mand (DAMD 17-82-C-2193).

Registry No. Ca, 7440-70-2; arylester hydrolase, 9032-73-9.

LITERATURE CITED

Aldridge, W. N. *Biochem. J.* **1953**, *53*, 110–117.
Brealey, C. J.; Walker, C. H.; Baldwin, B. C. *Pestic. Sci.* **1980**, *11*, 546.
Chemnitius, J. M.; Losch, H.; Losch, K.; Zech, R. *Comp. Biochem. Physiol.* **1983**, *76C*, 85–93.
Eiberg, H.; Mohr, J.; Schmiegelow, K.; Nielsen, L. S.; Williamson, R. *Clin. Genet.* **1985**, *28*, 265–271.
Grothusen, J. R.; Bryson, P. K.; Zimmerman, J. K.; Brown, T. M. *J. Agric. Food. Chem.*, previous paper in this issue.
Kojima, K.; O'Brien, R. D. *Agric. Food Chem.* **1968**, *16*, 574–584.
Laemmli, M. K. *Nature* **1970**, *227*, 680–685.
Lenz, D. E.; Deguehery, L. E.; Holton, J. S. *Biochim. Biophys. Acta* **1973**, *321*, 189–196.
Mackness, M. I.; Walker, C. H. *Biochem. Pharmacol.* **1983**, *32*, 2291–2296.
Main, A. R. *Biochem. J.* **1960**, *74*, 10–20.
McIlvain, J. E.; Timoszyk, J.; Nakatsugawa, T. *Pestic. Biochem. Physiol.* **1984**, *21*, 162–169.
Neilsen, B. L.; Brown, L. R. *Anal. Biochem.* **1984**, *141*, 311–315.
Walker, C. H.; Mackness, M. I. *Biochem. Pharmacol.* **1983**, *32*, 3265–3269.
Zech, R.; Wigand, K. D. *Experientia* **1975**, *31*, 157–158.
Zech, R.; Zücher, K. *Comp. Biochem. Physiol.* **1974**, *48B*, 427–433.
Zimmerman, J. K.; Brown, C. S. *A Biochemical Laboratory Manual*, 2nd ed.; Burgess Publishing: Minneapolis, MN, 1977.

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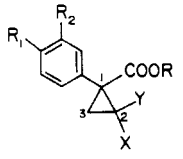
Synthesis and Biological Activity of DDT–Pyrethroid Insecticides

George Holan, Wynona M. Johnson,* Christopher T. Virgona, and Reimund A. Walser

Thirty-five examples of DDT–pyrethroid insecticides have been synthesized. The halo-substituted cyclopropyl rings were formed by the addition of thermally or phase-transfer generated halocarbenes, to suitably substituted 2-aryl acrylates **3**. It was found that the 1-aryl-2,2-difluorocyclopropane-1-carbonyl chlorides were susceptible to ring cleavage to give substituted butyrates as products. In contrast, the 1-aryl-2,2-dichlorocyclopropane-1-carbonyl chlorides underwent ring-opening–ring-closure reactions as demonstrated by the racemization of these compounds during esterification reactions. Structure–activity studies revealed that for optimum insecticidal activity the substituents required at C-2 of the cyclopropane ring were two fluorine, one chlorine and one fluorine, or two chlorine atoms. These studies also revealed that substitution by fluorine at the 4-position of the 3-phenoxybenzyl moiety increased the toxicity of these compounds to *Heliothis punctigera* (Wall) but not to *Lucilia cuprina* (Weid.) or *Blatella germanica* (L.)

The rational design of a group of insecticides that possesses combined DDT–pyrethroid structures, e.g. **1**, has



1

X = Y = F, Cl, Br
X = F, Y = Cl
X = F, Y = Br
X = Cl, Y = Br
R_1 = OEt, Cl, F, etc., R_2 = H
R_1R_2 = $-OCH_2O-$
R = pyrethroid alcohol component

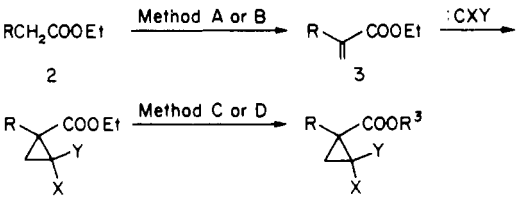
been reported previously (Holan et al., 1979). The biological activities of DDT and pyrethroid compounds have been compared to some of these new structures (Holan et al., 1978). This paper describes the preparation of some of these structures and extends the above work by describing the synthesis and biological activity of several new series of insecticidal DDT–pyrethroid esters.

It is hoped that the systematic structure–activity analysis will assist in the design of new highly active and selective insecticides, as well as in the future elucidation of the shape and nature of the neuroreceptor(s) for the DDT–pyrethroid compounds.

EXPERIMENTAL SECTION

General Procedures. Microanalyses were performed by Microanalytical Services, Amdel, Melbourne. Melting points were determined with a Mettler FP5/FP51/FP52. Proton (^1H) NMR spectra were recorded at 60, 90, or 250 MHz with Varian Associates EM 360, EM 390, or Bruker WH 250 spectrometers, respectively. Tetramethylsilane was used as an internal standard, and deuteriochloroform was used as solvent. IR spectra were recorded on Perkin-Elmer 710B or 783 spectrometers. High-performance liquid chromatography (HPLC) was carried out with a Waters Associates M-6000 pump with a Model U6K valve injector. Eluates from the column were monitored with a Model 440 UV detector. The chromatographic columns used were (A) 250 × 21.2 mm Du Pont SIL and (B) 300 × 3.9 mm μ-Porasil. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter using solution of 1% in $CHCl_3$ unless otherwise stated. Supplementary material containing spectral and analytical data is available (see paragraph at end of paper regarding supplementary material).

Scheme I



Method A (1) $(EtOOC)_2$, NaOEt (2) HOAC (3) HCHO, K_2CO_3

Method B HCHO, K_2CO_3, DMF

Method C (1) 1N NaOH/EtOH (2) $SOCl_2$, pyr (3) R^3OH, pyr

Method D (1) 1N NaOH/EtOH (2) Et_3N, R^3Br, acetone

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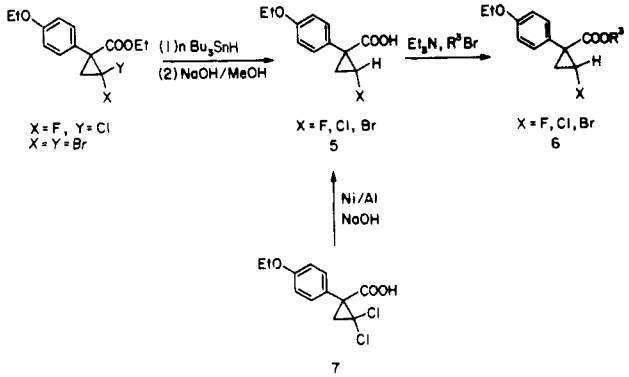
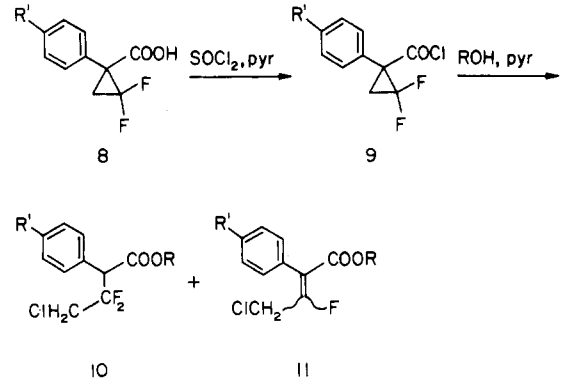
Scheme II



Scheme III



Synthetic Methods. The syntheses of the insecticidal esters **1** and **6** are shown in Schemes I and II. The synthetic details and proof of the relative stereochemistry of the substituents around the cyclopropyl ring for esters **6** (Scheme II) are reported elsewhere (Johnson et al., 1986). The key intermediate acrylates **3** were prepared by either method A—a published three-step method (Holan and Walser, 1982)—or method B—a one-step procedure described herein. Esters **4**, after hydrolysis, were reesterified by either method C—conversion to the acid chloride, followed by the addition of an alcohol (Holan and Walser, 1982)—or method D—an alkylation with a substituted benzyl halide in the presence of a tertiary amine base. The authors gratefully acknowledge the generous gift of 4-fluoro-3-phenoxybenzaldehyde from Dr. K. Naumann of Bayer AG. The 4-fluoro-3-phenoxybenzaldehyde was transformed to 4-fluoro-3-phenoxybenzyl bromide by standard procedures ($NaBH_4$, PBr_3). Resolution of the acids to produce optically pure esters **1** were carried out with either (−)-α-methylbenzylamine (Holan and Walser, 1982) or (−)-pantolactone (Duke and Wells, 1982) as the resolving agents.

Ethyl 2-(4-Ethoxyphenyl)propenoate. [Method B is typical of the one-step preparation used to prepare many of the acrylates **3**.] To a solution of ethyl (4-ethoxyphenyl)acetate (41.6 g, 0.2 mol), DMF (100 mL), and tetrahydroquinone (0.1 g), at 60 °C, was added (1.5-g portions), at 15-min intervals, a mixture of finely ground K_2CO_3 (27.6 g, 0.2 mol) and paraformaldehyde (12 g, 0.4 mol). At the end of the addition, the reaction mixture was kept at 60 °C for a further 18 h and cooled, and ether was added. The mixture was filtered, and the filtrate was washed with water and dried (Na_2SO_4). The concentrated residue was triturated with petroleum ether (40–60 °C), and the solution was filtered through a short silica gel column to afford the desired acrylate (20 g, 45%) as a colorless oil: 99.5% pure by GLC analysis; IR (film) 1728, 1625, 1590 cm^{-1}; NMR δ 1.33, 1.43 (2 t, J = 7 Hz, 2 CH_3), 4.07, 4.32, (2 q, J = 7 Hz, 2 CH_2CH_3), 5.83, 6.25 (2 d, 2, J = 2 Hz, $=CH_2$), 7.15 (AA'BB', 4, aromatic H).

Ethyl 1-(4-Ethoxyphenyl)-2,2-difluorocyclopropane-1-carboxylate. To a solution of acrylate **3** (R = 4-ethoxyphenyl) (55 g, 0.25 mol) in anhydrous sulfolane (150 mL) at 160 °C was added portionwise over 3 h sodium chlorodifluoroacetate (95 g, 0.63 mol). Additional sulfolane was added as required to maintain stirring. At the end of the addition, the cooled reaction mixture was quenched in water (1.5 L) and the aqueous solution extracted with ether. The combined ether layers were washed with water and brine and dried (Na_2SO_4). The concentrated residue was distilled to afford 55 g (82%) of the desired ester: bp 88–92 °C (0.03 mm); IR (film) 1735 (sh), 1725, 1610, 1575 cm^{-1}; NMR δ 1.20, 1.41 (2 t, J = 7 Hz, 2 CH_3), 1.81–1.97, 2.51–2.63 (2 m, 2 1 H, cyclopropyl H), 4.03, 4.16 (2 q, J = 7 Hz, CH_2CH_3), 7.09 (AA'BB', 4, aromatic H). Anal. Calcd for $C_{14}H_{16}F_2O_3$: C, 62.2; H, 6.0; F, 14.1. Found: C, 62.3; H, 6.0; F, 13.7.

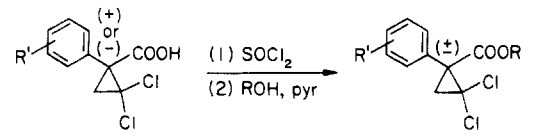
Ethyl 1-(4-Ethoxyphenyl)-2,2-dibromocyclopropane-1-carboxylate. [This procedure is typical of the phase-transfer method of preparation of the 2,2-dihalocyclopropyl esters **4**.]

To a solution of acrylate **3** (R = 4-ethoxyphenyl) (5.5 g, 0.025 mol), bromoform (13.3 g, 0.053 mol), and benzyl triethylammonium chloride (50 mg) in CH_2Cl_2 (5 mL) was added, dropwise over 2 h, a solution of 50% w/w NaOH (10 mL). The temperature was maintained below 30 °C by external cooling. The progress of the reaction was monitored by GLC. When no acrylate remained (~1 h), water (50 mL) was added and the solution was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with water, 10% HCl, water, and brine and dried (Na_2SO_4). The concentrated residue was recrystallized from petroleum ether (40–60 °C) to afford 8.8 g (90%) of the desired ester as white needles: mp 64 °C; IR (KBr) 1718, 1605, 1575 cm^{-1}; NMR δ 1.3, 1.43 (2 t, J = 7 Hz, 2 CH_3), 2.21, 2.56 (AB q, 2, J = 8.5 Hz, cyclopropyl H), 4.06, 4.19 (2 q, J = 7 Hz, 2 CH_2CH_3), 7.2 (AA'BB', 4, aromatic H). Anal. Calcd for $C_{14}H_{16}Br_2O_3$: C, 42.9; H, 4.1; Br, 40.8. Found: C, 42.6; H, 4.4; Br, 40.5.

4-Fluoro-3-phenoxybenzyl 1-(4-Ethoxyphenyl)-2,2-difluorocyclopropane-1-carboxylate. [Method D is typical of the synthesis and purification of the DDT-pyrethroid esters.] To a solution of 1-(4-ethoxyphenyl)-2,2-difluorocyclopropane-1-carboxylic acid (242 mg, 1 mmol) in acetone (2 mL) was added triethylamine (162 μL, 1.2 mmol), followed by 4-fluoro-3-phenoxybenzyl bromide (281 mg, 1 mmol). The reaction mixture was stirred at room temperature for 18 h. At the end of this period, the mixture was filtered and concentrated. The residue was chromatographed on Merck silica gel, mesh 230–400, with 5% EtOAc/petroleum ether (40–60 °C) as eluting solvent to afford 380 mg (86%) of the desired ester as a colorless oil: IR (film) 1735, 1610, 1590 cm^{-1}; NMR δ 1.37 (t, 3, J = 7 Hz, CH_3), 1.6–2.07, 2.3–2.77 (2 m, 2, cyclopropyl H), 3.93 (q, 2, J = 7 Hz, CH_2CH_3), 5.0 (s, 2, CH_2), 6.57–7.48 (m, 12, aromatic H). Anal. Calcd for $C_{25}H_{21}F_3O_4$: C, 67.87; H, 4.78; F, 12.9. Found: C, 67.84; H, 4.92; F, 12.6.

Esterification Reaction—Scheme III. A solution of 1-(4-ethoxyphenyl)-2,2-difluorocyclopropane-1-carboxylic acid (2.42 g, 0.01 mol) in thionyl chloride (2.4 g, 0.02 mol) containing dry pyridine (3 drops) was heated to 60 °C for 2 h. The excess thionyl chloride was removed under reduced pressure, and dry benzene (5 mL) was added to the residue. To this solution was added 3-phenoxybenzyl alcohol (2 g, 0.01 mol) and pyridine (0.8 g, 0.01 mol) in dry benzene (5 mL). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was filtered,

Scheme IV



12 13

and the filtrate was washed with 10% HCl, water, 10% $NaHCO_3$, and water and dried (Na_2SO_4). The concentrated residue was chromatographed on silica gel to yield 4.1 g (90%) of a 7:3 mixture of ring-opened esters **10** and **11**. These compounds were separated by HPLC, column B, 1.5% EtOAc/petroleum ether (40–60 °C). Ester **10** was eluted first as a colorless oil: IR (film) 1735, 1615, 1585 cm^{-1}; NMR (250 MHz) δ 1.40 (t, 3, J = 7 Hz, CH_3), 3.5, 3.91 (2 q, 2 1 H, J = 13 Hz, CH_2Cl), 4.43 (dd, 1, J = 11.9 and 15.3 Hz, –CH–), 5.11, 5.17 (AB q, 2, J = 12.5 Hz, CH_2Ph), 6.81–7.4 (m, 13, aromatic H). Anal. Calcd for $C_{25}H_{23}ClF_2O_4$: C, 65.2; H, 5.0; Cl, 7.7; F, 8.2. Found: C, 65.1; H, 4.9; Cl, 7.6; F, 8.0.

Ester **11** was eluted second as a pale yellow oil: IR (film) 1720, 1710, 1650, 1605, 1580 cm^{-1}; NMR δ 1.22 (t, 3, J = 7 Hz, CH_3), 4.02 (q, 2, J = 7 Hz), 4.61 (d, 2, J = 23 Hz, CH_2Cl), 5.19 (s, 2, CH_2Ph), 6.78–7.44 (m, 13, aromatic H). High-resolution mass spectrum for $C_{25}H_{22}ClFO_4$: calcd m/e 440.119; found m/e 440.118.

Racemization Studies—Scheme IV. (+)-Methyl 1-(4-Ethoxyphenyl)-2,2-dichlorocyclopropane-1-carboxylate. (+)-1-(4-Ethoxyphenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (275 mg, 1 mmol), $[\alpha]^{20}_D$ +98.6° (Holan and Walser, 1982), was dissolved in dry ether (10 mL), and a slight excess of diazomethane was added. The solvent was removed under reduced pressure and the distilled residue, bp 135 °C (0.1 mm), was then chromatographed by HPLC, column B, 3% EtOAc/petroleum ether (40–60 °C). This yielded the desired ester as a white crystalline substance: $[\alpha]^{20}_D$ +81.5°; IR (KBr) 1730, 1605, 1585 cm^{-1}; NMR δ 1.37 (t, 3, J = 7 Hz), 1.97, 2.56 (AB q, 2, J = 9 Hz, cyclopropyl H), 3.7 (s, 3), 4.0 (q, 2, J = 7 Hz), 7.12 (AA'BB', 4, aromatic H). Anal. Calcd for $C_{13}H_{14}Cl_2O_3$: C, 54.0; H, 4.88; Cl, 24.52. Found: C, 53.93; H, 4.81; Cl, 24.45.

Esterification Procedure. (+)-1-(4-Ethoxyphenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (100 mg, 0.36 mmol), $[\alpha]^{20}_D$ +98.6°, was heated to 90 °C for 1.5 h in fractionally distilled thionyl chloride (1 mL). At the end of this time, the excess thionyl chloride was removed under reduced pressure and anhydrous methanol (3 mL) was added. The resulting solution was stirred at room temperature for 2 h, and the concentrated residue was distilled and chromatographed by HPLC, column B, 3% EtOAc/petroleum ether (40–60 °C), to yield the methyl ester, $[\alpha]^{21.5}_D$ +4.27°.

When the thionyl chloride was purified by a reported method (Perrin et al., 1980), the methyl ester formed (six experiments) gave a specific rotation of $[\alpha]^{20}_D$ +79.2° to +81.5°.

Resolution of 1-(3-Nitrophenyl)-2,2-dichlorocyclopropane-1-carboxylic Acid. The published resolution method (Duke and Wells, 1982) was used. The diastereomeric mixture of esters was separated by HPLC, column B, 3:1 CH_2Cl_2/petroleum ether (40–60 °C), to yield two pale yellow oils. The first and second eluting diastereomers were hydrolyzed to yield the desired acids, $[\alpha]^{20}_D$ +75.9° and –75.0°, respectively.

Biological Methods. *Toxicity to Lucilia cuprina.* Mortality tests were carried out on 3- to 5-day-old male *L. cuprina* (Weid.) flies. The esters were applied topically in acetone solution. The treated flies were held at 26 °C, and mortalities were recorded at 48 h. The data were analyzed to give LD_{50} values. LD_{50} values with synergist were obtained as above, except that the flies were pretreated with 0.1% sesamex.

Toxicity to Blatella germanica. Male cockroaches *B. germanica* (L.) were selected from a stock culture, and groups of 10 insects were counted into 200-mL glass jars, coated on the inside with Fluon. Two replicates were tested for each compound. A serial dilution of the test compound was freshly prepared, and doses were topically applied to the ventral thorax of anaesthetized insects. After treatment, the insects were given dry dog food and maintained at 26 °C. Mortalities were recorded after 24 and 48 h.

Toxicity to Heliothis punctigera. Third-instar larvae of the native budworm *H. punctigera* (Wall) of approximately the same size were selected for each test. A serial dilution of the test compound was freshly prepared, and doses were topically applied to the ventral surface of each larva. After dosing, each larva was placed in a separate container with a small amount of larval medium, and the container was capped. Treated larvae were maintained at 26 °C, and mortalities were recorded after 24 and 48 h.

RESULTS AND DISCUSSION

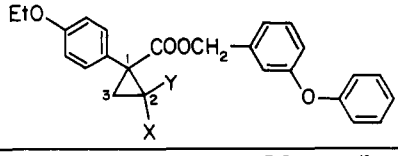
Chemistry. The synthesis of the insecticidal esters **1** and **6** are shown in Schemes I and II. The intermediate acrylates **3** were made from the phenyl acetates **2** by either method A [(1) $(EtO_2C)_2$, NaOEt; (2) HOAc; (3) HCHO, K_2CO_3] or method B (HCHO, K_2CO_3, DMF). In general, method A is a time-consuming three-step procedure, but it gives crude acrylates **3** of higher purity and in better yields than the more convenient one-step procedure (method B). The acrylates **3** prepared by method A were not purified further, but those prepared by Method B required filtering through a short silica gel column. The pure acrylates **3** were unstable and polymerized on storage. Carbene addition reactions (phase transfer or thermal) to the acrylates **3** were used to generate the cyclopropyl esters **4**. The esters **4**, after hydrolysis, were esterified by either method C [(1) $SOCl_2$; (2) ROH, py] or method D (Et_3N, RBr). Method D was straightforward and gave the insecticidal esters **1** and **6** in good yields. However, in some cases, the use of method C gave undesired products (Schemes III and IV). Scheme III shows that the esterification of acid **8**, by method C, produced none of the desired ester, but instead a good yield (90%) of the ring-opened esters **10** and **11** was obtained. Investigation of this reaction revealed that acid chloride **9** was unstable in the presence of pyridine. For example, acid chloride **9**, where R^1 = OEt, in the presence of pyridine, required 18 h at 0 °C for complete ring opening or only 10 min at 60 °C, whereas in the absence of pyridine this acid chloride was stable and could be distilled without decomposition.

The 2,2-difluorocyclopropyl esters or carboxylic acids **8** were stable at elevated temperatures (60 °C) with added pyridine or added pyridinium hydrochloride. No ring-opened products were detected. Additionally, it was found that if R^1 in acid chloride **9** was an electron-withdrawing group (e.g., fluoro), the acid chloride was relatively more stable to ring-opening conditions than when R^1 was an electron-donating substituent (e.g., ethoxy).

The 2,2-difluorocyclopropyl acids **8** were successfully esterified by elimination of pyridine from the acid chloride procedure or by using method D.

Esterification of the resolved 2,2-dichlorocyclopropyl carboxylic acids **12** (Scheme IV) by method C yielded partially or fully racemized ester products. This racemi-

Table I. Effect of Substitution at C-2 of the Cyclopropyl Ring on Insecticidal Activity



compd no.	X	Y	LD_{50}, mg/kg *L. cuprina*	*B. germanica*	*H. punctigera*
14	H	H	>200	>200	>45
15	H	F	29.6	130.9	12.0
16	F	H	98.9	>200	6.3
17	H	Cl	14.0	>200	>40
18	Cl	H	>177.0	>200	>64
19	H	Br	65.0	>150	>45
20	Br	H	48.6	>150	>64
21	F	F	3.9	9.3	6.2
22	Cl (F)	F (Cl)	3.0	44.0	11.8
23	Cl	Cl	3.9	31.5	2.1
24	Cl (Br)	Br (Cl)	6.1	>200	5.1
25	Br	Br	22.5	>146	>36

zation during the esterification reaction was investigated further with compound 12 R^1 = 4-OEt.

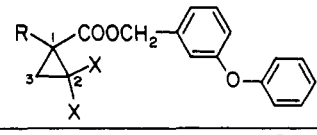
It was found that no racemization took place if thionyl chloride was replaced by oxalyl chloride in the formation of the acid chloride. It was also shown that no racemization took place if highly purified thionyl chloride was used. It is known that thionyl chloride contains trace amounts of ferric chloride (Kirk-Othmer, 1969). Therefore, it seemed likely that the presence of this Lewis acid catalyst could be responsible for the racemization. To test this possibility, trace amounts of ferric chloride were added to a highly purified sample of thionyl chloride and the esterification procedure was repeated. As predicted, the resulting ester 13 was completely racemized. Additionally, where R^1 in compound 12 was an electron-withdrawing group, the compound was more stable to racemization than where R^1 was an electron-donating group. For example, compound 12 where R^1 was the electron-withdrawing 3-NO_2 group racemized only 8% under the conditions, which gave total racemization for the compound where R^1 = 4-OEt.

Biology. The biological objectives of the synthesis program were to determine: (1) the effect of the substituents at C-2 (see structure 1), (2) the effect of the substituents in the C-1 phenyl ring, (3) the influence of the relative stereochemistry of substituents around the cyclopropane ring, (4) the effect of resolution at C-1, and (5) the effect of different alcohols on the insecticidal activity of the compounds on the three test insects.

Table I shows the effect of the substitution at C-2 of the cyclopropyl ring on the insecticidal activity (LD_{50} values). It is clear that the 2,2-difluoro, 2-chloro-2-fluoro, and 2,2-dichloro substituents produce the most active insecticides. Generally removal of one of the halogens reduces the insecticidal activity while removal of both of the halogens produces an inactive compound. There is one exception to the above generralization. The removal of one halogen from compound 21 produces compounds 15 and 16 (see Table I), one of which, 16, shows similar insecticidal activity to the parent compound 21 on *H. punctigera*.

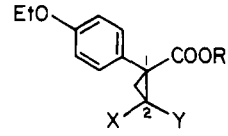
Table II shows the effect of the substitution on the C-1 aromatic ring on the insecticidal activity. A QSAR study of DDT analogues has been reported (Holan and Spurling, 1974). This study found a correlation between the electron-donating ability of substituents on the aromatic rings and insecticidal activity for houseflies. For the esters listed

Table II. Effect of Substitution within the R Substituent on Insecticidal Activity



compd no.	R	X	LD_{50}, mg/kg *L. cuprina*	*B. germanica*	*H. punctigera*
26	3,4-(methylenedioxy)phenyl	F	3.6	20.8	7.8
21	4-ethoxyphenyl	F	3.9	9.3	6.2
27	4-chlorophenyl	F	29.0	>200	2.5
28	4-fluorophenyl	F	59.0	>200	6.5
29	2-naphthyl	F	>200	>200	21.0
30	3,4-(methylenedioxy)phenyl	Cl	3.8	11.2	4.5
23	4-ethoxyphenyl	Cl	3.9	31.5	2.1
31	4-chlorophenyl	Cl	10.8	8.1	4.8
32	phenyl	Cl	24.6	>100	29.9
33	4-nitrophenyl	Cl	261	121.3	40.1

Table III. Effect of Relative Spatial Arrangement of Substituents on the Cyclopropane Ring on LD_{50} Values for *L. cuprina*



compd. no	X	Y	R[a]	LD_{50}, mg/kg *L. cuprina*	+ synerg	synerg ratio
15	H	F	PB	29.6	4.2	7
16	F	H	PB	98.9	9.2	11
17	H	Cl	PB	14.0	1.0	14
18	Cl	H	PB	>177.0	22.0	>8
34	H	Cl	PBF	19.4	0.7	28
35	Cl	H	PBF	31.6	2.7	12
36	H	Cl	PF	22.8	6.1	4
37	Cl	H	PF	34.0	13.8	2.5
38	H	Cl	α-CN	14.3	0.9	16
39	Cl	H	α-CN	21.2	1.7	12
19	H	Br	PB	65.0	2.7	24
20	Br	H	PB	48.6	7.4	7

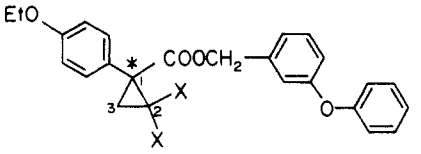
[a] Key: PB = 3-phenoxybenzyl; PBF = 4-fluoro-3-phenoxybenzyl; PF = pentafluorobenzyl; α-CN = α-cyano-3-phenoxybenzyl.

in Table II, there appears to be a similar relationship between the electron-donating ability of the substituent and the LD_{50} values on *L. cuprina* with the most active compounds (**26, 21, 30, 23**) possessing either a 4-ethoxyphenyl ring or a 3,4-(methylenedioxy)phenyl ring (i.e., good electron-donating substituents). However, there are no similar parallels for *B. germanica* or *H. punctigera*. A QSAR study is in progress for the DDT–pyrethroid esters.

Table III summarizes the effect of the relative stereochemistry of substituents around the cyclopropyl ring on the mortality values (LD_{50}) for *L. cuprina*. Examination of the LD_{50} values in the presence of the synergist sesamex shows that the isomer with the C-2 halogen cis to the C-1 ester group is always the more active diastereomer by a factor of 2–3, except for compounds 17 and 18 where the factor is 22. Generally, the LD_{50} values without synergist show smaller differences between diastereomers.

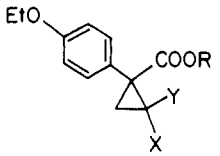
The results presented in Table IV demonstrate the effect of resolution at C-1 on the cyclopropyl ring, on the insecticidal activity (LD_{50} values) for the test insects shown. There were significant differences in insecticidal activity of the resolved enantiomers. On the three insects tested, the (−) enantiomer is the more insecticidally active.

Table IV. Effect of Chirality at C-1 on Insecticidal Activity



compd no.	isomer	$[\alpha]^{20}_D$, deg (EtOH)	X	LD_{50}, mg/kg *L. cuprina*	*B. germanica*	*H. punctigera*
23	±		Cl	3.9	31.5	2.1
40	−	−33.3	Cl	2.1	4.3	2.2
41	+	+33.8	Cl	70.3	>200	>40
21	±		F	3.9	9.3	6.2
42	−	−81.6	F	4.8	8.4	0.9
43	+	+72.2	F	14.5	>146	32.9

Table V. Effect of Alcohol Component R on Insecticidal Activity



compd no.	X	Y	R[a]	LD_{50}, mg/kg *L. cuprina*	*B. germanica*	*H. punctigera*
21	F	F	PB	3.9	9.3	6.2
44	F	F	PBF	5.5	10.2	1.0
45	F	F	PF	10.2	40	2.9
22	F (Cl)	Cl (F)	PB	3.0	44	11.8
46	F (Cl)	Cl (F)	PBF	3.9	13.8	0.4
47	F (Cl)	Cl (F)	PF	3.9	12.2	11.8
23	Cl	Cl	PB	3.9	31.5	2.1
48	Cl	Cl	PBF	4.8	8.0	1.7
49	Cl	Cl	PF	1.8	34.0	>40

[a] Key: PB = 3-phenoxybenzyl; PBF = 4-fluoro-3-phenoxybenzyl; PF = pentafluorobenzyl.

Table V compares the effect of three alcohol moieties, 3-phenoxybenzyl, 4-fluoro-3-phenoxybenzyl, and pentafluorobenzyl, on the mortality values (LD_{50}) for several insects. The data show that for *L. cuprina* the mortality values, within a series, vary by only a small amount, with no pattern being evident. The variation in LD_{50} values for *B. germanica* is slightly larger (up to 4-fold), but again no pattern is evident. However, on *H. punctigera*, compounds possessing the 4-fluoro-3-phenoxybenzyl moiety are consistently the most active compounds.

Further research is in progress to synthesize analogues of the DDT–pyrethroid compounds to find new highly active and selective insecticides.

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Registry No. **1** (R = *m*-$CH_2C_6H_4OC_6H_4F$-*p*, R_1 = OEt, x = y = F), 101492-40-4; **1** (R = R_2 = H, R_1 = OEt, x = y = F), 63935-55-7; **3** (R = *p*-$EtOC_6H_4$), 63935-52-4; **3** (R = *p*-ClC_6H_4), 101492-44-8; **3** (R = *p*-FC_6H_4), 72800-64-7; **3** (R = 2-naphthyl), 72800-66-9; **3** (R = Ph), 22286-82-4; **3** (R = *p*-$O_2NC_6H_4$), 72800-63-6; **4** (R = *p*-$EtOC_6H_4$, x = y = Br), 63935-27-3; **4** (R = *p*-$EtOC_6H_4$, x = y = H), 88934-82-1; **4** (R = *p*-$EtOC_6H_4$, x = y = F), 63935-29-5; **4** (R = *p*-$EtOC_6H_4$, x = Cl, y = F) isomer 1, 101492-45-9; **4** (R = *p*-$EtOC_6H_4$, x = Cl, y = F) isomer 2, 101492-46-0; **4** (R = *p*-$EtOC_6H_4$, x = y = Cl), 63935-25-1; **4** (R = *p*-$EtOC_6H_4$, x = Cl, y = Br) isomer 1, 101492-47-1; **4** (R = *p*-$EtOC_6H_4$, x = Cl, y = Br) isomer 2, 101492-48-2; **4** (R = *p*-$EtOC_6H_4$, x = y = Br), 63935-27-3; **4** (R = 3,4-(methylenedioxy)phenyl, x = y = F), 101492-49-3; **4** (R = 3,4-(methylenedioxy)phenyl, x = y = Cl), 63958-13-4; **4** (R = *p*-ClC_6H_4, x = y = F), 101492-50-6; **2** (R = *p*-$EtOC_6H_4$), 40784-88-1; **4** (R = *p*-ClC_6H_4, x = y = Cl), 63935-23-9; **4** (R = *p*-FC_6H_4, x = y = F), 101492-51-7; **4** (R = 2-naphthyl, x = y = F), 101492-52-8; **4** (R = Ph, x = y = Cl), 101492-53-9; **4** (R = *p*-$O_2NC_6H_4$, x = y = Cl), 101492-54-0; **7**, 63935-60-4; **7** (Me ester), 101492-41-5; **10** (R = *m*-$PhOC_6H_4$, R′ = OEt), 101492-18-6; **11** (R = *m*-$PhOC_6H_4$, R′ = OEt), 101492-19-7; (+)-**12** (R′ = *m*-O_2N), 101492-42-6; (−)-**12** (R′ = *m*-O_2N), 101492-43-7; **13** (R′ = *p*-OEt, R = Et), 63935-29-5; **14**, 101492-20-0; **15**, 101492-21-1; **16**, 101492-22-2; **17**, 101492-23-3; **18**, 101492-24-4; **19**, 101492-25-5; **20**, 101492-26-6; **21**, 63935-36-4; **22** (isomer 1), 101492-27-7; **22** (isomer 2), 101492-29-9; **23**, 63935-32-0; **24** (isomer 1), 101492-28-8; **24** (isomer 2), 101492-30-2; **25**, 63935-34-2; **26**, 101492-31-3; **27**, 101492-32-4; **28**, 101492-33-5; **29**, 101492-34-6; **30**, 63958-15-6; **31**, 63935-30-8; **32**, 63935-47-7; **33**, 63935-45-5; **34**, 101492-35-7; **35**, 101492-36-8; **36**, 101492-37-9; **37**, 101492-38-0; **38**, 101492-39-1; **40**, 67597-20-0; **41**, 67597-21-1; **42**, 67597-22-2; **43**, 67597-23-3; NaO_2CCClF_2, 1895-39-2; *p*-$FC_6H_4OC_6H_4CH_2Br$-*m*, 68359-55-7.

Supplementary Material Available: Tables VI–XIII listing principal IR bands of acrylates **3**, ^1H NMR parameters of acrylates **3**, principal IR bands of esters **4**, ^1H NMR parameters of esters **4**, elemental analysis of esters **4**, ^1H NMR parameters of the insecticidal esters **14**, **21–33**, and **44–49**, principal IR bands of the insecticidal esters **14**, **21–33**, and **44–49**, and elemental analysis of the insecticidal esters **14**, **21–33**, and **44–49** (8 pages). Ordering information is given on any current masthead page.

LITERATURE CITED

Duke, C. C.; Wells, R. J. Eur. Pat. Appl. EP 60 445, 1982.
Holan, G.; O'Keefe, D. F.; Virgona, C. T. F.; Walser, R. *Nature* **1978**, *272*, 734.
Holan, G.; O'Keefe, D. F.; Rihs, K.; Walser, R.; Virgona, C. T. *Advances in Pesticide Science*, Part 2; Geissbuhler, H., Ed.; Pergamon: Oxford, 1979; p 201.
Holan, G.; Spurling, T. H. *Experientia* **1974**, *30*, 480.
Holan, G.; Walser, R. U. S. Patent 4 309 305, 1982.
Johnson, W. M. P.; Holan, G.; Jarvis, K. E. *Aust. J. Chem.* **1986**, *39*, 271.
Kirk-Othmer Encyclopedia of Chemical Technology; Interscience: New York, 1969; Vol. 19, p 400.
Perrin, D. D.; Amarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1980; p 541.

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