terpretation may be correct since some of the resmethrin metabolites [(+)-*trans*-CA, BFA, and BFCA] are much more toxic than resmethrin. However, it is obvious that these metabolites do not accumulate to toxic levels except when exceedingly high doses of (+)-*trans*-resmethrin are administered.

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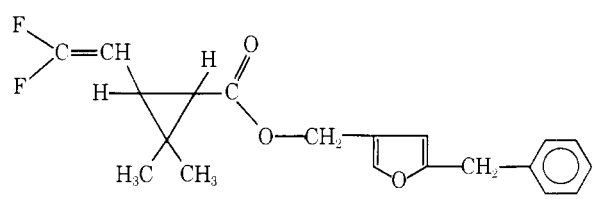
Halopyrethroids. II. A Difluoropyrethroid

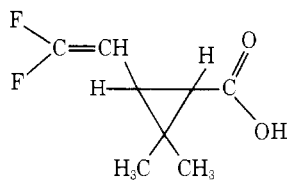
Dale G. Brown, Otelia F. Bodenstein, and Scott J. Norton*

The fluorine-containing pyrethroid, (±)-*trans*-(5-benzyl-3-furyl)methyl 3-(2,2-difluorovinyl)-2,2-dimethylcyclopropanecarboxylate, has been synthesized and its insecticidal potency studied in DDT-susceptible house flies, yellow-fever mosquitoes, and chlordane resistant German cockroaches. This pyrethroid, called fluorethrin, is superior to both bromethrin and resmethrin in insecticidal quality. Additional insect toxicity studies of bromethrin are also included.

Studies in this and other laboratories have involved the synthesis of pyrethroids having increased insecticidal toxicity. In an earlier paper we reported the synthesis of a potent pyrethroid, bromethrin, and preliminary toxicity data were given (Brown *et al.*, 1973). This pyrethroid, which has also been synthesized and reported by others (Elliott *et al.*, 1973), resulted from the replacement of the isobutenyl methyl groups of chrysanthemic acid with bromine atoms followed by esterification of this acid moiety with (5-benzyl-3-furyl)methyl alcohol. Comparative toxicity studies of this compound were made with the known pyrethroid of analogous structure, resmethrin (Elliott, 1967). Due to the previous successes with both bromine and chlorine replacements of the isobutenyl methyl groups of the chrysanthemic acid moiety (Elliott *et al.*, 1973; Farkas *et al.*, 1958), we wished to investigate the insecticidal activity of analogous pyrethroids having fluorine atom replacements. We wish to report the synthesis and certain toxicity data for the difluoro analog (±)-*trans*-(5-benzyl-3-furyl)methyl 3-(2,2-difluorovinyl)-2,2-dimethylcyclopropanecarboxylate (I), which we call fluorethrin. Additionally, we wish to report more extensive insect toxicity data for the previously reported pyrethroid, bromethrin.



I



II

The acid moiety (II) was synthesized starting from commercial ethyl chrysanthemate as the starting material. This material, after initial ester hydrolysis and isolation of

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Table I. Relative Effectiveness of Fluorethrin and Bromethrin against DDT-Susceptible House Flies[a]

Compound	Rel 5-min KD_{90}	Rel LC_{50}	Slope of probit regression lines[b]
(±)-*trans*-Fluorethrin	5	84	3.0
(±)-*trans*-Bromethrin	1	28	2.7
Pyrethrins	1[c]	1[d]	2.6

[a] See Biological Testing section. [b] Finney (1947). [c] Pyrethrins standard assigned a value of unity. The $KD_{90} \simeq 1.1$ mg/ml. [d] Pyrethrins standard assigned a value of unity. The $LC_{50} \simeq 1.2$ mg/ml.

Table II. Relative Toxicity of Fluorethrin and Bromethrin against Free-Flying Yellow-Fever Mosquitoes[a]

Compound	Rel LC_{50}	Slope of probit regression lines[b]
(±)-*trans*-Fluorethrin	3	1.6
(±)-*trans*-Bromethrin	2	3.3
Pyrethrins	1[c]	1.8

[a] See Biological Testing section. [b] Finney (1947). [c] Pyrethrins standard assigned a value of unity. The $LC_{50} \simeq 0.09$ mg/ml.

the trans acid (Matsui and Ueda, 1971), was reesterified with *tert*-butyl alcohol, and then ozonized according to the procedure of Ueda and Matsui (1970). The resulting aldehyde was then allowed to react with the appropriate ylide, (difluoromethylene)triphenylphosphorane, which was generated *in situ* from sodium chlorodifluoroacetate in the presence of triphenylphosphine. The resulting *tert*-butyl ester of II was then hydrolyzed and reesterified with (5-benzyl-3-furyl)methyl alcohol to give the desired (±)-*trans* ester (I). Purification of the final product was accomplished by silica gel column chromatography. Biological testing was performed by the Biological Evaluation of Chemicals Laboratory, U. S. Department of Agriculture, Beltsville, Md.

Biological Testing. (±)-*trans*-I and (±)-*trans*-bromethrin were tested against DDT-susceptible house flies, *Musca domestica* L., and free-flying yellow-fever mosquitoes, *Aedes aegypti* (L.), with pyrethrins as a standard. The insecticides were tested in spray formulations against house flies by the Peet–Grady method (CSMA, 1969) and against mosquitoes by a modification of this method (Fales *et al.*, 1952). Spray formulations were prepared employing a commercial brand of deodorized kerosene. Relative effectiveness was calculated by comparison of KD_{90} and LC_{50} values which were taken from probit analysis of replicate tests (Finney, 1947). Pyrethrin standards were assigned a value of unity for both knockdown and kill. Residue tests on I and (±)-*trans*-bromethrin against chlordane-susceptible male German cockroaches, *Blattella germanica* (L.), were made by the residue jar method (Keller *et al.*, 1956) at a concentration of 10 mg/929 cm^2.

RESULTS AND DISCUSSION

Relative effectiveness data for the halogen-containing pyrethroids are given in Tables I and II. These pyrethroids were tested in oil base sprays against DDT-susceptible house flies and against yellow-fever mosquitoes with pyrethrins as a standard.

In Table I fluorethrin is shown to be about three times more lethal to susceptible house flies than bromethrin. It is also interesting to note the substantial enhancement of knockdown activity exhibited by fluorethrin (fivefold greater than that of bromethrin). As seen in this and in our earlier report (Brown *et al.*, 1973) bromethrin has knockdown activity that is no greater than that of pyrethrins. It is apparent that the nature of the halogen substituents in the dihalovinyl side chain is a major influence in determining rapid knockdown potency. In a preliminary study (parallel tests, data not given here), fluorethrin exhibited greater knockdown activity than NRDC 106 (1-methyl 3-(5-benzyl-3-furyl)methyl *trans*-(+)-3-carboxy-α,2,2-trimethylcyclopropaneacrylate), one of the most potent pyrethroids in knockdown activity (Fales, *et al.*, 1972).

Table III. Effectiveness of Residues against Adult Male Chlordane-Resistant German Cockroaches[a]

Compound	Age of residue, weeks	% dead plus moribund at days 0	1	2	3
	Series I				
(±)-*trans*-Bromethrin	Fresh	100			
	1	100			
	2	0	10	10	10
Chlordane	Fresh	0	0	0	60
	1	0	0	0	50
	2	0	0	0	10
	Series II				
(±)-*trans*-Fluorethrin	Fresh	100			
	1	100			
	2	0	80	100	
	4	0	20	20	60
Chlordane	Fresh	0	0	0	0
	1	0	0	0	10
	2	0	0	0	0

[a] Single test at 10 mg/929 cm^2.

In dose–mortality tests against free-flying yellow-fever mosquitoes (Table II) fluorethrin and bromethrin are both superior to pyrethrins. The trend of increased toxicity going from bromo substituents to fluoro substituents on house flies is also borne out in the mosquito toxicity tests, although the difference in relative toxicities (LC_{50} values) for the two halopyrethroids is not great. Moreover, it should be noted that the slope of the regression line for bromethrin is considerably greater than that for fluorethrin. At higher kill percentages (>70%), bromethrin would be superior to fluorethrin in kill of yellow-fever mosquitoes. Preliminary tests of relative knockdown have shown fluorethrin to be superior to pyrethrins against free flying yellow-fever mosquitoes.

Table III gives residue toxicity data for both bromethrin and fluorethrin against chlordane-resistant male German cockroaches. As can be seen from this table the effectiveness of these pyrethroids after application is approximately 1 week under the conditions employed in this study.

Halogen substitutions for the methyl groups of the isobutenyl side chain of the chrysanthemic acid moiety of resmethrin have been shown in this study and in others to enhance both knockdown and toxicity for certain insects (Brown *et al.*, 1973; Elliott *et al.*, 1973). It appears from data reported in the above studies, and also from unpublished data in this laboratory, that the halogen substituent effectiveness in a variety of halogen-containing pyrethroids is (in increasing order of toxicity) Br < Cl ≲ F. Data are not available for iodine atom substituents in pyrethroids.

(+)-*trans*-Bromethrin has been resolved from the racemic mixture by use of D(−)-threo-2-(dimethylamino)-1-(*p*-nitrophenyl)-1,3-propanediol (Muller *et al.*, 1968). Preliminary toxicity studies of the resolved compound have shown that the (+) form is approximately twice as active as the (±) form ((+)-*trans*-resmethrin is also approximately twice as toxic to insects as the racemic form) (Casida, 1973). It is probable that the resolution of (±)-*trans*-fluorethrin to the (+) enantiomer will also result in a significant increase in insecticidal activity.

EXPERIMENTAL SECTION

All melting and boiling points were uncorrected. Ethyl chrysanthemate was purchased from Pfaltz and Bauer, Inc., Flushing, N.Y. Nmr spectra were taken employing a Jeolco JNM-PS-100 or a JNM-MH60-II.

(±)-*trans*-3-(2,2-Difluorovinyl)-2,2-dimethylcyclopropanecarboxylic Acid. *tert*-Butyl (±)-*trans*-3-formyl-2,2-dimethylcyclopropanecarboxylate, 22.0 g, and triphenylphosphine, 33.5 g, were dissolved in 100 ml of dimethylformamide and placed in a three-necked flask. The flask was fitted with a nitrogen inlet tube, reflux condenser, and powder inlet port, and was heated in an oil bath to 165–170° (bath temperature). Sodium chlorodifluoroacetate, 25.5 g, was added over 1 hr (carbon dioxide was evolved). The reaction flask was cooled and the contents were washed with water and diethyl ether. The ether was dried over anhydrous magnesium sulfate and removed *in vacuo*. Distillation of the residue afforded 9.0 g of colorless oil: bp 80–90° (17 mm); nmr ($CDCl_3$) δ 3.98 (ddd, 1, J = 3, 8, 24 Hz, =CH), 1.89 (m, 1), 1.52 (d, 1, J = 5 Hz, $CHCO_2$), 1.44 (s, 9), 1.22 (s, 3), and 1.12 ppm (s, 3). Hydrolysis of the *tert*-butyl ester, 9.0 g, was carried out with *p*-toluenesulfonic acid in refluxing toluene to give 5.0 g of crude acid. Recrystallization from cold hexane gave 4.5 g of white solid which melted below room temperature: nmr ($CDCl_3$) δ 11.98 (s, 1), 4.06 (ddd, 1, J = 3, 8, 24 Hz, =CH), 2.00 (m, 1), 1.47 (d, 1, J = 6 Hz, $-CHCO_2$), 1.28 (s, 3), and 1.12 ppm (s, 3). An amine salt of the acid was prepared from D(−)-*threo*-2-dimethylamino-1-(*p*-nitrophenyl)-1,3-propanediol, mp 132–134°. *Anal.* Calcd for $C_{19}H_{26}F_2N_2O_5$: C, 56.99; H, 6.55; N, 7.00. Found: C, 56.84; H, 6.78; N, 7.15.

(5-Benzyl-3-furyl)methyl (±)-*trans*-3-(2,2-Difluorovinyl)-2,2-dimethylcyclopropanecarboxylate. 3-(2,2-Difluorovinyl)-2,2-dimethylcyclopropanecarboxylic acid, 4.5 g, was added to 50 ml of hexane containing 2.7 ml of thionyl chloride. After standing 24 hr, the hexane was removed and excess $SOCl_2$ removed *in vacuo*. The crude acid halide was added to a solution of 3.0 ml of pyridine and 3.7 g of (5-benzyl-3-furyl)methyl alcohol in 250 ml of dry benzene. After standing overnight in the dark, the pyridine hydrochloride was filtered off and the benzene removed *in vacuo*. The ester was purified employing silica gel chromatography and eluting with hexane–ethyl acetate (9:1). Removal of the solvents *in vacuo* gave a colorless oil: nmr ($CDCl_3$) δ 7.28 (s, 1, =CHO), 7.18 (s, 5, C_6H_5), 6.00 (s, 1), 4.88 (s, 2), 4.00 (ddd, 1, J = 3, 8, 24 Hz), 3.88 (s, 2), 2.00 (m, 1), 1.44 (d, 1, J = 6 Hz, $-CHCO_2$), 1.20 (s, 3), and 1.05 ppm (s, 3). *Anal.* Calcd for $C_{20}H_{20}F_2O_3$: C, 69.35; H, 5.82. Found: C, 69.54; H, 6.11.

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COMMUNICATIONS

Effects of Freeze-Drying on Residues of TDE, DDT, and Endosulfan in Tobacco

This study was conducted to examine the effect of freeze drying of cured tobacco shreds, with or without extraction, on removal of TDE, DDT, and endosulfan residues. Tobaccos were utilized having initially low and high levels of pesticide. Freeze drying of cured tobacco shreds significantly reduced residue levels, with up to 42% reduction for total TDE, 41% for total DDT, and 43% for total endosulfan. Because of the expansive effect of freeze drying, residue levels on a volumetric basis (micrograms/milliliter) were reduced up to 74%. With the exception of the group of tobacco having low initial levels of TDE and DDT, the extraction step prior to freeze drying did not contribute significantly to pesticide reduction in comparison with standard freeze drying. Analyses of water extracts substantiated this conclusion.

Recognition of pesticide residues on tobacco as a potential health hazard has led to increased emphasis on measures for reducing pesticide levels. The problem of pesticide residues on tobacco was recently discussed (Guthrie and Sheets, 1970; Guthrie, 1973) in the context of changes necessitated by legislation in the Federal Republic of Germany which extended pesticide tolerances to tobacco (Bundesgestzblatt, 1972). This legislation, providing regulations to become effective January 1, 1978, may preclude sale of tobacco to the German manufacturer if residues on