Synthesis and Insecticidal Activity of the Stereoisomers of α-Cyano-3-phenoxybenzyl 2-[2-Chloro-4-(trifluoromethyl)anilino]-3-methylbutanoate (Fluvalinate) and Related Analogues

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The stereoisomers of the pyrethroid, α-cyano-3-phenoxybenzyl 2-[2-chloro-4-(trifluoromethyl)-anilino]-3-methylbutanoate (fluvalinate, **3**) and several related analogues have been prepared, and their toxicity on *Heliothis virescens* and *Musca domestica* has been determined. Both the acid components, (*R*)-(+)- and (*S*)-(−)-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid, and the alcohol components, (*R*)-(+)- and (*S*)-(−)-α-cyano-3-phenoxybenzyl alcohol, of fluvalinate were synthesized in high enantiomeric purity and then used to obtain the four stereoisomers of **3** in high optical purity. The $R_{ac}S_{al}$ stereoisomer of **3** and related analogues is highly insecticidal while the other isomers are much less biologically active. The configuration of the active isomer of **3** is sterically equivalent to that of the biologically active stereoisomer of other pyrethroids, such as cypermethrin (**1**) and fenvalerate (**2**).

During recent years, much attention has been given to the research and development of synthetic pyrethroids for insect control. As this research has progressed, it has become increasingly clear that the insecticidal activity of the pyrethroids is related to their molecular shape. With the natural pyrethrins serving as a model, Elliott and coworkers prepared the photostable and agriculturally useful dihalovinylcyclopropanecarboxylates typified by cypermethrin (**1**) (Elliott et al., 1975) and observed that pyrethroid esters derived from (1*S*)-cyclopropanecarboxylic acids are much less active than those derived from (1*R*)-cyclopropanecarboxylic acids (Burt et al., 1974), a finding consistent with the stereochemistry of the natural pyrethrins. The stereochemistry of the alcohol portion of cypermethrin (**1**) is also important for biological activity. Thus, the isomer of **1** derived from the 1*R* acid and the (*S*)-(−)-α-cyano-3-phenoxybenzyl alcohol ($1R,S_{al}$-**1**) shows much higher insecticidal activity than the corresponding ester derived from the *R* alcohol (Elliott et al., 1978a; Aketa et al., 1978). In accord with these results, the most insecticidal stereoisomer of the dibromo analogue of **1** (Elliott et al., 1974) is the $1R,S_{al}$ isomer, as determined by X-ray analysis (Owen, 1975).

The dependence of biological activity on molecular stereochemistry has also been demonstrated for the pyrethroid esters of 3-methyl-2-phenylbutanoic acids, such as fenvalerate (**2**), which do not contain the cyclopropanecarboxylic ester moiety of the natural pyrethrins. Thus, Miyakado et al. (1975) reported that only 3-methyl-2-phenylbutanoates derived from acids of *S* configuration are highly insecticidal, while several groups (Clements and May, 1977; Aketa et al., 1978; Elliott et al., 1978a) demonstrated that the active isomer of fenvalerate (**2**) has the *S* configuration at the α-cyanobenzylic carbon atom.

We recently reported on a novel class of synthetic pyrethroids, the substituted 2-anilino-3-methylbutanoates (Henrick et al., 1980), typified by fluvalinate (**3**), and have also studied the stereochemical requirements of this class for insecticidal activity. A preliminary report of this stereochemical study has been presented earlier (Anderson et al., 1980), and the complete details of the synthesis and biological activity of the stereoisomers of fluvalinate (**3**) and related analogues are now reported below.

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MATERIALS AND METHODS

All solvents were dried over activated 4Å molecular sieves. Radial thin-layer chromatography (TLC) was carried out by using a Harrison Model 7824 Chromatotron equipped with a 2-mm silica gel rotor. Infrared (IR) spectra were obtained by using a Unicam SP 200 G spectrophotometer or a Perkin-Elmer Model 283 spectrophotometer. Proton nuclear magnetic resonance (NMR) spectra were determined on a Varian T-60 or a Varian EM360L spectrometer. Chemical shifts were measured in parts per million (δ) relative to tetramethylsilane as the internal reference. Mass spectra were measured on a Hewlett-Packard Model 5984A or Model 5985 GLC–MS data system. Optical rotations were determined on a Perkin-Elmer Model 141 or a Rudolph Autopol III polarimeter. Gas–liquid chromatographic (GLC) analyses were performed on Hewlett-Packard Model 5711A or Model 3700 Varian (capillary GLC) instruments equipped with flame ionization detectors. Elemental analyses were performed by Erich Meier at the Stanford University Chemistry Department microanalytical laboratories. Melting points are uncorrected, and all temperatures are in °C.

(*R*)- and (*S*)-2-Bromo-3-methylbutanoic Acid. To a solution of 10.0 g (85.4 mmol) of L-valine (Aldrich, $[\alpha]^{25}_D$ +26.9° (*c* 0.0097 g/mL, 6 N HCl) in 100 mL of 6 N HBr at 0 °C was added portionwise over 1 h 9.0 g (0.13 mol) of sodium nitrite. After 2 h the solution was extracted several times with chloroform. The combined chloroform extracts were washed with aqueous saturated sodium bisulfite and brine and then were dried ($MgSO_4$). Removal of the solvent in vacuo gave 9.76 g (63%) of (*S*)-2-bromo-3-methylbutanoic acid: IR (CCl_4) 1700 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.10 (d, 3 H), 1.13 (d, 3 H), 2.20 (m, 1 H), 4.07 (d, 1 H); $[\alpha]^{25}_D$ −17.2° (*c* 0.010 g/mL, MeOH) [lit. $[\alpha]^{25}_D$ −16.8° (MeOH, Gaffield and Galetto, 1971)].

Similarly, (*R*)-2-bromo-3-methylbutanoic acid, $[\alpha]^{25}_D$ +15.5° (*c* 0.009 g/mL, MeOH), was prepared from D-valine (Aldrich), $[\alpha]^{25}_D$ −25.8° (*c* 0.010 g/mL, 6 N HCl).

(*R*)- and (*S*)-3-Methyl-2-[4-(trifluoromethyl)-anilino]butanoic Acid. The potassium salt of (*S*)-2-bromo-3-methylbutanoic acid was prepared by titrating a solution of 2.0 g (11 mmol) of the acid in 5 mL of methanol with 1 M potassium hydroxide in methanol to a phenolphthalein end point. After solvent removal in vacuo, the salt was dried thoroughly and mixed with 6.20

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g (38.5 mmol) of 4-(trifluoromethyl)aniline. This mixture was heated at 95 °C under a nitrogen atmosphere for 20 min. It was then cooled, poured into 5% aqueous sodium hydroxide, and extracted several times with hexane to remove excess aniline. The aqueous fraction was acidified with cold concentrated hydrochloric acid and extracted twice with diethyl ether. The combined ether extracts were washed with brine and were dried ($MgSO_4$). Removal of the solvent in vacuo gave a solid which was washed several times with hexane to give 1.15 g (40%) of (*S*)-3-methyl-2-[4-(trifluoromethyl)anilino]butanoic acid: mp 82–87 °C; NMR ($CDCl_3$) δ 1.05 (d, 6 H), 2.17 (m, 1 H), 3.97 (d, 1 H), 6.67 (d, 2 H), 7.43 (d, 2 H). Anal. Calcd for $C_{12}H_{14}F_3NO_2$: C, 55.17; H, 5.40; F, 21.82. Found: C, 54.93; H, 5.51; F, 21.6.

Treatment of a portion of the acid with excess diazomethane in ether followed by radial TLC purification gave methyl (*S*)-3-methyl-2-[4-(trifluoromethyl)anilino]butanoate: $[\alpha]^{25}_D$ −108.4° (*c* 0.010 g/mL, MeOH); mass spectrum (70 eV), *m/e* (relative intensity) 275 (8, M+), 216 (100).

In a similar manner, (*R*)-3-methyl-2-[4-(trifluoromethyl)anilino]butanoic acid was prepared, mp 97.5–99.5 °C.

The optical purity of these acids was determined by esterification with *l*-menthol and examination of the diastereomeric products by capillary GLC. Thus, a solution of the *S* acid (50 mg, 0.19 mmol), *l*-menthol (47 mg, 0.30 mmol), dicyclohexylcarbodiimide (58 mg, 0.28 mmol), and 4-(dimethylamino)pyridine (3 mg, 0.02 mmol) in 0.6 mL of dichloromethane was stirred at 0 °C under a nitrogen atmosphere for 30 min. Ether was added to the reaction mixture, and the ether solution was washed with water and brine and dried ($MgSO_4$). Removal of solvent in vacuo gave the menthyl ester: NMR ($CDCl_3$) δ 0.63 (d, 3 H), 0.87 (br d, 6 H), 1.00 (d, 3 H), 1.03 (d, 3 H). Analysis of the ester product by capillary GLC (20 m × 0.25 mm ID wall coated open tubular glass capillary, Carbowax 20M, 195 °C) indicated a diastereomer ratio of 98.6:1.4 or an optical purity for the *S* acid of 97.2% ee. Similar derivatization of the *R* acid and analysis of the ester product, NMR ($CDCl_3$) δ 0.53 (d, 3 H), 0.73 (d, 3 H), 0.83 (d, 3 H), 1.03 (d, 6 H), indicated a diastereomer ratio of 94.8:5.2 or an optical purity for the *R* acid of 89.6% ee.

(*R*)- and (*S*)-2-[2-Chloro-4-(trifluoromethyl)-anilino]-3-methylbutanoic Acid. To a solution of 712 mg (2.73 mmol) of (*S*)-3-methyl-2-[4-(trifluoromethyl)-anilino]butanoic acid in 12 mL of CCl_4 was added 364 mg (2.73 mmol) of *N*-chlorosuccinimide, and the resulting mixture was heated to 60 °C under a nitrogen atmosphere. After 2 h, the reaction mixture was poured into ether and water. The ether fraction was washed with water and brine and was dried ($MgSO_4$). Removal of solvent in vacuo gave 740 mg (2.51 mmol, 92%) of (*S*)-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid: mp 64–65 °C; IR (CCl_4) 3400 (NH), 1710 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.05 (d, 3 H), 1.10 (d, 3 H), 2.20 (m, 1 H), 3.90 (d, 1 H), 6.52 (d, 1 H), 7.23 (d of d, 1 H), 7.40 (d, 1 H); $[\alpha]^{25}_D$ −24.4° (*c* 0.011 g/mL, MeOH); mass spectrum of methyl ester (70 eV), *m/e* (relative intensity) 309 (14, M^+), 250 (100).

Similarly, (*R*)-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid was prepared: $[\alpha]^{25}_D$ 23.8° (*c* 0.011 g/mL, MeOH).

The optical purities of the *R* and *S* acids were again determined by analysis of diastereomeric menthyl esters, which were resolved by analytical high-performance LC (25 cm × 0.46 cm 5 μm LiChrosorb SI-100, 0.5% EtOAc in water-saturated pentane, 1.5 mL/min, 675 psi) with *k'* values of 1.39 for the ester derived from *S* acid and 1.94 for the ester of the *R* acid (α = 1.39). From this analysis the optical purities of the *S* and *R* acids were 97.2% ee and 91.6% ee, respectively.

(*R*)- and (*S*)-α-Cyano-3-phenoxybenzyl (*R*)-*N*-[1-(1-Naphthyl)ethyl]carbamate. Enantiomerically pure (*R*)-(+)-1-(1-naphthyl)ethylamine was prepared as described previously (Bergot et al., 1978) and converted to its corresponding *R* isocyanate with phosgene (Pirkle and Hoekstra, 1974). Likewise (*S*)-(−)-1-(1-naphthyl)ethylamine was converted to the *S* isocyanate. To determine optical purity, each isocyanate was reacted with *l*-menthol (1.5 equiv) in pyridine at 85 °C for 24 h to give the carbamate. The diastereomeric carbamates were resolved by analytical high-performance LC (25 cm × 0.46 cm 5 μm LiChrosorb SI-100, 10% EtOAc in water-saturated pentane, 2.1 mL/min, 1000 psi) with *k'* values of 0.71 for the carbamate derived from the *S* isocyanate (98.4% ee) and 1.35 for the carbamate derived from the *R* isocyanate (99.8% ee). The *R* isocyanate was used in the following resolution.

Thus, a solution of 11.0 g (56.0 mmol) of *R* isocyanate, 12.6 g (56.0 mmol) of α-cyano-3-phenoxybenzyl alcohol, and 150 mg of 4-(dimethylamino)pyridine in 75 mL of toluene was heated at 50 °C for 20 h. The mixture was cooled and poured into ether and 5% hydrochloric acid. The organic phase was separated and washed with saturated sodium bicarbonate and brine, and was dried (Na_2SO_4). Removal of solvent in vacuo gave a quantitative recovery of carbamate diastereomers, which were separated by preparative LC (2 PrepPAK-500 silica cartridges in tandem, 23% ether in hexane, 2 recycles) with a Waters Prep 500 HPLC. Recrystallization of the faster eluting diastereomer gave (*R*)-α-cyano-3-phenoxybenzyl (*R*)-*N*-[1-(1-naphthyl)ethyl]carbamate in 98.9% optical purity as determined by analytical LC (25 cm × 0.46 cm 5 μm LiChrosorb SI-100, 12.5% EtOAc in water-saturated pentane, 2 mL/min, 1000 psi, *k'* = 2.00 for the faster eluting diastereomer, *k'* = 2.27 for the slower eluting diastereomer): mp 121.5–122.0 °C; IR (CCl_4) 3440 (NH) and 1735 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.67 (d, 3 H), 6.38 (s, 1 H); $[\alpha]^{25}_D$ −15.2° (*c* 0.010 g/mL, $CHCl_3$). Anal. Calcd for $C_{27}H_{22}O_3N$: C, 76.76; H, 5.25; N, 6.63. Found: C, 76.70; H, 5.33; N, 6.80.

The slower eluting carbamate diastereomer, (*S*)-α-cyano-3-phenoxybenzyl (*R*)-*N*-[1-(1-naphthyl)ethyl]carbamate, was obtained in 97.8% optical purity from the above preparative HPLC separation: mp 41–41.5 °C; IR (CCl_4) 3450 (NH) and 1735 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.60 (d, 3 H), 6.37 (s, 1 H); $[\alpha]^{25}_D$ −19.6° (*c* 0.010 g/mL, $CHCl_3$).

(*R*)- and (*S*)-α-Cyano-3-phenoxybenzyl Alcohol. The carbamate diastereomers were cleaved by the method of Pirkle and Hauske (1977). Thus, to a solution of 1.99 g (4.7 mmol) of (*R*)-α-cyano-3-phenoxybenzyl (*R*)-*N*-[1-(1-naphthyl)ethyl]carbamate and 0.73 mL (5.2 mmol) of triethylamine in 20 mL of benzene under a nitrogen atmosphere was added 0.51 mL (5.0 mmol) of trichlorosilane. The reaction mixture was warmed to 50 °C for 2.5 h and then was poured into aqueous saturated ammonium chloride. The organic products were extracted into ether, and the ether layer was washed with saturated ammonium chloride and brine and then was dried (Na_2SO_4).

Solvent was removed in vacuo, and the residue was washed repeatedly (8 × 5 mL) with hexane to remove isocyanate. The hexane insoluble cyanohydrin was then dissolved in ether/hexane, 1:1, to separate a minor amount of an insoluble contaminant. The solvent was removed to

give 0.92 g (4.1 mmol) of (*R*)-α-cyano-3-phenoxybenzyl alcohol in 87% yield: IR (CCl_4) 3580 cm^{-1} (OH); NMR ($CDCl_3$) δ 5.40 (s, 1 H), 6.94–7.44 (m, 9 H). A 50-mg sample was further purified by rapid preparative TLC (30% EtOAc in hexane) for optical rotation: $[\alpha]^{25}_D$ 15.2° (*c* 0.010 g/mL, acetone).

Similarly, (*S*)-α-cyano-3-phenoxybenzyl alcohol was prepared from (*S*)-α-cyano-3-phenoxybenzyl (*R*)-*N*-[1-(1-naphthyl)ethyl]carbamate: $[\alpha]^{25}_D$ −14.6° (*c* 0.010 g/mL, acetone).

α-Cyano-3-phenoxybenzyl 2-[2-Chloro-4-(trifluoromethyl)anilino]-3-methylbutanoate Stereoisomers. The following experiment is typical for the preparation of the ester stereoisomers in high optical purity.

To a cooled (0 °C) solution of 439 mg (1.49 mmol) of (*R*)-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid, 329 mg (1.46 mmol) of (*S*)-α-cyano-3-phenoxybenzyl alcohol, and 22 mg (0.18 mmol) of 4-(dimethylamino)pyridine (DMAP) in 5 mL of dichloromethane under nitrogen was added 380 mg (1.84 mmol) of dicyclohexylcarbodiimide (DCC). After stirring at 0 °C for 1 h, the mixture was poured into ether and water. The organic fraction was separated, washed with water and brine, and then was dried ($MgSO_4$). Removal of solvent in vacuo gave about 600 mg of crude product which was purified by radial TLC (12% ether in hexane) to give 300 mg of ester. Analysis by HPLC (25 cm × 0.46 cm 5 μm LiChrosorb SI-100, 2.5% EtOAc in water-saturated pentane, 1.5 mL/min, 800 psi) indicated a ratio of 90:10 (theoretical 93:7) for the sets of enantiomers, $R_{ac}S_{al}$·$S_{ac}R_{al}$–$R_{ac}R_{al}$·$S_{ac}S_{al}$, respectively. (Subscript ac refers to the acid component and subscript al refers to the alcohol component of the stereoisomer.) Further purification of this mixture by radial TLC with recycle (7.5% EtOAc in hexane) gave 200 mg with an isomer ratio of 97.7:2.3. Since the contribution of the $S_{ac}R_{al}$ stereoisomer to this ratio can be calculated and is negligible, the optical purity of the $R_{ac}S_{al}$ stereoisomer then is 97.7%: IR ($CDCl_3$) 3410 (NH), 2275 (CN), and 1755 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.03 (d, 6 H), 2.22 (m, 1 H), 4.0 (d of d, 1 H), 6.37 (s, 1 H), 6.53 (d, 1 H), 6.68–7.55 (m, 11 H); $[\alpha]^{25}_D$ 46.3° (*c* 0.0085 g/mL, $CHCl_3$); mass spectrum (70 eV), *m/e* (relative intensity) 502 (3, M+), 252 (28), 250 (100), 181 (18).

Likewise, the other three isomeric esters were prepared from their corresponding acid and cyanohydrin, both of high optical purity, and were purified by radial TLC. For the $S_{ac}R_{al}$ stereoisomer which was obtained in a final optical purity of 97.4% $[\alpha]^{25}_D$ −44.6° (*c* 0.0049 g/mL, $CHCl_3$). The $S_{ac}S_{al}$ stereoisomer was obtained in 99.3% optical purity: NMR ($CDCl_3$) δ 1.08 (d, 3 H), 1.12 (d, 3 H), 2.22 (m, 1 H), 3.97 (d of d, 1 H), 6.35 (s, 1 H), 6.45 (d, 1 H), 6.85–7.55 (m, 11 H). Finally, the $R_{ac}R_{al}$ isomer was secured in 98.4% optical purity, $[\alpha]^{25}_D$ 0.2° (*c* 0.026 g/mL, $CHCl_3$).

α-Cyano-3-phenoxybenzyl 3-Methyl-2-[4-(trifluoromethyl)anilino]butanoate Stereoisomers. Each of the stereoisomers was prepared from (*R*)- or (*S*)-3-methyl-2-[4-(trifluoromethyl)anilino]butanoic acid and (*R*)- or (*S*)-α-cyano-3-phenoxybenzyl alcohol by using the DCC/DMAP esterification procedure as above and was purified by radial TLC eluting with 20% ether in hexane. The optical purity of each of the isomers was determined by HPLC (25 cm × 0.46 cm 5 μm LiChrosorb SI-100, 6% EtOAc in water-saturated pentane, 1.4 mL/min, 700 psi) with *k'* values of 2.44 and 3.22 for the $R_{ac}R_{al}$·$S_{ac}S_{al}$ and the $R_{ac}S_{al}$·$S_{ac}R_{al}$ sets of enantiomers, respectively. Thus, the optical purity of the $R_{ac}S_{al}$ isomer was 97.4%: IR (CCl_4) 3430 (NH), 1760 cm^{-1} (CO); NMR ($CDCl_3$) δ 0.98 (d, 6 H), 2.05 (m, 1 H), 3.93 (d of d, 1 H), 4.30 (br d, 1 H), 6.33 (s, 1 H) 6.53 (d, 2 H), 6.83–7.43 (m, 11 H); $[\alpha]^{25}_D$ 62.1° (*c* 0.009 g/mL, $CHCl_3$); mass spectrum (70 eV), *m/e* (relative intensity) 468 (7, M^+), 217 (15), 216 (100), 181 (16). Likewise, the $S_{ac}R_{al}$ isomer was secured in 95.1% optical purity, $[\alpha]^{25}_D$ −60.8° (*c* 0.011 g/mL, $CHCl_3$).

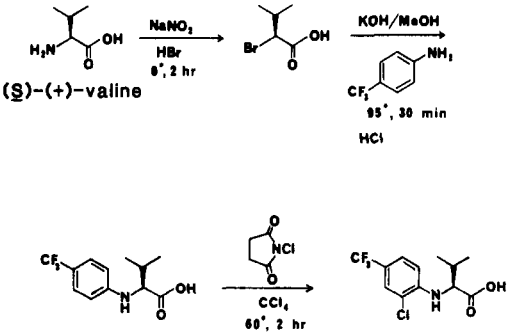
For the other set of enantiomers, the optical purity of the $S_{ac}S_{al}$ isomer was 98.3% as determined by HPLC: IR (CCl_4) 3420 (NH), 1750 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.05 (d, 3 H), 1.08 (d, 3 H), 2.13 (m, 1 H), 3.93 (d of d, 1 H), 4.38 (br d, 1 H), 6.37 (s, 1 H), 6.57 (d, 2 H), 6.93–7.43 (m, 11 H); $[\alpha]^{25}_D$ −9.20° (*c* 0.011 g/mL, $CHCl_3$); mass spectrum (70 eV), *m/e* (relative intensity) 468 (6, M^+), 217 (14), 216 (100), 181 (15). Finally, the $R_{ac}R_{al}$ isomer was obtained in 96.8% optical purity, $[\alpha]^{25}_D$ 7.76° (*c* 0.007 g/mL, $CHCl_3$).

α-Cyano-3-phenoxybenzyl 2-[2-Fluoro-4-(trifluoromethyl)anilino]-3-methylbutanoate Stereoisomers. To a cooled (0 °C) solution of 446 mg (1.6 mmol) (*RS*)-2-[2-fluoro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid (Henrick et al., 1980), 360 mg (1.6 mmol) of (*S*)-α-cyano-3-phenoxybenzyl alcohol, and 24 mg (0.2 mmol) of 4-(dimethylamino)pyridine in 4.5 mL of dichloromethane under nitrogen was added 412 mg (2.0 mmol) of dicyclohexylcarbodiimide. After stirring at 0 °C for 1 h, the mixture was diluted with pentane and filtered. The pentane filtrate was washed with 5% aqueous hydrochloric acid, 2 M aqueous sodium carbonate, and brine and was dried (Na_2SO_4). Solvent was removed in vacuo, and the residue was purified by preparative TLC (1 m × 20 cm plates coated with 1.5 mm of Merck silica gel PF-254, developed in 25% ether in hexane) to give 655 mg (1.35 mmol, 85% yield) of (*S*)-α-cyano-3-phenoxybenzyl (*RS*)-2-[2-fluoro-4-(trifluoromethyl)anilino]-3-methylbutanoate. The diastereomers could be separated by preparative HPLC (2 PrepPAK-500 silica cartridges in tandem, 8% ether in hexane, 2 recycles) with a Waters Prep 500 instrument followed by radial TLC with recycle (7.5% ethyl acetate in hexane). The less polar $S_{ac}S_{al}$ diastereomer was obtained in 98.8% optical purity: IR (CCl_4) 3430 (NH), 1760 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.07 (d, 3 H), 1.10 (d, 3 H), 2.2 (m, 1 H), 3.92 (d of d, 1 H), 4.60 (br d, 1 H), 6.33 (s, 1 H), 6.53 (d, 1 H), 6.83–7.47 (m, 11 H); $[\alpha]^{25}_D$ −14.7° (*c* 0.009 g/mL, $CHCl_3$); mass spectrum (70 eV), *m/e* 486 (5, M^+), 235 (12), 234 (100), 181 (13). The more polar $R_{ac}S_{al}$ diastereomer was obtained in 99.0% optical purity: IR (CCl_4) 3430 (NH), 1755 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.0 (d, 6 H), 2.18 (m, 1 H), 3.97 (d of d, 1 H), 4.55 (br d, 1 H), 6.38 (s, 1 H), 6.52 (d, 1 H), 6.88–7.38 (m, 11 H); $[\alpha]^{25}_D$ 62.8° (*c* 0.009 g/mL, $CHCl_3$); mass spectrum (70 eV), *m/e* (relative intensity) 486 (4, M^+), 235 (12), 234 (100), 181 (12).

In a similar manner, (*RS*)-2-[2-fluoro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid was reacted with (*R*)-α-cyano-3-phenoxybenzyl alcohol to give a mixture of the $R_{ac}R_{al}$ and $S_{ac}R_{al}$ diastereomeric esters. Chromatographic separation as above gave the $R_{ac}R_{al}$ diastereomer in 98.2% optical purity, $[\alpha]^{25}_D$ 14.0° (*c* 0.010 g/mL, $CHCl_3$), and the $S_{ac}R_{al}$ isomer in 98.4% optical purity, $[\alpha]^{25}_D$ −66.1° (*c* 0.010 g/mL, $CHCl_3$).

(6-Phenoxy-2-pyridinyl)methyl (*R*)- and (*S*)-2-[2-Chloro-4-(trifluoromethyl)anilino]-3-methylbutanoate. To a cooled (0 °C) solution of 204 mg (0.69 mmol) of (*R*)-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid, 197 mg (0.98 mmol) of (6-phenoxy-2-pyridinyl)methyl alcohol, and 10 mg (0.08 mmol) of 4-(dimethylamino)pyridine in 2 mL of dichloromethane under nitrogen was added 190 mg (0.92 mmol) of dicyclohexylcarbodiimide. After stirring at 0 °C for 1.5 h, the reaction mixture was worked up as above. Purification

Scheme I. Synthesis of (*S*)-2-[2-Chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic Acid



of the product by radial TLC (20% ether in hexane) gave 240 mg (0.50 mmol, 72% yield) of (6-phenoxy-2-pyridinyl)methyl (*R*)-2-[2-chloro-4-(trifluoromethyl)-anilino]-3-methylbutanoate: IR (neat) 3400 (NH) and 1735 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.00 (d, 3 H), 1.05 (d, 3 H), 2.17 (m, 1 H), 3.95 (d of d, 1 H), 5.10 (s, 2 H), 6.55 (d, 1 H), 6.72–7.65 (m, 10 H); $[\alpha]^{25}_D$ 13.8° (*c* 0.010 g/mL, $CHCl_3$). Anal. Calcd for $C_{24}H_{22}ClF_3N_2O_3$: C, 60.19; H, 4.63; Cl, 7.40; F, 11.90; N, 5.85. Found: C, 59.32; H, 4.73; Cl, 7.67; F, 12.08; N, 5.80.

In an identical manner, the *S* enantiomer was prepared from (*S*)-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid: $[\alpha]^{25}_D$ −15.6° (*c* 0.010 g/mL, $CHCl_3$).

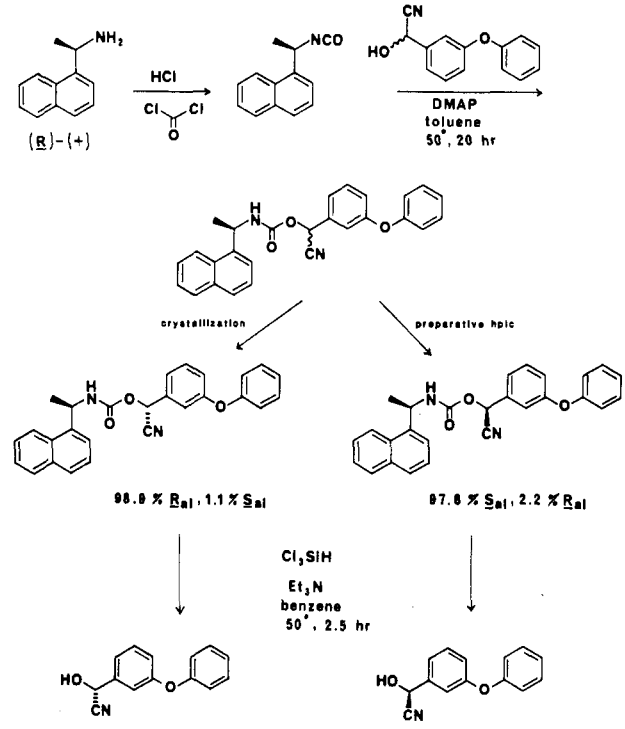
RESULTS AND DISCUSSION

To obtain the four stereoisomers of fluvalinate (**3**), in the highest possible optical purity, we chose to attempt the synthesis of both the acid and alcohol components of **3** in high enantiomeric purity and then couple these components to give the four isomeric esters.

The synthesis of the substituted 2-anilinoisovaleric acid component of *S* configuration is outlined in Scheme I. Thus, treatment of (*S*)-(+)-valine in 6 N HBr with sodium nitrite resulted in a smooth conversion to (*S*)-2-bromo-3-methylbutanoic acid, a transformation known to proceed with overall retention of configuration (Neuberger, 1948). Reaction of the corresponding potassium carboxylate with excess 4-(trifluoromethyl)aniline at 95 °C for 30 min gave after acidification, the 2-anilino-3-methylbutanoic acid system of *S* configuration. This assignment is based on the work of Klebe and Finkbeiner (1968) who unambiguously demonstrated that the reaction of 2-halo-3-methylbutanoic acids with anilines proceeds with retention of configuration under conditions identical with those we employed. Finally, the synthesis of the *S* acid portion of fluvalinate was completed by the regiospecific *N*-chlorosuccinimide chlorination of (*S*)-3-methyl-2-[4-(trifluoromethyl)anilino]butanoic acid in carbon tetrachloride. In an identical manner, (*R*)-(−)-valine was converted to (*R*)-3-methyl-2-[2-chloro-4-(trifluoromethyl)anilino]butanoic acid.

To ensure that the reactions depicted in Scheme I yielded products of high optical purity, a quantitative method for the determination of optical purity was developed. Thus, esterification of (*S*)-3-methyl-2-[4-(trifluoromethyl)anilino]butanoic acid with *l*-menthol using dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)-pyridine (DMAP) in dichloromethane at 0 °C (Neises and Steglich, 1978) gave a menthyl ester which was readily separable from the diastereomer prepared from the (*R*)-anilino acid and *l*-menthol by both capillary GLC and analytical HPLC. The same method could also be applied to the chlorinated anilino acids, and in this case the diastereomeric esters were resolved by HPLC. By means of this method, the optical purities of the (*R*)-and (*S*)-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic acids were determined as 91.6% and 97.2% enantiomeric excess (ee), respectively. The requisite acids for the synthesis of the four stereoisomers of fluvalinate (**3**) were therefore available in high optical purity.

Scheme II. Synthesis of (*R*)- and (*S*)-α-Cyano-3-phenoxybenzyl Alcohol

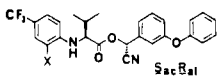
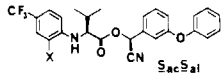
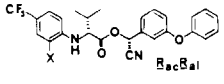
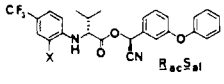
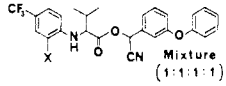


The synthesis of the enantiomers of α-cyano-3-phenoxybenzyl alcohol posed a somewhat more formidable problem. At the outset of our work, there were no literature reports on the successful preparation of this cyanohydrin in high optical purity. Elliott and co-workers (1978b) had obtained an optically enriched sample of (*R*)-(+)-α-cyano-3-phenoxybenzyl alcohol from an enzyme mediated synthesis by using 3-phenoxybenzaldehyde, HCN, and D-oxynitrilase. However, the cyanohydrin product was obtained in only 50% enantiomeric excess, and the *R* cyanohydrin gives pyrethroid esters in both the cyclopropanecarboxylate (Elliott et al., 1978a; Aketa et al., 1978) and the 2-phenylisovalerate series (Clements and May, 1977; Aketa et al., 1978; Elliott et al., 1978a) which are much less active than those derived from *S* cyanohydrin.

Our synthesis of the enantiomeric forms of α-cyano-3-phenoxybenzyl alcohol is presented in Scheme II. (*R*)-(+)-1-(1-naphthyl)ethylamine was purified to greater than 99.9% optical purity (Bergot et al., 1978) and then was converted to the corresponding isocyanate with phosgene. Reaction of the *R* isocyanate with racemic α-cyano-3-phenoxybenzyl alcohol gave a mixture of two diastereomeric carbamates which were separated by preparative HPLC. The faster eluting diastereomer, after one recrystallization, was obtained in 98.9% optical purity from HPLC analysis, while the slower eluting diastereomer was obtained in 97.8% optical purity. The faster eluting diastereomer could also be obtained directly from the mixture by crystallization.

We next addressed the problem of regenerating the chemically labile cyanohydrins from their respective carbamates without racemization or decomposition. Pirkle and Hauske (1977) had reported a mild method of ob-

Table I. Chemical and Optical Purities of the Stereoisomers of α-Cyano-3-phenoxybenzyl 2-[2-Substituted-4-(trifluoromethyl)anilino]-3-methylbutanoates

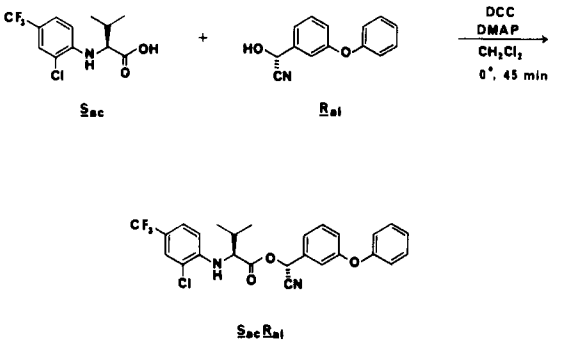
stereoisomer	X	chem purity, %[a]	opt purity, %[b]	% $R_{ac}S_{al}$, est[c]
 $S_{ac}R_{al}$	H	98.1	95.1	<0.1
	F	99.1	98.4	1.0
	Cl	96.5	97.4	<0.1
 $S_{ac}S_{al}$	H	97.3	98.3	0.7
	F	99.3	98.2	<0.1
	Cl	96.2	99.3	0.3
 $R_{ac}R_{al}$	H	99.3	96.8	0.5
	F	99.1	98.2	<0.1
	Cl	99.1	98.4	0.3
 $R_{ac}S_{al}$	H	98.3	97.4	
	F	98.6	99.0	
	Cl	98.4	97.7	>97
 Mixture (1:1:1:1)	H	97.0		25
	F	99.4		25
	Cl	96.8		25

[a] Determined by GLC analysis; includes all stereoisomers. [b] Determined by HPLC analysis. [c] Calculated value based on HPLC analysis and optical purities of starting material.

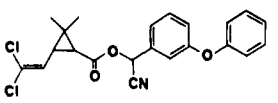
taining carbinols from their carbamates by trichlorosilane mediated cleavage, a reaction that proceeds without racemization or rearrangement of the carbinol. Application of this method to the diastereomeric carbamates of α-cyano-3-phenoxybenzyl alcohol resulted in the desired cleavage and recovery of the cyanohydrin enantiomers in high yield. Based on the earlier work of Elliott and coworkers (1978b) in which they obtained partially enriched (*R*)-α-cyano-3-phenoxybenzyl alcohol with a positive rotation, we could assign the *R* configuration to the cyanohydrin derived from the faster eluting carbamate diastereomer and the *S* configuration to the cyanohydrin obtained from the slower eluting carbamate. Shortly after the completion of our synthesis of (*R*)- and (*S*)-α-cyano-3-phenoxybenzyl alcohol, an alternative preparation of the resolved cyanohydrins was reported (Martel et al., 1980) which is based on an elegant resolution and epimerization of diastereomeric bicyclic acetals. Recently, Choi and co-workers (1984) reported another synthesis of the *S* cyanohydrin by cyanation of a chiral 3-phenoxybenzaldehyde acetal.

To determine the extent of racemization, if any, of the cyanohydrins during the trichlorosilane-induced cleavage, the cyanohydrins were reacted with the anilino acids of high optical purity as depicted in Scheme III. Thus, for example, esterification of (*S*)-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid of 98.6% enantiomeric purity with (*R*)-α-cyano-3-phenoxybenzyl alcohol derived from a carbamate of 98.9% optical purity by means of the DCC-DMAP method (Neises and Steglich, 1978) mentioned above gave the $S_{ac}R_{al}$ isomer of fluvalinate, **3**-($S_{ac}R_{al}$) in an optical purity of 94%. This value, obtained by HPLC analysis of the ester, can be compared to the theoretical value of 97.5% which would derive from a coupling of acid and alcohol with no racemization of the acid moiety during esterification or of the alcohol moiety during carbamate cleavage and subsequent esterification. This slight observed loss of optical purity may be due to diastereoselectivity in the esterification (Elliott et al., 1980), since the ester is not racemized under esterification conditions. The optical purity of **3**-($S_{ac}R_{al}$) was improved to 97.4% by careful radial thin-layer chromatography. In a

Scheme III. Synthesis of the $S_{ac}R_{al}$ Stereoisomer of Fluvalinate (3)



similar manner, the other three stereoisomers of fluvalinate were also synthesized. (Commercially available fluvalinate is the mixture of $R_{ac}S_{al}$ and $R_{ac}R_{al}$ diastereomers; Anderson et al., 1981.)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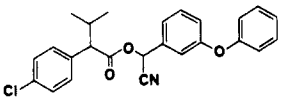
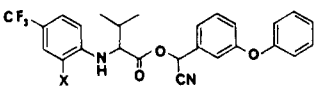
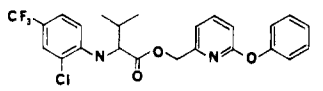

2

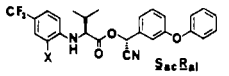
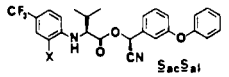
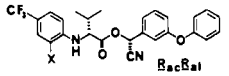
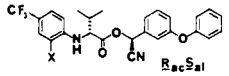
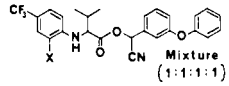
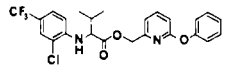

3; X = Cl
4; X = H
5; X = F


6

Incidental to this work was the preparation of the stereoisomers of two closely related pyrethroids, **4** and **5**, as well as the enantiomers of **6**. The four optical isomers of **4** were prepared by esterification of (*R*)- and (*S*)-3-methyl-2-[4-(trifluoromethyl)anilino]butanoic acid with (*R*)- and (*S*)-α-cyano-3-phenoxybenzyl alcohol, and the enantiomers of **6** were obtained in a straightforward esterification of (*R*)- and (*S*)-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid with (6-phenoxy-2-pyridinyl)methyl alcohol. The synthesis of the four stereoisomers of **5** was completed in a slightly modified manner. Racemic 2-[2-fluoro-4-(trifluoromethyl)-anilino]-3-methylbutanoic acid (Henrick et al., 1980) was esterified with (R)- and (*S*)-α-cyano-3-phenoxybenzyl alcohol to give diastereomeric mixtures of esters, $R_{ac}R_{al}$-$S_{ac}R_{al}$ and $R_{ac}S_{al}$-$S_{ac}S_{al}$, respectively. The diastereomers could be resolved by preparative HPLC followed by radial thin-layer chromatography.

In Table I are tabulated the chemical and optical purities of the four stereoisomers of fluvalinate (**3**), **4** and **5**. The optical purity, determined by HPLC analysis, denotes the percent of that isomer in the sample and does not include nonisomeric contaminants. Due to the synthetic

Table II. Toxicity of the Stereoisomers of α-Cyano-3-phenoxybenzyl 2-[2-Substituted-4-(trifluoromethyl)anilino]-3-methylbutanoates and Analogues

stereoisomer	X	*Heliothis virescens*, III instar LD_{50}, μg	*Musca domestica*, adult LD_{50}, μg
 $S_{ac}R_{al}$	H	>100	2.3
	F	0.18	0.28
	Cl	91	30
 $S_{ac}S_{al}$	H	2.5	0.17
	F	0.71	0.48
	Cl	>100	40
 $R_{ac}R_{al}$	H	0.53	0.82
	F	0.18	0.59
	Cl	0.32	2.2
 $R_{ac}S_{al}$	H	0.018	0.033
	F	0.0059	0.015
	Cl	0.018	0.038
 Mixture (1:1:1:1)	H	0.059	0.084
	F	0.018	0.052
	Cl	0.080	0.16
	*R*	0.014	0.070
	S	5.6	8.1
	RS	0.020	0.15

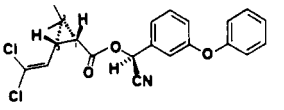
approach used for the optical isomers of **3** and **4**, the contribution of the enantiomer, which of course is not separable on an achiral HPLC column, to this value is negligible and can be calculated to be less than 0.1%. For the stereoisomers of **5**, however, enantiomer contamination is more significant and can be calculated to be about 1%. The significance of the last column of Table I will be apparent in the following discussion of biological activity.

The biological activity of each of the isomers and the mixture of isomers of fluvalinate (**3**), **4**, and **5** on third instar *Heliothis virescens* larvae and on *Musca domestica* adults is presented in Table II. From these data it is readily apparent that for fluvalinate (**3**) and the related analogues **4** and **5**, the $R_{ac}S_{al}$ stereoisomer is far more insecticidal than the other three isomers.

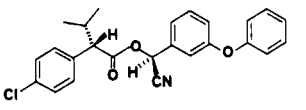
For fluvalinate (**3**), the $R_{ac}R_{al}$ diastereomer is significantly less active than the $R_{ac}S_{al}$ isomer on both *Heliothis virescens* and on *Musca domestica*. The estimated 0.3% of $R_{ac}S_{al}$ isomer in the $R_{ac}R_{al}$ diastereomer of **3**, however, cannot account for the weak but measurable activity of the latter noted in Table II. This low but significant level of activity may be due to some epimerization of the $R_{ac}R_{al}$ isomer within the insect to produce the highly insecticidal $R_{ac}S_{al}$ isomer, since this process has been demonstrated to occur in weakly basic medium (Baum and Koo, 1979). The two diastereomers of **3** derived from the *S* acid, on the other hand, are essentially inactive, both being over 4000 times less active than the $R_{ac}S_{al}$ isomer on *Heliothis virescens* and 800–1000 times less active on *Musca domestica*. This very low level of activity for the $S_{ac}R_{al}$ and $S_{ac}S_{al}$ diastereomers may in fact be due to a 0.1% or less amount of the $R_{ac}S_{al}$ isomer in these samples. The approximately 4-fold greater activity of the $R_{ac}S_{al}$ stereoisomer of fluvalinate (**3**) than that of the mixture of all four isomers is consistent with our observations that only the $R_{ac}S_{al}$ isomer is highly insecticidal and also suggests that the other three optical isomers are not significant inhibitors of the $R_{ac}S_{al}$ isomer.

The stereoisomers of **4** and **5** generally gave a similar pattern of activity to those of **3**, i.e., the $R_{ac}S_{al}$ isomers are significantly more active than the other isomers and 2.5–3.5 times as active as the mixture of all four stereoisomers.

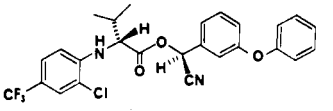
Chart I. Absolute Configuration of the Most Insecticidal Stereoisomer of Cypermethrin (**1**), Fenvalerate (**2**), and Fluvalinate (**3**)



1 - 1R, S$_{al}$



2 - S$_{ac}$ S$_{al}$



3 - R$_{ac}$ S$_{al}$

This pattern of highly biologically active esters deriving from anilino acid of *R* configuration continued for the (6-phenoxy-2-pyridinyl)methyl ester **6** (Table II). Thus, the *R* enantiomer of **6** is highly insecticidal and 1.5–2.0-fold more active than the racemic mixture, while the *S* enantiomer of **6** is essentially inactive.

The highly insecticidal $R_{ac}S_{al}$ stereoisomer of fluvalinate (**3**) is stereochemically equivalent to the biologically active $S_{ac}S_{al}$ isomer of fenvalerate (**2**) and to the active $1R_{ac}S_{al}$ stereoisomers of the cyclopropanecarboxylate pyrethroids such as **1** (Chart I), suggesting a similar binding site for all three structural types.

ACKNOWLEDGMENT

We are grateful for the assistance of David Cerf, Anne Kilkenny, Maureen McNally, and Gerardus Staal in conducting the insect bioassays.

Registry No. (±)-**3**, 69409-94-5; ($S_{ac}R_{al}$)-**3**, 76821-59-5; ($S_{ac}S_{al}$)-**3**, 76821-60-8; ($R_{ac}R_{al}$)-**3**, 76821-52-8; ($R_{ac}S_{al}$)-**3**, 76821-53-9; (±)-**4**, 69409-94-5; ($S_{ac}R_{al}$)-**4**, 78512-27-3; ($S_{ac}S_{al}$)-**4**, 78512-28-4; ($R_{ac}R_{al}$)-**4**, 78512-26-2; ($R_{ac}S_{al}$)-**4**, 78512-25-1; (±)-**5**, 69409-99-0; ($S_{ac}R_{al}$)-**5**, 78038-41-2; ($S_{ac}S_{al}$)-**5**, 78038-39-8; ($R_{ac}R_{al}$)-**5**, 78038-40-1; ($R_{ac}S_{al}$)-**5**, 78038-38-7; (*R*)-2-bromo-3-methylbutanoic acid, 76792-22-8; (*S*)-2-bromo-3-methylbutanoic acid, 26782-75-2; (*R*)-3-methyl-2-[4-(trifluoromethyl)anilino]butanoic acid, 78445-41-7; (*S*)-3-methyl-2-[4-(trifluoromethyl)anilino]butanoic acid, 78445-42-8; (*R*)-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid, 76769-07-8; (*S*)-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoic acid, 74971-63-4; (*R*)-α-cyano-3-phenoxybenzyl (*R*)-*N*-[1-(1-naphthyl)ethyl]carbamate, 78445-39-3; (*S*)-α-cyano-3-phenoxybenzyl (*R*)-*N*-[1-(1-naphthyl)ethyl]carbamate, 78445-40-6; (*R*)-α-cyano-3-phenoxybenzyl alcohol, 71962-66-8; (*S*)-α-cyano-3-phenoxybenzyl alcohol, 61826-76-4.

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Persistence of Captan on Apples, Grapes, and Pears in Ontario, Canada, 1981–1983

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Blocks of apples, grapes, and pears were treated with captan at 1.7, 2.8, or 3.4 kg ha^{-1} for 1–15 applications. Captan residues were measured over a 14-day period following the last application. Residues declined significantly in seven of nine experiments. Correlations between rainfall and captan residues were observed in five experiments. No correlations were observed in four experiments in which little or no rain fell in the first 7 days. In four of the trials the captan residues immediately following the last application did not exceed the 5 mg kg^{-1} maximum residue limit permitted under the Canadian Food and Drug Act. The longest periods required for residues to decline below the 5 mg kg^{-1} tolerance were 5 days for grapes, 3 days for pears, and 7 days for apples.

INTRODUCTION

The fungicide captan, *N*-[(trichloromethyl)thio]-4-cyclohexene-1,2-dicarboximide is widely used for the prevention of fungal diseases of pome fruits and grapes around the world. During 1980 22 000 ha of apples, grapes, and pears were grown in Ontario (Ontario Ministry of Agriculture and Food, 1980) and treated with 130 000 kg of captan to prevent fungal diseases on foliage and fruit. The weather conditions during the growing season and especially prior to harvest are generally conducive to heavy fungal infection and serious crop losses. In Ontario, the major diseases of apple, pear, and grape against which captan is effective are respectively apple scab (*Venturia inaequalis* (Cke) Wint.), pear scab (*V. pirina* Aderh.), downy mildew (*Plasmopara viticola* (Berk. and Curt.) Berl. and de Toni), and Botrytis bunch rot (*Botrytis cinerea* Pers.). Captan has been recommended (Ontario Ministry of Agriculture and Food, 1983) and extensively used for over 30 years and its importance has increased recently with the loss of efficacy of benomyl, dodine, and iprodione as the result of development of fungicide-resistant pathogens. Applications of captan prior to harvest are often necessary for the protection of fruit during the preharvest period, and this could result in residues that exceed the established residue tolerance.

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Table I. Official Maximum Residue Limits for Captan on Pome Fruit and Grapes in 18 Countries[a]

country	maximum residue limits of captan, mg/kg^{-1}		
	apples	pears	grapes
Japan	5		
Canada	5	5	5
Switzerland	3	3	15
New Zealand	10	10	10
Belgium, France, Italy, Netherlands, Singapore, South Africa, Spain, Sweden, West Germany, Yugoslavia	15	15	15
Kenya	40	30	
Israel	40	30	15
Mexico, U.S.A.	25	25	50

[a] Health and Welfare Canada, 1981.

On a global scale, official maximum residue limits for captan range from 3 to 50 mg kg^{-1} (Table I). Canadian maximum residue limits were reduced from 25 to 5 mg kg^{-1} on 24 March, 1983 (Health and Welfare, Canada, 1983). These studies were undertaken to measure the rate of disappearance of captan and to determine preharvest intervals adequate to meet the new residue tolerance and were part of a larger study on several fruit crops jointly reported with Northover et al.

MATERIALS AND METHODS

Nine field experiments were undertaken and all except two (2 and 6) were conducted on large blocks of mature grapes, apples, and pears located on the Agriculture Canada Research Station, Jordan, Ontario. The soil at this

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