Herbicidal activity was also lost when the ring nitrogen in 1 was alkylated (20 and 21).

Many analogs of 1 in which substituents at ring positions 2 and 3 varied were highly active as herbicides (Table III). Acid 22 showed no activity. Methyl ester 23 was surprisingly inactive, while the ethyl (1) and higher esters (24–34) were all highly active. The *n*-propyl (25) and *n*-butyl (27) esters were both less active than their branched-chain isomers (26 and 28–30, respectively). The methyl substituent at position 3 (R_2) was not essential for activity; compounds in which R_2 was hydrogen, trifluoromethyl, ethyl, and propyl (35–38) were all herbicidal

Amide 2 also was one of a series of related pyrrole herbicides (Table IV). Primary (39) and secondary (40–42) amides were inactive while tertiary aliphatic amides 2, 43–48, and 50 were herbicidal. For high activity one of the alkyl groups (R_1, R_2, Table IV) must be methyl (2, 43–48). The diethylamide 50 showed low activity and dipropylamide 51 was inactive. Also inactive were tertiary aromatic amide 49 and cyclic amide 52.

As was found for the pyrrole ester herbicides (Table II), the 4-carbomethoxy substituent was necessary for optimum activity in the amide series (Table V). The propionyl (55) and methylcarbamyl (56) derivatives also were herbicidal but were less active than 43.

Under field conditions, postemergence applications of 1 and incorporated treatments of 2 have controlled tall morningglory (*Ipomoea purpurea*), lambsquarters (*Chenopodium album*), and redroot pigweed (*Amaranthus retroflexus*). Compound 2 has also shown promising results in the greenhouse on cocklebur (*Xanthium pensylvanicum*) and jimsonweed (*Datura stramonium*). Corn (*Zea mays*) exhibited tolerance to both compounds, while peanut (*Arachis hypogaea*) is also tolerant to 1.

The exact mode of action of compounds 1 and 2 has not been studied, but they appear to be slow-acting translocated herbicides. Injury symptoms become apparent about 1 week after treatment. Chlorotic cotyledonary leaf margins are the first visible symptoms, followed by overall chlorosis and then necrosis of the whole leaf. Usually vegetative buds produce only one or two more true leaves following treatment. Neither compound inhibits germination, and plants treated preemergence with 2 rarely produce true leaves.

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New Potent Pyrethroid, Bromethrin

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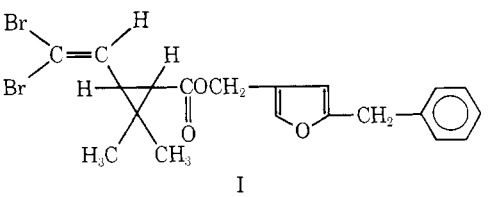
A new pyrethroid was synthesized with insecticidal characteristics similar to those of resmethrin. The new compound, called bromethrin, resembles resmethrin in structure, with replacement of the isobutenyl methyls by bromine atoms. Toxicity studies indicate the *dl-trans*-bromethrin to be similar in toxicity to *d-trans*-resmethrin.

Several studies reported in the literature have indicated that the major pathway of catabolism of pyrethroids in houseflies is through the oxidative degradation of the isobutenyl *trans*-methyl group of the chrysanthemic acid moiety to an inactive carboxyl function (Yamamoto and Casida, 1966, 1969). These findings suggested to us that replacement of the isobutenyl methyl groups by functions resistant to degradation might yield an insecticide of enhanced stability and potency. Farkas *et al.* (1958) have reported the replacement of the isobutenyl methyl groups by chlorine atoms; the resulting toxicity in the allethrin series was found to be similar to that of allethrin. The replacement of the methyl groups by bromine atoms was proposed because of the successes of such replacements in the synthesis of other bioactive analogs (Davern, 1960). We now report the synthesis and preliminary toxicity data for the dibromo analog (5-benzyl-3-furyl)methyl 2-(2,2-dibromovinyl)-3,3-dimethylcyclopropanecarboxylate (I).



I

The acid II was synthesized using commercial ethyl chrysanthemate as the starting material. The ester was ozonized according to the procedure of Ueda and Matsui (1970). The aldehyde produced was then reacted with

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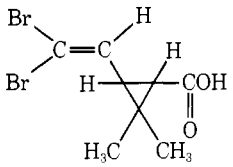
Table I. Dosage–Mortality Test Against Male German Cockroaches by Direct Spray[a]

Compd	% concn	Dosage, ml	% knockdown, min 15	30	60	% kill, hr 24	48
I, *dl-cis:trans* (40:60)	0.075	0.7	58.0	79.5	58.5	84.0	91.0
OTI[b]		0.7	81.5	71.0	77.5	52.0	71.0

[a] Data furnished by Research Laboratory of S. B. Penick and Co. [b] Official Test Insecticide, pyrethrins (1 mg/ml).

dibromomethylenetriphenylphosphorane to give the ethyl ester of II. Esterification of II with (5-benzyl-3-furyl)-



II

methyl alcohol was accomplished to give the ester I, which was purified by recrystallization and column chromatography. Pure *dl-trans*-I was obtained by recrystallization from hexane. Biological testing was performed by S. B. Penick and Co., Orange, N. J., and by the Biological Evaluation of Chemicals Laboratory, USDA, Beltsville, Md.

Toxicity Data. Preliminary toxicity studies of the *cis:trans* pyrethroid (I) (40:60) were made using chlordane-susceptible male German cockroaches, *Blattella germanica* (L.), by the official Cockroach Spray Method (CSMA, 1969) using the Official Test Insecticide (pyrethrins 1.0 mg/ml) as the standard. I at 0.075% concentration had greater toxicity than the standard over 24 hr, but generally had less knockdown activity than the standard (Table I). The *dl-trans*-I was tested against DDT-resistant houseflies, *Musca domestica* L., with *d-trans*-resmethrin and pyrethrins as standards. The insecticides were tested in spray formulations by the Peet-Grady method (CSMA, 1969). The 24-hr LD_{50} values for *dl-trans*-I, *d-trans*-resmethrin, and pyrethrins, respectively, are 0.1, 0.07, and 1.8 mg/ml. These values were obtained from log probability plots of dosage–mortality data (Table II).

DISCUSSION

On a weight basis, *dl-trans*-pyrethroid I is somewhat less toxic than *d-trans*-resmethrin. However, when comparing activities on a molar basis (mol. wt 468 *vs.* mol. wt 338), they are very nearly the same in specific activity. The data presented by Elliott *et al.* (1965) showed that the *d-trans* isomer of resmethrin was more toxic than the *dl* pair. Other *dl* pyrethroids have been shown to have about one-half the toxicity of the pure *d* form (Crombie *et al.*, 1957). Assuming the *l* form of I to be inactive, we may project the LD_{50} value of *d-trans*-I to be 0.05 mg/ml against resistant houseflies.

On the basis of the toxicity studies to date and the comparison with other literature reports, it appears that the replacement of the isobutenyl methyls by bromine atoms has been effective in producing an insecticide of increased toxicity.

EXPERIMENTAL SECTION

All melting and boiling points were uncorrected. The ethyl chrysanthemate used was purchased from Aldrich Chemical Co., Milwaukee, Wis. Dichloromethane was distilled over phosphorous pentoxide and used immediately. Nmr spectra were recorded using a Jeolco JNM-PS-100. Where analyses are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values.

Table II. Dosage–Mortality Tests Against Resistant Houseflies by Peet-Grady Method

Insecticide, mg/ml of Bayol	No. of tests	% knockdown, min 5	10	% kill in 1 day Total insects	Male	Female
			dl-trans-Bromethrin			
0.0625	3	0	1	37	54	18
0.125	2	0	8	53	67	18
0.25	2	0	74	72	88	50
0.5	2	2	91	89	96	82
1.0	3	36	97	99	100	98
2.0	2	74	100	100	100	100
			d-trans-Resmethrin			
0.0625	3	0	1	47	65	24
0.125	2	0	5	74	92	44
0.25	2	0	84	92	98	84
0.5	2	7	94	98	100	96
1.0	3	48	98	100	100	100
2.0	3	76	100	99.67	100	99
			Pyrethrins			
0.0625	2	0	4	4	5	4
0.125	2	0	10	2	2	0
0.25	2	18	64	7	8	6
0.5	2	57	92	4	4	3
1.0	3	78	98	36	48	17
2.0	2	95	98	54	79	16

Ethyl 2,2-Dimethyl-3-formyl-1-cyclopropanecarboxylate. Ethyl chrysanthemate, 39.0 g, was added to 150 ml of glacial acetic acid. The solution was cooled to 8–12° and ozone was introduced for 5 hr in a stream of oxygen at a rate such that no ozone could be detected using moist potassium iodide–starch paper. When ozone was detected in the effluent gas, 150 ml of diethyl ether was added and ozonolysis was discontinued. Zinc powder, 51.0 g, was added with stirring to the ozonized solution; the temperature was not allowed to rise above 17°. After 1½ hr, the solution was filtered and 500 ml of distilled water was added to the filtrate, along with 100 ml of diethyl ether. The ether extract was washed with 300 ml of water and then with 500 ml of 5% aqueous sodium carbonate. The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give 26.5 g of clear oil. Gas chromatographic analysis indicated two major components in the ratio of 63:37. The oil was not purified further, but was used directly.

Ethyl 2-(2,2-Dibromovinyl)-3,3-dimethyl-1-cyclopropanecarboxylate. Carbon tetrabromide, 46.0 g, was added to 600 ml of dichloromethane. Triphenylphosphine, 75.0 g in 150 ml of dichloromethane, was added dropwise with stirring under nitrogen to the carbon tetrabromide solution at 20–35°. A red color appeared initially and after 10 min a yellow precipitate formed. The addition was complete after 15 min, and stirring was continued for an hour. The aldehyde prepared above, 26.5 g, was then added in 50 ml of dichloromethane (dropwise with cooling) to the solution containing the yellow precipitate. The temperature was maintained at 20–30° and stirring was continued for 2 hr. The dichloromethane was removed *in vacuo* and hexane was added to the residual oil. A precipitate formed and was removed by filtration. Evaporation of the filtrate *in vacuo* gave 26.5 g of oil. The precipitate obtained from the above solution was refluxed 1½ hr in benzene, and the benzene was removed *in vacuo*. Hexane was added and the white crystalline material which formed was removed by filtration. The filtrate was evaporated *in vacuo* to give 13.4 g of light brown oil. The oil fractions were combined and distilled to give 25.8 g of clear liquid: bp 95–97° at 0.4 mm; nmr $\delta_{TMS}^{CDCl_3}$ 6.08 (1 H, d), 6.70 (1 H, d), 4.1 (2 H, m).

Fifteen grams of the above ester was hydrolyzed in 25% aqueous ethanol with 3.0 g of sodium hydroxide for 3 hr. The ethanol was removed *in vacuo*. The residual solution was extracted with diethyl ether to remove unhydrolyzed material. The aqueous phase was acidified with 10% sulfuric acid and extracted with diethyl ether. The ether extract was dried with anhydrous magnesium sulfate. The ether was removed *in vacuo* to give 10.0 g of crude light yellow oil which crystallized on standing in the refrigerator. Recrystallization from ethanol-water gave 7.7 g of white crystals, mp 82–84°. Fractional crystallization from ethanol-water gave white needles: mp 117–118°; nmr δ_{TMS}^{CDCl3} 1.22 (3 H, s), 1.32 (3 H, s), 1.63 (1 H, d), 10.36 (1 H, s). *Anal.* for $C_8H_{10}O_2Br_2$, C, H.

(5-Benzyl-3-furyl)methyl 2-(2,2-Dibromovinyl)-3,3-dimethylcyclopropanecarboxylate. 2-(2,2-Dibromovinyl)-3,3-dimethylcyclopropanecarboxylic acid, 2.5 g, was added to 500 ml of dry benzene. 5-Benzyl-3-furyl methyl alcohol, 4.0 g, was dissolved in 50 ml of dry benzene and added to the acid solution in the dark. Cyclohexylcarbodiimide, 3.0 g, was then added to the solution, which then stood for 48 hr in the dark. A white precipitate formed, which was filtered from the solution. The benzene was removed from the filtrate *in vacuo* in the dark to give a light yellow oil. Purification of the final product was accomplished employing silica gel chromatography. Two fractions, obtained by elution with hexane, gave, upon concentration *in vacuo*, 1.9 g of a clear oil. Recrystallization from hexane gave the pure *dl-trans* isomer, 0.5 g: mp 65°; nmr δ_{TMS}^{CDCl3} 1.12 (3 H, s), 1.20 (3 H, s), 1.56 (1 H, d), 2.10 (1 H, m), 3.84 (2 H, s), 4.80 (2 H, s), 5.88 (1 H, s), 6.00 (1 H, d), 7.08 (6 H, m). *Anal.* for $C_{20}H_{20}O_3Br_2$, C, H; ir (carbonyl) 1730 cm^{-1}.

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Metabolism of Methomyl in the Rat

John Harvey, Jr.,* Arthur G. Jelinek, and Henry Sherman

Radiolabeled methomyl (*S*-methyl [1-^{14}C]*N*-[(methylcarbamoyl)oxy]thioacetimidate) was administered orally to rats. Essentially all of the radioactivity was rapidly eliminated from the animal body within 24 hr in the ratio of 1 part [^{14}C]carbon dioxide, 2 parts [1-^{14}C]acetonitrile, and 1 part urinary metabolites. Although the chemical identity of the polar radiolabeled material excreted in the urine has not been established, the absence of methomyl, *S*-methyl *N*-hydroxythioacetimidate, the *S*-oxide of methomyl, and the *S,S*-dioxide of methomyl and conjugates thereof has been demonstrated. The synthesis of these compounds is described.

Methomyl (*S*-methyl *N*-[(methylcarbamoyl)oxy]thioacetimidate) is the active ingredient in Lannate methomyl insecticide (formerly Du Pont Insecticide 1179, E. I. du Pont de Nemours & Co., Inc.). It is effective against pests such as beetles, aphids, thrips, leaf hoppers, and caterpillars, and particularly loopers, beet armyworm, and corn earworm. At the present time, it has been registered by the Environmental Protection Agency for insect control on 13 crops, including tobacco, sweet corn, tomatoes, cabbage, cauliflower, broccoli, and head lettuce.

A method for the determination of methomyl residues using microcoulometric gas chromatography has been published by Pease and Kirkland (1968). Metabolism information furnished in support of registration for methomyl in the United States has been summarized by the IUPAC Commission on Terminal Residues (1970) and by Baron (1971). The original information contained in this and the two papers immediately following presents the experimental details and complete data.

Biochemicals Department and Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours & Co., Inc., Wilmington, Delaware 19898.

EQUIPMENT AND METHODS

Countercurrent fractionations were carried out in a Model EC-520 countercurrent fractionator (100 tubes, 10 ml/phase/tube) manufactured by the E-C Apparatus Company, Philadelphia, Pa.

Gas chromatography was carried out using a F&M model 720 dual-column programmed temperature gas chromatograph equipped with a thermal conductivity detector.

Silica gel tlc plates were prepared by the following procedure: 3.6 g of Du Pont luminescence chemical No. 609 and 152 ml of water were mixed in a Waring blender at low speed. To this was added 1.8 g of Baymal and 54 g of Kieselgel and the mixture was blended for 3 min. Thin-layer chromatographic apparatus from Colab (Shandon Unoplan Leveller) was used to spread the films with a thickness of 250 μ. The plates were allowed to air-dry for 24 hr, and then were placed in an oven at room temperature. The oven was slowly heated to 110° and held at this temperature for 2 hr. Finished plates were stored in a desiccator until used.

Instruments used in the characterization of the methomyl metabolites were the Bendix Time-of-Flight Model