Chemical Studies on Pyrethroids

Part II. Synthesis and Toxicity of Allethrin II Isomers

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To obtain (Z)-pyrethric acid, a geometrical isomer of pyrethric acid, the condensation between 1-methoxycarbonylethylphosphonate (II) and *tert*-butyl 2, 2-dimethyl-3-formylcyclopropane-1-carboxylate (I) was reinvestigated, the yield of the (Z)-isomer was increased to 61.5% in the reaction mixture. (Z)- and (E)-Isomers were separated effectively by recrystallization from acetonitrile after alkaline hydrolysis of the reaction product.

(Z)-Isomer of allethrin II was synthesized from (Z)-pyrethric acid and allethrolone. Toxicity of the (Z)-isomer to houseflies was compared with those of allethrin I and II.

In a preceeding paper¹⁾ the authors described synthesis of allethrin derivatives oxidized at the *trans*-methyl group of ($\pm$)-*trans*-chrysanthemic acid moiety. To achieve the syntheses of all allethrin metabolites with the possible structures,²⁾ it became necessary to prepare *cis*-methyl oxidized derivatives of ($\pm$)-*trans*-chrysanthemic acid. Among these derivatives ($\pm$)-*trans*-2, 2-dimethyl-3-(2'-methoxycarbonylprop-(Z)-1'-enyl)cyclopropane-1-carboxylic acid (($\pm$)-*trans*-(Z)-pyrethric acid)* (IVb) is supposed to be the key compound in the synthetic route of the (Z)-series.

The present paper is concerned with an improved synthetic method of (Z)-isomer of pyrethric acid (IVb) and allethrin II (IVc). The latter's toxicity to houseflies was also examined from the view point of correlation between chemical structure and biological activity.

($\pm$)-*trans*-(Z)-Pyrethric acid was previously

synthesized³⁾ by the Wittig type condensation of diethyl 1-methoxycarbonylethylphosphonate (IIb) with *tert*-butyl 2, 2-dimethyl-3-formylcyclopropane-1-carboxylate (I). However, the product was a mixture of the (E)- and (Z)-isomers (IIIa and IVa), and the content of the (Z)-isomer was less than 17%. Therefore, it became necessary to reinvestigate the reaction to increase the content of the (Z)-isomer. About the reaction of phosphonate carbanion in olefin synthesis Wadsworth and Emmons⁴⁾ proposed the presence of a betain type intermediate which may or may not be in equilibrium with a four-membered ring containing oxygen and phosphorus atoms. Two possible structures of the intermediate are expressed as VII and VIII, which in fragmentation yields (E)- or (Z)-configuration, respectively and a phosphate ester. Since the reaction is exothermic, it is expected that when the reaction is operated at room temperature, the equilibrium between VII and VIII may shift to the former which is thermodynamically more stable and the (E)-isomer may become the main product. On the other hand, an increase in the yield of

* The prefix *trans* refers to the geometry of cyclopropane rings. Z and E are adopted to express the configuration of the trisubstituted double bond in the chrysanthemic acid moiety.

the (Z)-isomer can be expected at lower temperature with polar solvents.

In addition, if the yield of the (E)- and (Z)-isomers is determined from the equilibrium between VII and VIII, the alkyl substituents of the phosphonate may also become an important factor, that is, the bulkier the alkyl group is, the more the content of the (E)-isomer may increase.

As shown in Table I, the yield of the isomers is closely related to the reaction temperature and the alkyl substituents on the phosphonate. These results show that the

condensation of diethyl 1-methoxycarbonyl-ethylphosphonate with aldo-ester (I) at low temperature gives the best result to prepare the (Z)-isomer.

The next problem was the separation of the (E)- and (Z)-isomers. Previous workers³¹ applied column chromatography to *tert*-butyl pyrethrates, however the separation was not complete and was not adequate to obtain the (Z)-isomer effectively. Therefore, the mixture was hydrolyzed at room temperature with an equimolar alkali to yield half-esters V and VI. A fair amount of a neutral oil was

TABLE I. YIELDS OF *tert*-BUTYL (E)- AND (Z)-PYRETHRATE AND PERCENTAGES OF THE (Z)-ISOMER IN THE PRODUCTS.

$\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \diagup \quad \diagdown \\ (\text{RO})_2\text{PCH} \\ \diagdown \quad \diagup \\ \text{COOCH}_3 \end{array}$ R:	Yields of (IIIa+IVa) % ^{a)}		% of IVa in (IIIa+IVa)	
	-60°C	room temp.	-60°C	room temp.
-CH ₃	42.0	54.0	58.0	34.7
-CH ₂ CH ₃	85.6	94.0 ^{b)}	61.5	16.7 ^{b)}
-CH(CH ₃) ₂	84.5	71.3	1.0	1.0

^{a)} based on the aldo-ester (I).^{b)} quoted from the literature³⁾TABLE II. LD₅₀ VALUES OF THE ALLETHRINS BY TWO DIFFERENT METHODS.

Numbers in parentheses show the percentages of dead houseflies at these concentrations.

	Topical application	Injection method	
		1st	2nd
<i>trans</i> -Allethrin I	LD ₅₀ =0.34	LD ₅₀ =0.13	LD ₅₀ =0.20
<i>trans</i> -(E)-Allethrin II	>2.0 (16.7%)	=2.0	=1.6
<i>trans</i> -(Z)-Allethrin II	>2.0 (8.3%)	=2.2	=2.0

LD₅₀: μg/fly

recovered and was proved to be the pure (Z)-ester (IVa). It is obvious that the sterically hindered carbomethoxy group in the (Z)-ester is less reactive than that in the (E)-ester. IVa was first crystallized the melting point being 38°C.

Half-esters V and VI were separated by fractional recrystallization from acetonitrile. The separated isomers were methylated with diazomethane and were changed to (E)- and (Z)-pyrethric acids by the known method,³⁾ respectively.

trans-(Z)-Allethrin II (IVc) was prepared from (±)-allethrolone and (±)-*trans*-(Z)-pyrethric acid (IVb) according to the general method.⁵⁾ The product is a mixture of diastereomers which was not separable on thin-layer or gas chromatograms. However, *trans*-(E)-allethrin II (IIIc) and *trans*-(Z)-allethrin II (IVc) were separated and identified on gas chromatogram.

LD₅₀ value for housefly (*Musca domestica* L.) of *trans*-(Z)-allethrin II (IVc) was determined

by two methods. As summarized in Table II, the toxicity of the (Z)-isomer is a little lower than that of normal allethrin II and this tendency is parallel with the results in topical application and injection methods. Therefore, it is thought that the geometrical isomerism of the trisubstituted double bond in the allethrin II molecule does not seriously affect the insecticidal activity.

EXPERIMENTAL

All boiling points and melting points are uncorrected.

The phosphonates (II) were prepared by the Michaelis-Arbuzov reaction^{3,4)} from methyl α-bromopropionate and the corresponding trialkyl phosphites.

1. Preparation of *tert*-butyl (±)-*trans*-(E)- and (Z)-pyrethrates (IIIa) and (IVa).

1) Condensation of an aldo-ester (I) with diethyl 1-methoxycarbonylethylphosphonate (IIb) at low temperature (general method). To a solution of sodium methoxide (1.2 g, 22.2 mmoles) in anhydrous dimethylformamide

(20 ml) was added diethyl 1-methoxy-carbonylethylphosphonate (IIb) (4.9 g, 21.9 mmoles) and the mixture was stirred for 1 hr at room temperature. The reaction mixture was cooled to -70°C in a dry ice-acetone bath, and the solution of the aldo-ester (I) (3.7 g, 18.7 mmoles) in anhydrous dimethylformamide (10 ml) was added dropwise at this temperature.

Stirring was continued for 4 hr below -60°C , and for further 10 hr at room temperature. The reaction mixture was poured into ice-water, acidified with hydrochloric acid and extracted with ether. The ether extract was washed with water and a sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the ether afforded an oily liquid which was distilled under reduced pressure. The fraction boiling at $115\sim 136^{\circ}\text{C}$ (6 mmHg) was proved to be a mixture of the (E)-isomer (IIIa) (38.5%) and the (Z)-isomer (IVa) (61.5) by gaschromatographic analysis. Yield: 4.3 g (85.6%).

2) *Condensation of the aldo-ester (I) with dimethyl 1-methoxycarbonylethylphosphonate (IIa) at low temperature.* Condensation of the aldo-ester (I) (3 g) with the phosphonate (IIa) (3.5 g) under the same condition as described above gave a mixture of IIIa (42.0%) and IVa (58.0%). Yield: 1.7 g (42%).

3) *Condensation of the aldo-ester (I) with diisopropyl 1-methoxycarbonylethylphosphonate (IIc) at low temperature.* The phosphonate (IIc) (16 g) was successively treated with an equimolar amount of sodium hydride, and the aldo-ester (I) (11 g) as described above to give almost the pure (E)-isomer (IIIa) (Contamination of IVa was less than 1%). Yield: 12.6 g (84.5%).

4) *Condensation of the aldo-ester (I) with dimethyl 1-methoxycarbonylethylphosphonate (IIa) at room temperature.* The phosphonate (IIa) (3.7 g) was treated with an equimolar amount of sodium methoxide in dimethylformamide, and then with a solution of the aldo-ester (I) (2.7 g) in dimethylformamide at room temperature as in the case of the condensation of I with IIb.³⁾ Working up in the usual manner gave a mixture of IIIa (65.3%) and IVa (34.7%). Yield: 1.97 g (54%).

5) *Condensation of the aldo-ester (I) with diisopropyl 1-methoxycarbonylethylphosphonate (IIc) at room temperature.* The phosphonate (IIc) (5.0 g) was treated with sodium hydride as in the case of 3), and then with a solution of the aldo-ester (I) (2.9 g) in dimethylformamide at room temperature to give almost pure IIIa, which

contained less than 1% of IVa. Yield: 2.8 g (71.3%).

2. Hydrolysis of a mixture of *tert*-butyl ($\pm$)-*trans*-(E)- and (*Z*)-pyrethrates, (IIIa and IVa), to half-esters (V and VI).

A mixture of IIIa and IVa (19.2 g containing 13.6 g of IVa) was treated with a methanolic solution (80 ml) of potassium hydroxide (4.6 g) at room temperature for 2 days. Methanol was removed under reduced pressure, and water was added to the residue. The neutral fraction was extracted with ether. From the ether extract, 5.3 g of an oil was recovered and proved to be pure IVa by gaschromatographic analysis and its IR spectrum. This diester solidified after vacuum distillation and was recrystallized from petroleum ether, bp $129\sim 134^{\circ}\text{C}$ (6 mmHg), mp $37.5\sim 8.5^{\circ}\text{C}$. *Anal.* Found: C, 67.47; H, 9.20. Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}_4$: C, 67.13; H, 9.03%. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (ϵ): 237.5 (6,100).

The aqueous layer was acidified with hydrochloric acid and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated to give 13.1 g of a crystalline mixture of V and VI.

3. Separation of V and VI by fractional recrystallization.

The above crystalline mixture was dissolved in twenty-fold volumes of acetonitrile and the solution was left stand overnight in a refrigerator. First crystals were obtained as hexagonal or tetragonal plates and recrystallized from *n*-hexane. The compound was determined to be VI by its IR and NMR spectra. Yield: 4.9 g. Mp 138°C . *Anal.* Found: C, 66.58; H, 8.62. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_4$: C, 66.11; H, 8.72%. IR $\nu_{\text{max}}^{\text{KBr}}$ (cm^{-1}): 2400, 1720, 1673, 1614, 1458, 1360, 1201, 1145, 1110, 942, 838, 820, 784, 732. NMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$: 1.20 (3H, s), 1.31 (3H, s), 1.47 (9H, s), 1.97 (3H, d, $J=1.5$ cps), 2.98 (1H, d-d, $J=8.5, 10$ cps), 5.81 (1H, d-q, $J=8.5, 1.5$ cps).

The second crop was needle crystals (2.0 g). This compound was identified as a compound having the structure (V) by the direct comparison of its melting point and IR spectrum with these of an authentic sample of V. Mp 128°C (lit.⁶⁾ 128°C).

The mother liquor was concentrated and repeated fractional recrystallization afforded overall 6.4 g of VI (recovery, 82%) and 4.5 g of V (recovery, 85%).

4. Esterification of VI with diazomethane.

Treatment of an ethereal solution of VI with ethereal diazomethane afforded the pure diester (IVa). Bp

129~34°C (6 mmHg).

5. ($\pm$)-*trans*-(Z)-Allethrin II (IVc).

tert-Butyl ($\pm$)-*trans*-(Z)-pyrethrate (IVa) (1.8 g) was refluxed in 10 ml of toluene with a small amount of *p*-toluenesulfonic acid for 1.5 hr. The acidic fraction was isolated in the usual way. Crude IVb was distilled under reduced pressure. Bp 159°C (5 mmHg). Yield: 1.3 g (91.5%).

The acid (IVb) solidified on standing in a refrigerator and was recrystallized from *n*-hexane-ethyl acetate. Mp 61°C (lit.³⁾ 62~3°C). The above acid (1.2 g) in 15 ml of dry benzene was refluxed with 2 g of thionyl chloride for 2 hr. The solvent and excess thionyl chloride were removed under reduced pressure and the residual oil was added to 20 ml of a dry benzene solution of allethrolone (2 g) and pyridine (3 g) with cooling in an ice-water bath. Stirring was continued for 4 hr, and the reaction mixture was left stand overnight at room temperature. The reaction mixture was poured into ice-dil. hydrochloric acid and extracted with ether. The ether extract was washed with water and a sodium bicarbonate solution and dried over anhydrous magnesium sulfate.

Evaporation of the solvent afforded a yellowish liquid which was chromatographed on neutral alumina. ($\pm$)-*trans*-(Z)-Allethrin II was obtained by benzene elution. Yield: 1.1 g (56.1%). $n_D^{20.6^\circ\text{C}}$ 1.5156. *Anal.* Found; C, 68.98; H, 7.94. Calcd. for $\text{C}_{20}\text{H}_{26}\text{O}_5$: C, 69.34; H, 7.57%. IR $\nu_{\text{max}}^{\text{film}}$ (cm^{-1}): 1730, 1717, 1640, 1318, 1241, 1218, 1155, 1114, 1080, 993, 830, 780. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $\text{m}\mu$ (ϵ): 232 (23,000).

Gaschromatographic analysis of ($\pm$)-trans-(E)-allethrin II (IIIc) and ($\pm$)-trans-(Z)-allethrin II (IVc).

Condition: Column; 1 m $\times$ 3 mm Stainless steel column packed with 10% Silicone SE-30 on chromosorb W. Column temp.; 208°C isothermal. Carrier gas; He (20 cc/min).

Retention time; IVc, 18.5 min; IIIc, 24.0 min.

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