# ALLETHRIN-TYPE ESTERS OF CYCLOPROPANECARBOXYLIC ACIDS AND THEIR RELATIVE TOXICITIES TO HOUSE FLIES

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The synthesis of 4-hydroxy-2-cyclopentenones with various substituting groups in the 2- and 3-positions has been described (1). When acylated with natural *d-trans*-chrysanthemum monocarboxylic acid, these synthetic cyclopentenolones furnished esters that were analogous to the pyrethrins and exhibited insecticidal activity (2). Some of these esters were less toxic to house flies, than the active principle of pyrethrum flowers, while others were considerably more toxic. The most toxic ester was prepared from the cyclopentenolone having as substituents an allyl group in position 2 and a methyl in position 3, by acylation with *d-trans*-chrysanthemum monocarboxylic acid. The same cyclopentenolone when acylated with the *dl*-mixture of the *cis* and *trans* acid furnished an ester which, as allethrin, is being produced commercially. The type of compounds considered is illustrated by the structural formula of allethrin shown below:
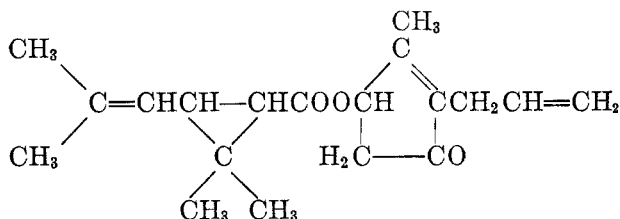
Since certain changes in the structure of the keto-alcoholic component increased the toxicity of the chrysanthemum acid esters, it seemed possible that a further increase might be attained by varying the structure of the cyclopropanecarboxylic acid component or by substituting an acid of entirely different structure.

The only known method for the preparation of chrysanthemum monocarboxylic acid is by the reaction of diazoacetic ester with 2,5-dimethyl-2,4-hexadiene and saponification of the resultant ester. This method, first employed by Staudinger and Ruzicka (3) and since improved by Campbell and Harper (4), is generally applicable to most unsaturated hydrocarbons.

The reaction, which is exothermic, is carried out at atmospheric pressure by adding the diazoacetic ester to an excess of the hydrocarbon, usually at its boiling point, in the presence of copper powder. The yields of the *dl*-cyclopropanecarboxylic acid esters are variable and may be low when the hydrocarbons are low-boiling. Mixtures of geometric isomers of cyclopropanecarboxylic esters are obtained from symmetrical dienes and of structural isomers from unsymmetrical dienes. When the reaction was applied to the two isomeric forms of diisobutylene, the ethyl diazoacetate reacted with 2,4,4-trimethyl-1-pentene but not with 2,4,4-trimethyl-2-pentene. The latter was recovered unchanged and could, in

fact, be separated from mixtures of the two isomers after treatment with diazo-acetic ester.

Several of the cyclopropanecarboxylic acids prepared by Staudinger, *et al.* (5) and esterified with the natural cyclopentenolones of pyrethrum flowers (pyrethrolone) showed definite toxicity to cockroaches, although none approached the pyrethrins in this respect. Of a number of pyrethrolone esters of aliphatic and aromatic acids not containing a cyclopropane group prepared and tested by them, none showed any insecticidal activity. It seemed desirable to repeat the preparation of some of those cyclopropanecarboxylic acids, the pyrethrolone esters of which showed activity against roaches, and to prepare some others of the same type.

The 2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one esters of these cyclopro-panecarboxylic acids were prepared and tested against house flies. The cor-responding esters of unsubstituted cyclopropanecarboxylic acid, 2-furoic acid, 2,2-dimethyl-3-nitrocyclopropanecarboxylic acid,[1] and the monomethyl ester of *d-trans*-chrysanthemum monocarboxylic acid were also prepared. The cor-responding esters of *l-trans*-chrysanthemum monocarboxylic acid,[2] and of *d-trans*-chrysanthemum monocarboxylic acid, previously prepared (1) were included in the group of compounds to be tested, the latter for more direct comparison with the *l-trans*-isomer and the type II analog.

An improved method for preparing diazoacetic esters is described and also a procedure for the preparation of chrysanthemum dicarboxylic acid monomethyl ester and its acid chloride, which was for the first time obtained in crystalline form.

The relative toxicity to house flies of the allethrin-type esters was determined as described in the Experimental section. To show the effect of the chemical changes involved, the toxicity of the esters may be compared with that of al-lethrin, which has been found in a number of comparisons by the Campbell turn-table method, two of which have been reported (6), to be about three times as toxic as the standard of natural pyrethrins. The toxicity relative to allethrin may therefore be obtained from the toxicity relative to pyrethrins, as determined, by simply dividing by three.

All of the new esters were less toxic than allethrin. It may be particularly pointed out that when the double bond in the side chain in the acid component of allethrin is saturated, the toxicity of the ester is decreased to one-third. The presence of this double bond, then, is of marked importance in the toxic action of allethrin, and presumably its analogs.

Previous work (6) had indicated that the ester formed by the acylation of allylmethylcyclopentenolone with the *l-trans*-chrysanthemum monocarboxylic acid would have little or no toxicity as compared with the *d-trans*-isomer. The results given in this article substantiate this conclusion, for they show that the *l-trans*-acid ester was but 2 percent as toxic as the *d-trans*-acid ester. Even this relatively slight toxicity may in fact be due to the presence of an impurity. Configuration is therefore of great importance in the acid component.

[1] Kindly furnished by Prof. L. I. Smith, University of Minnesota.
[2] Kindly furnished by S. H. Harper.

An addition is made to the information on the relationship of the toxicity of type I to type II in the pyrethroids. The ester of *d-trans*-chrysanthemum monocarboxylic acid with the cyclopentenolone having the allyl side chain was 4.4 times as toxic as the ester of *d-trans*-chrysanthemum dicarboxylic acid monomethyl ester with the same cyclopentenolone. In a previous study (7) this ratio for the corresponding esters with the 2,4-pentadienyl side chain (pyrethrin I to pyrethrin II) was found to be 4.3, and for the corresponding esters with the 2-butenyl side chain (cinerin I to cinerin II) 4.0.

Knockdown of flies was high with all compounds, in general paralleling mortality. However, with none of the compounds was it so high as with natural pyrethrins or allethrin.

EXPERIMENTAL

The general procedure for preparing the cyclopropanecarboxylic acids is illustrated by the following example:

2-(1-Methylvinyl)-2-methylcyclopropanecarboxylic acid, ethyl ester. 2,3-Dimethyl-1,3-butadiene (8) (17.2 g., 0.21 mole) was refluxed in a flask containing 1 g. of copper powder. Then 8 g., (0.7 mole) of ethyl diazoacetate was added dropwise for two hours. At the end of this time 1800 ml. of nitrogen had evolved. Upon distillation 6.1 g. of the original hydrocarbon was recovered (b.p. 68–75°/760) and the ester distilled at 80–90°/17; n_D^{25} 1.4450, yield 4.6 g. (39%) based on ethyl diazoacetate.

Anal. Calc'd for $C_{10}H_{16}O_2$: C_2H_5O, 26.8. Found: C_2H_5O, 27.0.

2-(1-Methylvinyl)-2-methylcyclopropanecarboxylic acid. The ethyl ester (4.6 g.) was

$$H_2C \overset{\displaystyle CH_3}{\underset{\displaystyle\quad\; HCCOOH}{\text{—}C\text{—}}}\overset{\displaystyle CH_3}{C}\!\!=\!\!=\!CH_2$$
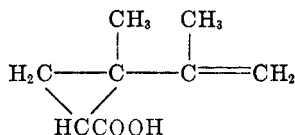
saponified by boiling in 40 ml. of ethanol and 10 ml. of water containing 3.2 g. of potassium hydroxide. The acid was isolated in the usual manner and distilled; b.p. 122–123°/15; yield 2.6 g., n_D^{25} 1.4648.

Anal. Calc'd for $C_8H_{12}O_2$: MW (titration), 140. Found: MW, 147.

The *acid chloride* was prepared with thionyl chloride in petroleum ether. The proportions employed were: acid, 4.4 g.; thionyl chloride, 4.5 g.; petroleum ether, 20 ml.; b.p. 75–85°/15; yield, 2.72 g.

The properties and yields of the other acids and their acid chlorides are presented in Table I and those of their ethyl esters in Table II. Several of the intermediate ethyl esters were not purified completely and those derived from unsymmetrical dienes probably were mixtures. The acids, however, were free of nonacidic impurities.

Acid chloride of chrysanthemum dicarboxylic acid monomethyl ester. First, 75 g. of a concentrate containing 70% of pyrethrin II and 19.5% of pyrethrin I was dissolved in 150 ml. of methanol and the calculated quantity of potassium hydroxide in an equal weight of water was added, allowance being made also for free acid in the concentrate. After standing about one hour at room temperature most of the methanol was distilled off in a vacuum. Water was added to the residue, and the neutral material was removed from the dark-colored solution by extraction with ether. An excess of barium chloride was added to the aqueous solution to remove fatty acids. After filtration with the aid of Filter-Cel the solution was acidified to Congo Red, the separated acids were extracted with petroleum ether, and the solvent was removed. The yield of crude acid mixture was 12–15 g. After most of the monocarboxylic acid had been removed by distillation (b.p. 70–80°/0.1–0.2), the residue was converted to the acid chloride at room temperature with thionyl

chloride (25% excess) in 1.5 volumes of petroleum ether with stirring. The excess solvent and reagent were removed in a vacuum and the acid chloride was distilled; b.p. 94–97°/0.1–0.2. Upon keeping it crystallized in large prisms. For complete purification it was dissolved in an equal volume of warm ligroin (b.p. 60–75°) from which it crystallized when cooled

TABLE I
CYCLOPROPANECARBOXYLIC ACIDS

FORMULA	CODE	B.P., °C.	MM.	MOL. WT. (TITRATION)		n_D^{25}	YIELD, %	ACID CHLORIDE B.P., °C.	MM.
				Calc'd	Found				
H $(CH_3)_2C$—$CCH_2CH(CH_3)_2$ \\/ HCCOOH	B	141–145	20	170	170	1.4490	76	94–96	15
H CH₃ | | H_2C—C—C=CH_2 \\\| H·CCOOH	C	116–118	15	126	128	1.4712	39	62–66	15
CH₃ CH₃ | | H_2C—CCH_2CH_2C=CH_2 \\\| HCCOOH	D	145–146	15	168	168	1.4650	85	102–106	15
CH₃ H CH₃ \ | | C—C—C=CHCH₃ / \\/ CH₃ HCCOOH	E	140–143	15	168	172	1.4695	—	90–95	15
H H_2C—CCH=CHCH₃ \\/ HCCOOH	F	125–128	14.5	130	126	1.4768	50	70–71	14
CH₃ | H_2C—$CCH_2C(CH_3)_3$ \\/ HCCOOH	G	139–141	14.5	170	173	1.4535	81	94–95	14

below 0°, and was washed with the cold solvent. Owing to its solubility there was some loss in this purification. It melted at 62–63°.

Anal. Calc'd for $C_{11}H_{15}ClO_3$: OCH_3, 13.0; Cl, 14.8.

Found: OCH_3, 13.4; Cl, 15.4.

Preparation of esters. The acids were esterified with synthetic 2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one in the manner previously described for the pyrethrins (9).

Ethyl diazoacetate. Several procedures have been described for the preparation of this compound. The one in *Organic Syntheses* (10) gives lower yields than is claimed, because,

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TABLE II

ETHYL ESTERS OF CYCLOPROPANECARBOXYLIC ACIDS

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NAME AND FORMULA	YIELD, %	B.P., °C.	MM.	n_D^{25}	ETHOXYL	
					Calc'd	Found
2-Isobutyl-3,3-dimethyl H $(CH_3)_2C$—$CCH_2CH(CH_3)_2$ $\bigvee$ $HCCOOC_2H_5$	68	100–103	16	1.4347	22.7	25.3
2-(1-Methylvinyl) H CH_3 H_2C—C—C=CH_2 $\bigvee$ $HCCOOC_2H_5$	—	73–75	16.5	1.4480	29.2	29.2
2-(3-Methyl-3-butenyl)-2-methyl CH_3 CH_3 H_2C—C—CH_2CH_2C=CH_2 $\bigvee$ $HCCOOC_2H_5$	58	110–115	15	—	23.0	23.8
2-(1-Methylpropenyl)-3,3-dimethyl CH_3 H CH_3 C—C—C=CHCH_3 CH_3 $HCCOOC_2H_5$	Small	109–114	15	1.4490	23.0	23.9
2-Propenyl H_2C—CH—CH=$CHCH_3$ $\bigvee$ $HCCOOC_2H_5$	—	80–90	14	—	—	—
2-Methyl-2-(2,2-dimethyl)propyl CH_3 H_2C—$CCH_2C(CH_3)_3$ $\bigvee$ $HCCOOC_2H_5$	53.5	98–101	14.5	1.4380	22.7	25.6

we believe, of too low a reaction temperature. The following modified procedure is therefore presented:

A cold solution of 420 g. (3.0 moles) of glycine ethyl ester hydrochloride and 2.1 g. of sodium acetate in 440 ml. of water is poured into a large, open container cooled in an ice-bath. While being stirred with a Hershberg-type stirrer, a cold solution of 315 g. (4.6 moles)

TABLE III

RELATIVE TOXICITY TO HOUSE FLIES OF ALLETHRIN-TYPE ESTERS OF
CYCLOPROPANECARBOXYLIC ACIDS[a]

ACID	CONCENTRATION, MG./ML.	KNOCKDOWN IN 25 MINUTES, %	MORTALITY IN 1 DAY, %	LC-50[b], MG./ML.	RELATIVE TOXICITY, %
		SERIES 1			
B	32	100	100[c]		
	8	100	97	2.73	103
	4	100	70		
	2	98	31		
C	32	100	91[c]		
	16	100	73	9.00	31
	8	100	50		
	4	92	15		
A	32	100	69[c]		
	32	100	69	21.2	13
	16	100	44		
	8	83	5		
E	32	98	84	21.0	13
	16	69	27		
D	32	61	39[d]	—	ca. 6
F	32	98	39	—	ca. 6
H	32	55	7	—	<3
G	32	32	10	—	<3
I	32	88[e]	4	—	<3
Natural pyrethrins	8	100	81	2.82	100
	4	100	66		
	2	100	36		
	1	100	18		
		SERIES 2			
K	16	100	75	10.8	12
	8	95	31		
Natural pyrethrins	8	100	89	1.33	100
	4	100	79		
	2	100	60		
	1	100	44		

of sodium nitrite in 440 ml. of water is added, followed by 250 ml. of ether. The temperature is kept at 20° or slightly lower by the addition of cracked ice. Then 50 ml. of 10% sulfuric acid is slowly added from a cylinder and the reaction mixture is stirred for 15–20

TABLE III—*Concluded*

ACID	CONCENTRATION, MG./ML.	KNOCKDOWN IN 25 MINUTES, %	MORTALITY IN 1 DAY, %	LC-50[b], MG./ML.	RELATIVE TOXICITY, %
		SERIES 3			
J	12.4	100[e]	44	—	16
	6.2	98[e]	20		
Natural pyrethrins	4	100	76	—	100
	2	100	45		
	1	100	25		
		SERIES 4			
L	8	100	78	2.90	135
	4	100	60		
	2	100	35		
	1	100	22		
M	2	100	84	0.658	594
	1	100	72		
	0.5	100	38		
	.25	99	16		
Natural pyrethrins	8	100	80	3.91	100
	4	100	55		
	2	100	16		
	1	100	6		

[a] Six replicates unless otherwise indicated. [b] The concentration causing 50% mortality· The relative standard error for a mean LC-50 estimated from six replications at three concentrations as obtained from an analysis of variance of the individual determinations was 13%. [c] Single test at this concentration. [d] Three replicates. [e] Knockdown increased by acetone.

minutes, or until the reaction subsides. It is then drawn into a separatory-funnel by the application of a vacuum, and the layers are separated. For large-scale runs it is preferable to keep the separatory-funnel cold in an ice-bath. The lower layer is returned to the reaction flask, and the upper ether layer transferred to a smaller separatory-funnel and washed quickly with cold 10% sodium carbonate.

The same cycle of operations is repeated with 200 ml. of ether and 50 ml. of 10% sulfuric acid. A third cycle with 200 ml. of ether and 150 ml. of 10% sulfuric acid solution is usually sufficient to complete the reaction, but if the last ether extract is appreciably yellow, one more cycle may be used. The ether solutions are combined, washed with saturated salt solution, and dried over sodium sulfate, and the ether is removed by careful distillation from a water-bath. To avoid danger of an explosion, the last portion of ether should be removed *in vacuo* with a water pump without heating the residue higher than about 40°. In this manner 297 g. (yield, 86.9%) of ethyl diazoacetate was obtained. This is pure enough for the preparation of the cyclopropanecarboxylic acids.

Approximately the same yield was obtained by this procedure when the proportions of reactants described in *Organic Syntheses* were used. Not only does the present method have the advantage of simple and quick temperature control of the exothermic reaction, but fewer extractions are required because the reaction takes place faster at the higher temperature employed.

RELATIVE TOXICITY

The relative toxicities of the esters as compared with the natural pyrethrins as a standard were evaluated against laboratory-reared adult house flies (*Musca domestica* L.). The compounds were dissolved in refined kerosene, two of them with the aid of acetone as an auxiliary solvent, and sprays were prepared at selected concentrations in the same vehicle. Knockdown and mortality were determined in replicated tests by the turntable method. The standard of comparison was a kerosene extract of pyrethrum flowers, chemical analysis (A.O.A.C. method) showing that 56% of the total pyrethrins consisted of pyrethrin I and cinerin I. Tests were also made at several concentrations with this standard. Approximately 100 flies, averaging 2 to 3 days in age, were used in each test.

Since all the compounds could not be tested against the same populations of flies, the tests were made in several series with the standard included in each series. However, in all but three series there was remarkable uniformity in susceptibility to the standard; the mortality results with pyrethrins were practically identical. Therefore, in Table III the results on the uniform groups are assembled as though made in one series. In the second and fourth series the flies were different in susceptibility; in the third, acetone was used in all the sprays, with the standard as well as the ester being tested.

The acids characterizing the esters are referred to by lettered designations given in part in Table III. A, the example showing the method of preparation is 2-(1-methylvinyl)-2-methylcyclopropanecarboxylic acid; H is cyclopropanecarboxylic acid; I is 2-furoic acid; J is 2,2-dimethyl-3-nitrocyclopropanecarboxylic acid; K is *l-trans*-chrysanthemum monocarboxylic acid; L is *d-trans*-chrysanthemum dicarboxylic acid methyl ester; and M is *d-trans*-chrysanthemum monocarboxylic acid.

The testing of only the more toxic compounds was extended to permit the estimation of the concentrations causing 50% mortality (LC-50). Estimations were made by plotting the mortality results on log-probability paper, fitting straight lines graphically, and then interpolating on these lines. The relative toxicity of the compounds was obtained from the inverse ratios of these concentrations. When the latter were not determined, as with the compounds of low toxicity, the approximate comparisons were made from the original mortality data.

SUMMARY

The allethrin-type esters of a number of cyclopropanecarboxylic acids were prepared, and their relative toxicity to house flies determined by the turntable method. All were less toxic than allethrin. The most toxic ester, that of *dl*-dihydrochrysanthemum monocarboxylic acid, was as toxic as natural pyrethrins. Since the *l-trans*-acid ester was but 2 percent as toxic as the *d-trans*-acid ester, configuration in the acid component is of great importance with respect to toxicity. The toxicity ratio of the type I ester to the type II ester for the allethrin-type esters of the natural *d-trans*-chrysanthemum acids was 4.4 to 1, which is about the same as for pyrethrins I and II and cinerins I and II.

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