 4'-methylenedioxyphenyl)-cyclopropane-1-carboxylate (XVIII). The acids (XVIIa, XVIIb) were esterified with allethrolone respectively. (XVIIIa) n_D^{20} 1.5410, (XVIIIb) n_D^{18} 1.5450.

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- (2) S. Takei, T. Sugita and Y. Inouye, *Ann.* **618**, 108 (1958).