is not difficult to envision situations in which daily exposures could be much greater than 130 ppb. Populations of workers that appear to be a greatest risk from prolonged exposure to EDB during outgassing include truck drivers and warehousemen. It is recommended that these exposures be investigated so that the extent of the problem can be understood and effective controls instituted.

If airborne exposures, and indeed residues of EDB in fumigated fruit, are to be minimized, it is important that both temperature and ventilation be considered during transport and storage. Since reduced temperature retards outgassing, the amount of EDB remaining in refrigerated fruit would be relatively great; outgassing could be significant upon warming of the fruit, even if many days have elapsed since fumigation. Essentially the same behavior would be expected for produce transported at ambient temperature without ventilation. It should be obvious that the transient ventilation of produce (transported without ventilation) immediately prior to unloading would not significantly alter either the magnitude or the duration of subsequent outgassing.

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Heterocyclic Analogues of Substituted [1,1′-Biphenyl]-3-methylpyrethroid Insecticides

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The effect of substitution on a series of 3-heterocyclic benzyl pyrethroid esters was investigated. Since 2-methyl-[1,1′-biphenyl]-3-methanol had been shown in earlier studies to produced the most active esters in the biphenyl series, the equivalent 2-methyl-3-heterocyclic esters were prepared first. The most active of these, the 1-pyrrole analogue, was then studied further for substituent effects. The alcohol that produced the most active esters in this series, 2-methyl-3-(1*H*-pyrrol-1-yl)benzenemethanol, was then esterified with a series of common pyrethroid acids. The synthesis of all the intermediate alcohols is presented as well as the activity of the final esters against *Spodoptera eridania* (SAW), *Epilachna varivestis* (MBB), *Oncopeltus fasciatus* (MWB), *Heliothis virescens* (TBW), *Trichopulsia ni* (CL), *Acyrthosiphon pisum* (PA), and *Tetranychus urticae* (TSM). The 2-methyl-3-heterocyclic benzyl esters are, in general, more active than their parent esters and like the analogous biphenyl esters have broader spectra of activity than permethrin.

It has been demonstrated that highly active pyrethroid insecticides can be prepared from benzyl alcohols with phenyl substituents in the meta position even if no bridging atom separates the two aromatic rings (Plummer and Pincus, 1981). It has also been demonstrated that the meta phenyl group can be replaced by a number of heterocyclic rings with a change in activity proportional to the lipophilicity of the heterocyclic ring (Plummer, 1983). Recently we reported (Plummer et al., 1983) the effect of substitution on the activity of pyrethroid esters derived from [1,1′-biphenyl]-3-methanol. It was found that substitution in the 2- and 2′-positions was most efficacious and further that 2-fluoro- and 2-methyl[1,1′-biphenyl]-3-methanol not only produced esters of increased activity against insects that are classical targets of synthetic pyrethroids but also provided broader spectrum insecticides and acaricides than other synthetic analogues of the pyrethrins. We now report the effect of substitution on a number of "B" ring heterocyclic analogues of the substituted [1,1′-biphenyl]-3-methyl pyrethroid esters.

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MATERIALS AND METHODS

Analysis of Products. Nuclear magnetic resonance (NMR) spectra were determined on a Varian T-60 spectrometer. Analyses by gas–liquid chromatography (GLC) were performed on Model 5830A Hewlett-Packard in-

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struments equipped with thermal conductivity detectors. Infrared spectra were measured on Perkin-Elmer 187 spectrophotometers. All esters were characterized by NMR, infrared, and elemental analysis of carbon and hydrogen.

Chemicals. *2-Methyl-3-(thien-2-yl)benzenemethanol (Method A).* To an ice-cold solution of 3-chloro-2-methylaniline (50.0 g) in thiophene (100 g) was added isoamyl nitrite (82.7 g) (Cadogen, 1962). The mixture was warmed to reflux for 0.5 h and then stirred for 16 h at room temperature. The reaction product was chromatographed (silica gel/heptane). The oil that was isolated was short-path vacuum distilled (78 °C at 0.05 mmHg) to give 1-chloro-2-methyl-3-(thien-2-yl)benzene, a clear oil (9.2 g, 12.5%): NMR δ 2.42 (s, 3 H, CH_3), 6.92–7.42 (m, 6 H, aromatic H's).

1-Chloro-2-methyl-3-(thien-2-yl)benzene (21.5 g) was treated with magnesium (2.5 g) in tetrahydrofuran. To this mixture was added excess solid carbon dioxide. The product was washed from the reaction mixture with aqueous sodium hydroxide (2 N). The basic solution was made acidic (2 N hydrochloric acid) and extracted with dichloromethane. The solvent was removed in vacuo and the residue chromatographed (silica gel/dichloromethane). After an additional cycle of base wash, dichloromethane wash, and acidification, 2-methyl-3-(thien-2-yl)benzoic acid was obtained as an oil that solidified on standing. Recrystallization from 9:1 heptane–toluene gave 6.9 g (31%): mp 91.5–93 °C; NMR δ 2.63 (s, 3 H, CH_3), 6.93–8.07 (m, 6 H, aromatic H's), 11.67 (s, 1 H, COOH).

This acid (5.7 g) was reduced by treatment with a borane–tetrahydrofuran complex (Yoon et al., 1973) (4.4 g) at reflux. Extraction with diethyl ether gave 2-methyl-3-(thien-2-yl)benzenemethanol (5.3 g, 100%) as an oil: NMR δ 2.37 (s, 3 H, CH_3), 4.75 (s, 2 H, CH_2), 5.07 (br s, 1 H, OH), 6.90–7.47 (m, 6 H, aromatic H's).

2-Methyl-3-(pyridin-2-yl)benzenemethanol and 2-Methyl-3-(pyridin-3-yl)benzenemethanol. The diazotization procedure above was repeated by using 3-chloro-2-methylaniline (75.0 g), *tert*-butyl nitrite (81.9 g), and pyridine (419.2 g). Subsequent chromatography (silica gel/1:4 ethyl acetate–heptane) and short-path vacuum distillation gave three products: 1-chloro-2-methyl-3-(pyridin-2-yl)benzene (7.9 g) [NMR δ 2.33 (s, 3 H, CH_3), 6.97–7.83 (m, 6 H, aromatic H's), 8.47–8.60 (m, 1 H, –N=CH–)]; 1-chloro-2-methyl-3-(pyridin-3-yl)benzene (2.9 g) [NMR δ 2.27 (s, 3 H, CH_3), 7.00–7.70 (m, 5 H, aromatic H's), 8.40–8.60 (m, 2 H, –N=CH–)]; 1-chloro-2-methyl-3-(pyridin-4-yl)benzene (1.6 g) [NMR δ 2.27 (s, 3 H, CH_3), 7.00–7.40 (m, 5 H, aromatic H's), 8.53–8.67 (m, 2 H, –N=CH–)]. The three isomers were assigned not only on the basis of proton NMR but also on the basis of ^{13}C NMR. Thus, the 2-isomer had a low-intensity resonance at 159.3 ppm (C-2') and a higher intensity resonance at 149.2 ppm (C-6'); the 3-isomer had resonances at 149.8 ppm (C-2') and 148.5 ppm (C-6'), both of about the same intensity; the 4-isomer had a degenerate resonance at 149.7 ppm (C-2' plus C-6') and a second degenerate resonance at 124.1 ppm (C-4' plus C-5').

Using the procedure of Newman (1955) 1-chloro-2-methyl-3-(pyridin-2-yl)benzene (1.2 g) was treated with cuprous cyanide (0.8 g) in pyridine (0.7 mL) at ca. 200 °C for 18 h. The product was taken up in dichloromethane and washed with 35% ammonium hydroxide. The solvent was removed in vacuo to give 2-methyl-3-(2-pyridinyl)-benzonitrile (0.8 g, 72%). This sample was treated with a 1 M solution of diisobutylammonium hydride (Trifimenko, 1964) (4.7 mL) in toluene (20 mL) to give 2-methyl-3-(pyridin-2-yl)benzaldehyde (0.5 g, 63%): IR (film) 1650 (C=O) cm^{-1}; NMR δ at 2.27 (s, 3 H, CH_3), 7.13–7.93 (m, 6 H, aromatic H's), 8.60–8.73 (m, 1 H, –N=CH–), 10.63 (s, 1 H, CHO). Reduction of this aldehyde (0.5 g) with sodium borohydride in ethanol gave 2-methyl-3-(pyridin-2-yl)benzenemethanol (0.46 g, 92%): NMR δ 2.10 (s, 3 H, CH_3), 3.10–3.53 (m, 1 H, OH), 4.53 (s, 2 H, CH_2), 7.20–7.90 (m, 6 H, aromatic H's), 8.30–8.60 (m, 1 H, –N=CH–).

2-Methyl-3-(pyridin-3-yl)benzenemethanol was produced by the same series of reactions: NMR δ 2.20 (s, 3 H, CH_3), 3.15–4.13 (m, 1 H, OH), 4.77 (s, 2 H, CH_2), 7.00–7.73 (m, 5 H, aromatic H's), 8.33–8.53 (m, 2 H, –N=CH–).

2-Methyl-3-(furan-2-yl)benzenemethanol. (3-Amino-2-methylphenyl)methyl acetate [from platinum oxide reduction of (3-nitro-2-methylphenyl)methyl acetate] (10.0 g) was dissolved in furan (37.4 g) and *tert*-butyl nitrite (8.6 g) added at reflux. After 1.5 h the reaction mixture was delivered to a column of silica gel and eluted with pentane. A second chromatography (silica gel/toluene) followed by short-path distillation (94 °C at 0.05 mm Hg) gave [3-(furan-2-yl)-2-methylphenyl]methyl acetate (4.1 g, 32%), an oil: NMR δ 2.10 (s 3 H, CH_3), 2.43 (s, 3 H, C=OCH_3), 5.20 (s, 2 H, CH_2), 6.47 (s, 1 H, furanyl H), 6.50 (s, 1 H, furanyl H), 7.07–7.67 (m, 4 H, aromatic H's).

This ester was hydrolyzed with potassium hydroxide in methanol to give 2-methyl-3-(furan-2-yl)benzenemethanol (100%): mp 48.5–50.0 °C; NMR δ at 1.83 (br s, 1 H, OH), 2.40 (s, 3 H, CH_3), 4.72 (s, 2 H, CH_2), 6.43 (s, 1 H, furanyl H), 6.47 (s, 1 H, furanyl H), 7.03–7.60 (m, 4 H, aromatic H's).

2-Methyl-3-(1-methyl-1H-pyrrol-2-yl)benzenemethanol. The procedure described above, using *N*-methylpyrrole as the solvent/substrate, gave [2-methyl-3-(1-methyl-1*H*-pyrrol-2-yl)phenyl]methyl acetate (38%): mp 80.5–81.5 °C; NMR δ 2.10 (s, 3 H, CH_3), 2.63 (s, 3 H, C=OCH_3), 3.95 (s, 3 H, NCH_3), 5.22 (s, 2 H, CH_2), 6.20–6.33 (dd, 1 H, –N=CH), 6.65–6.75 (dd, 1 H, pyrrole H), 6.83–6.93 (dd, 1 H, pyrrole H), 7.05–7.67 (m, 3 H, aromatic H's).

This ester was hydrolyzed with potassium hydroxide in methanol to give 2-methyl-3-(1-methyl-1*H*-pyrrol-2-yl)-benzenemethanol (100%): mp 118–119 °C; NMR δ at 1.73–1.93 (br t, 1 H, OH), 2.63 (s, 3 H, CH_3), 3.97 (s, 3 H, NCH_3), 4.72–4.83 (br d, 2 H, CH_2), 6.20–6.33 (dd, 1 H, –N=CH), 6.65–6.75 (dd, 1 H, pyrrole H), 6.83–6.93 (dd, 1 H, pyrrole H), 7.03–7.67 (m, 3 H, aromatic H's).

2-Methyl-3-(pyrazin-2-yl)benzenemethanol. The pyranyl ether of 3-amino-2-methylbenzenemethanol [from reduction of the pyranyl ether (Miyashita et al., 1977) of 3-nitro-2-methylbenzenemethanol with platinum oxide] was treated with pyrazine as above to give the pyranyl ether of 2-methyl-3-(pyrazin-2-yl)benzenemethanol (14%): NMR δ 1.37–2.00 (br m, 6 H, $-CH_2CH_2CH_2-$), 2.33 (s, 3 H, CH_3), 3.37–4.20 (m, 2 H, $-OCH_2$), 4.47–5.05 (q, 1 H, –OCHO–), 4.80 (s, 2 H, CH_2), 7.13–7.67 (m, 4 H, aromatic H's), 8.47–8.67 (m, 2 H, –N=CH–).

Ether cleavage (Miyrashita et al., 1977) with pyridinium *p*-toluenesulfonic acid gave 2-methyl-3-(pyrazin-2-yl)-benzenemethanol (94%): NMR peaks at 2.27 (s, 3 H, CH_3), 2.63 (br s, 1 H, OH), 4.73 (s, 2 H, CH_2), 7.60–7.17 (m, 4 H, aromatic H's), 8.50–8.63 (m, 2 H, –N=CH–).

2-Methyl-3-(imidazol-1-yl)benzenemethanol. (3-Amino-2-methylphenyl)methyl acetate (33.4 g) was treated with thiophosgene by using the method of Dyson (1944) to give (3-isothiocyanato-2-methylphenyl)methyl acetate (24.0 g, 58%). Treatment of this isothiocyanate (24.4 g) with 1-aminoacetaldehyde diethyl acetal (16 mL) using the method of Johnson et al. (1969) gave *N*-(diethoxy-

ethyl)-*N'*-[2-methyl-3-(acetoxymethyl)phenyl]thiourea (35.6 g, 91%): mp 65–68 °C. This product (33.1 g) was treated with 10% hydrochloric acid at reflux. A solid, 2-methyl-3-(2-mercaptoimidazol-1-yl)benzenemethanol (16.3 g), precipitated on cooling to 0 °C: mp 231–233 °C. Heating this product with 20% nitric acid to 85 °C caused a *violent* evolution of gas. After cessation of evolution, the mixture was cooled and made basic with 15% ammonium hydroxide. Extraction with dichloromethane following by removal of the solvent in vacuo gave a solid that on recrystallization (toluene) gave 2-methyl-3-(imidazol-1-yl)-benzenemethanol (3.9 g, 32%): mp 132–134 °C; NMR δ 2.10 (s, 3 H, CH_3), 4.80 (s, 2 H, CH_2), 5.72 (br s, 1 H, OH), 7.00–7.73 (m, 6 H, aromatic H's).

2-Methyl-3-(1H-pyrrol-1-yl)benzenemethanol. 3-Chloro-2-methylaniline (80.3 g) and 2,5-dimethoxytetrahydrofuran (75 g) were heated to reflux in glacial acetic acid (120 mL) (Elming and Clauson-Kaas, 1952). After 3 h the mixture was diluted with water and extracted with diethyl ether to give, after washing with saturated aqueous potassium carbonate and removal of the solvent in vacuo, 1-(3-chloro-2-methylphenyl)pyrrole (98.8 g, 91%): NMR δ 2.20 (s, 3 H, CH_3), 6.27–6.33 (m, 2 H, –N=CH–), 6.67–6.75 (m, 2 H, –N=CH–C*H*=), 7.07–7.43 (m, 3 H, aromatic H's). The same processes as used for method A were used to convert this product to 2-methyl-3-(1*H*-pyrrol-1-yl)benzenemethanol: NMR δ 1.67–2.20 (br m, 1 H, OH), 2.07 (s, 3 H, CH_3), 4.63 (s, 2 H, CH_2), 6.23–6.37 (m, 2 H, –N=CH–), 6.67–6.73 (m, 2 H, –N=CH–CH=), 7.10–7.47 (m, 3 H, aromatic H's).

2-Methyl-3-(2,5-dimethyl-1H-pyrrol-1-yl)benzenemethanol. 3-Chloro-2-methylaniline (50.0 g) and acetonylacetone (40.3 g) were refluxed in toluene (300 mL) in the presence of *p*-toluenesulfonic acid (0.5 g) with continuous withdrawal of the water formed (Buu-Hoi, 1949). After 2.5 h the solvent was removed in vacuo, the residue taken up in dichloromethane, washed with 2 N sodium hydroxide, and short-path distilled (90 °C at 0.05 mmHg) to give 1-(3-chloro-2-methylphenyl)-2,5-dimethylpyrrole: NMR δ at 1.92 (s, 6 H, pyrrole CH_3's), 1.97 (s, 3 H, phenyl CH_3), 5.93 (s, 2 H, pyrrole H's), 7.00–7.53 (m, 3 H, phenyl H's). This compound was converted as above to 2-methyl-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzenemethanol: NMR δ at 1.77–2.13 (m, 1 H, OH), 1.89 (s, 3 H, phenyl CH_3), 1.90 (s, 6 H, pyrrole CH_3's), 4.77 (br s, 2 H, CH_2), 5.93 (s, 2 H, pyrrole H's), 7.00–7.57 (m, 3 H, phenyl H's).

2,6-Dichloro-3-(1H-pyrrol-1-yl)benzenemethanol was prepared from 3-amino-2,6-dichlorobenzenemethanol by the method of Elming and Clauson-Kaas (1952): NMR δ 2.50–2.87 (br t, 1 H, OH), 4.93–5.00 (br d, 2 H, CH_2), 6.27–6.33 (m, 2 H, –N=CH–), 6.73–6.83 (m, 2 H, –N=CH–CH=), 7.08–7.43 (m, 2 H, phenyl H's).

2-Bromo-3-(1H-pyrrol-1-yl)benzenemethanol. 2-Bromo-3-nitrotoluene was prepared from 2-methyl-6-nitroaniline by the method of Gibson and Johnson (1929). This was brominated with *N*-bromosuccinimide (Grovenstein and Wentworth, 1967) to give 1-bromo-2-(bromomethyl)-6-nitrobenzene. The benzyl bromide was converted to (2-bromo-3-nitrophenyl)methyl acetate with potassium acetate in acetonitrile in the presence of tetrabutylammonium chloride (Normant et al., 1975). Catalytic reduction of this nitro compound in the presence of platinum oxide and morpholine (Kosak, 1980) gave (3-amino-2-bromophenyl)methyl acetate, which was converted to [2-bromo-3-(1*H*-pyrrol-1-yl)phenyl]methyl acetate (64%) by the method of Elming and Clauson-Kaas (1952). Hydrolysis with potassium hydroxide in methanol gave 2-bromo-3-(1*H*-pyrrol-1-yl)benzenemethanol (90%): mp 78–80 °C; NMR δ 2.37–2.67 (br t, 1 H, OH), 4.82–4.88 (br d, 2 H, CH_2), 6.33–6.43 (m, 2 H, –N=CH–), 6.80–6.90 (m, 2 H, –N=CH–C*H*=), 7.20–7.67 (m, 3 H, aromatic H's).

2,6-Difluoro-3-(1H-pyrrol-1-yl)benzenemethanol. 2,6-Difluorobenzoic acid was treated with nitric acid and sulfuric acid to give 2,6-difluoro-3-nitrobenzoic acid (22%). This was reduced (platinum oxide catalyst and morpholine) and the resultant amine converted to 2,6-difluoro-3-(1*H*-pyrrol-1-yl)benzoic acid (43%) by the method of Elming and Clauson-Kaas (1952). This was then reduced to 2,6-difluoro-3-(1*H*-pyrrol-1-yl)benzenemethanol as described in method A: NMR δ at 2.65 (br s, 1 H, OH), 4.85 (br s, 2 H, CH_2), 6.33–6.43 (m, 2 H, –N=CH–), 6.97–7.03 (m, 2 H, –N=CH–CH=), 6.77–7.53 (m, 2 H, phenyl H's).

6-Methyl-3-(1H-pyrrol-1-yl)benzenemethanol. 1-(3-Chloro-4-methylphenyl)pyrrole was prepared from 3-chloro-4-methylaniline by the method of Elming and Clauson-Kaas (1952) (85%). This was transformed to 6-methyl-3-(1*H*-pyrrol-1-yl)benzenemethanol by method A: mp 68–69.5 °C; NMR δ at 1.83 (br s, 1 H, OH), 2.33 (s, 3 H, CH_3), 4.70 (s, 2 H, CH_2), 6.27–6.37 (m, 2 H, –N=CH–), 7.00–7.13 (m, 2 H, –N=CH–C*H*=), 7.00–7.40 (m, 3 H, phenyl H's).

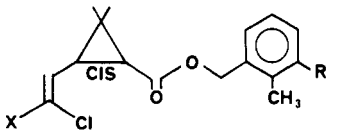
2,5-Dichloro-3-(1H-pyrrol-1-yl)benzenemethanol. Prepared from 3-amino-2,5-dichlorobenzoic acid by the method of Elming and Clauson-Kaas (1952) (81%) followed by the procedure in method A: mp 80–82 °C; NMR δ 2.77 (br s, 1 H, OH), 4.80 (s, 2 H, CH_2), 6.30–6.37 (m, 2 H, –N=CH–), 6.78–6.90 (m, 2 H, –N=CH–C*H*=), 7.20–7.55 (m, 2 H, phenyl H's).

2,3,4,6-Tetrafluoro-3-(1H-pyrrol-1-yl)benzenemethanol. 1-(2,3,4,6-Tetrafluorophenyl)pyrrole (92%) was prepared by the method of Elming and Clauson-Kaas (1952). Following the method of Tamborski and Solobski (1966), a solution of this compound (14.0 g) in diethyl ether was cooled to –78 °C in a dry ice–acetone bath. To this solution was added *n*-butyl lithium (4.2 g) in hexane (41 mL). After 4 h at –78 °C excess solid carbon dioxide was added. 2,3,4,6-Tetrafluoro-3-(1*H*-pyrrol-1-yl)benzoic acid (12.3 g, 66%) was isolated by base wash followed by neutralization and extraction: mp 163.5–165 °C. The acid was reduced with a diborane–tetrahydrofuran complex to give 2,3,4,6-tetrafluoro-3-(1*H*-pyrrol-1-yl)benzenemethanol: NMR δ at 2.17 (m, 1 H, OH), 4.77–4.90 (m, 2 H, CH_2), 6.33–6.43 (m, 2 H, –N=CH–), 6.80–6.93 (m, 2 H, –N=CH–C*H*=).

2,6-Dimethyl-3-(1H-pyrrol-1-yl)benzenemethanol. (3-Amino-2,6-dimethylphenyl)methyl acetate was converted to [2,6-dimethyl-3-(1*H*-pyrrol-1-yl)phenyl]methyl acetate (63%) by the method of Elming and Clauson-Kaas (1952). This was hydrolyzed with sodium hydroxide in aqueous ethanol to give 2,6-dimethyl-3-(1*H*-pyrrol-1-yl)benzenemethanol: NMR δ at 1.53 (br s, 1 H, OH), 2.20 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3), 4.80 (s, 2 H, CH_2), 6.26–6.35 (t, 2 H, –N=CH), 6.70–6.78 (t, 2 H, –N=CH–C*H*–), 7.13 (s, 2 H, phenyl H's).

Synthesis of Esters. All esters were prepared from the appropriate acid chloride and alcohol by using methods already described (Plummer and Pincus, 1981). As an example, [2-methyl-3-(1*H*-pyrrol-1-yl)phenyl]methyl *cis*-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate (**8**) had NMR peaks at δ 1.32 (s, 6 H, cyclopropyl CH_3's), 1.80–2.37 (m, 2 H, cyclopropyl H's), 2.12 (s, 3 H, CH_3), 5.18 (s, 2 H, CH_2), 6.20–6.35 (m, 2 H, –N=CH–), 6.70–6.80 (m, 2 H, –N=CH–CH=), 6.83–7.03 (m, 1 H, vinylic H), and 7.17–7.40 (m, 3 H, phenyl H's). All other esters had NMR spectra consistent with their proposed structures.

Table I. Insecticidal Activity of Heterocyclic "B" Ring Analogues of 2-Methyl[1,1'-biphenyl]-3-methyl Esters



compound			topical relative potency (permethrin = 1.00)					foliar relative potency (permethrin = 1.00)			
no.	X	R	SAW	TBW	CL	MBB	MWB	SAW	MBB	PA	TSM[a]
1	Cl	phenyl	0.8	1.3	2.1	1.6	4.2	1.2	23.0	4.1	0.1
2	CF_3	phenyl	1.8	1.3	2.2	2.4	11.6	1.8	54.0	28.0	0.6
3	Cl	2-furanyl	0.3	0.6	0.3	0.3	0.3	0.1	<0.05	0.5	<0.01
4	CF_3	2-furanyl	0.4	1.1	0.5	0.5	2.5	0.2	0.4	0.9	<0.01
5	Cl	2-thienyl	0.4	0.5	0.6	2.5	4.3	0.3	1.02	0.9	<0.01
6	CF_3	2-thienyl	0.9	1.2	1.5	2.9	13.9	1.0	5.2	1.5	<0.06
7	Cl	1-pyrrolyl	0.4	0.9	1.7	0.6	3.3	0.3	NT	1.8	<0.06
8	CF_3	1-pyrrolyl	1.3	4.0	3.0	0.7	4.1	0.7	6.1	3.4	0.1
9	Cl	2,5-diCH_3 1-pyrrolyl	0.01	NT[b]	NT	0.02	<0.1	<0.06	<0.3	<0.3	NT
10	CF_3	2,5-diCH_3 1-pyrrolyl	0.01	NT	NT	0.05	<0.1	<0.06	0.7	0.4	NT
11	Cl	1-methyl 2-pyrrolyl	<0.005	NT	NT	<0.003	<0.1	<0.01	<0.3	<0.3	<0.01
12	CF_3	1-methyl 2-pyrrolyl									
13	Cl	1-imidazoyl	<0.005	NT	NT	0.1	0.4	<0.06	<0.3	<0.3	<0.01
14	CF_3	1-imidazoyl	<0.005	NT	NT	0.1	0.7	<0.06	<0.3	<0.3	<0.01
15	Cl	2-pyrazinyl	0.01	NT	NT	0.1	0.2	<0.06	~0.3	~0.3	<0.01
16	CF_3	2-pyrazinyl	0.01	NT	NT	0.3	1.1	<0.06	0.8	1.8	<0.06
17	Cl	3-pyridinyl	0.01	NT	NT	0.02	0.5	<0.06	<0.3	<0.3	<0.01
18	CF_3	3-pyridinyl	0.01	NT	NT	0.02	0.50	<0.06	<0.3	<0.3	<0.01
19	Cl	2-pyridinyl									
20	CF_3	2-pyridinyl	0.3	NT	NT	0.5	1.4	0.3	0.7	<0.3	~0.01

[a] monocrotophos standard = 1.00. [b] NT = not tested.

Biological Studies. All biological studies were conducted as previously reported (Plummer and Pincus, 1981). Topical LD_{50} values (in nanograms per insect) and 95% confidence limits for permethrin over the period of these test were as follows: SAW = 23.1 (13.9–32.2); MBB = 12.8 (7.8–17.8); MWB = 660 (311–1008); CL = 102.9 (52.4–153.3); TBW = 57.1 (34.2–80.0). In foliar tests the LC_{50} values (in ppm) and 95% confidence limits for permethrin were as follows: SAW = 3.4 (1.3–5.5); MBB = 17.9 (0–36.1); PA = 21.1 (3.6–38.6). For monocrotophos, TSM = 3.0 (0.27–5.37).

RESULTS AND DISCUSSION

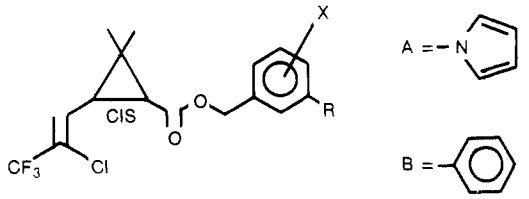
Substitution at the 2-position of [1,1'-biphenyl]-3-methyl pyrethroid esters produces insecticides with increased activity and broader spectrum than the parent esters (Engel et al., 1983; Plummer et al., 1983). This was especially true when the 2-substituent was a methyl group or a fluorine atom. Since it had been previously noted that substitution of a heterocyclic ring for the phenyl "B" ring leads to compounds with good activity, it seemed reasonable that improvements in activity would occur if these systems were similarly substituted. Rather than repeat the same substituent study with each of a series of heterocyclic "B" rings, the 2-methyl group was chosen as a probe of the effect of substitution. Table I shows the insecticidal data for two esters of nine heterocyclic analogues compared with that of the parent biphenyl esters (Plummer et al., 1983; Engel et al., 1983).

Compounds **3**, **5**, and **7** are more active than their heterocyclic parent esters [see Plummer (1983) for comparative data]. For compounds **18** and **20** the equivalent parent was not prepared; however, the parents of **17** and **19** had been prepared and were significantly less active than **17**, **18**, or **20** (Plummer, 1983). Only for compounds **9** and **10** were the unsubstituted parents more active [X = Cl, SAW LD_{50} = 728 ng/insect [relative potency (RP) = 0.02], MBB LD_{50} = 284 ng/insect (RP = 0.04); X = CF3, SAW LD_{50} = 542 ng/insect (RP = 0.03), MBB LD_{50} = 389 ng/insect (RP = 0.05)]. A steric origin for this low activity is suggested, i.e., eclipsing methyl groups or overall steric bulk leading to poor fit at the active site.

None of the "B" ring heterocyclic analogues fully paralleled the parent phenyl compound in activity or spectrum. However, against selected insects, at least in topical testing, compounds **6** and **8** equaled or exceeded the phenyl parent **2**. In topical testing, compound **8** is actually equal to or more active than **2** against lepidopteran species, the traditional strength of synthetic pyrethroids. Although this compound does not have the broad spectrum activity of **2** against MBB and MWB, it does share with **1** and **2** significant acaricidal activity as represented by TSM (compound **8** has a relative potency of 35.5 to permethrin against TSM). The foliar activity of the "B" ring heterocyclic compounds does not parallel the topical activity. One can speculate that this is due to the lower photostability of the heterocyclic rings vis-à-vis a phenyl ring.

Of the 2-methyl substituted heterocyclic "B" rings, the 1-pyrrole analogues, compounds **7** and **8**, are the most active overall. In view of this, is seemed reasonable to pursue other substitution patterns on the 3-(1*H*-pyrrol-1-yl)benzenemethanol nucleus. Compounds **9**, **10**, and **11** are "B" ring substituted analogues of the 2'-substituted [1,1'-biphenyl]-3-methanols. Although such a pattern was efficacious in the biphenyl series, it was not here. Therefore, further probes of the effect of substitution were limited to the "A" ring. In Table II the insecticidal activity of a series of substituted [(1*H*-pyrrol-1-yl)phenyl]methyl esters is compiled along with comparative data for the equivalent phenyl compounds. The general trends for the two series are the same. Compounds **8** and **25** are the most active in this series. Compound **27** is, however, the only compound other than compound **8** that displayed significant acaricidal activity [TSM LD_{50} = 50 ppm (RP =

Table II. Insecticidal Activity of Substituted [3-(1*H*-Pyrrol-1-yl)phenyl]methyl *cis*-3-(2-Chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylates



compound			topical relative potency (permethrin = 1.00)		
no.	X	R	SAW	MBB	MWB
8	2-CH_3	A	1.3	0.7	4.1
2	2-CH_3	B	1.8	2.4	11.6
21	2-Br	A	0.6	0.8	2.0
22	2-Br	B	0.2	0.9	1.8
23	6-CH_3	A	0.09	0.1	1.0
24	6-CH_3	B	0.1	0.03	0.3
25	2,6-diCH_3	A	1.3	1.0	6.3
26	2,6-diCH_3	B	0.7	0.7	4.6
27	2,6-diCl	A	0.8	0.8	2.4
28	2,6-diCl	B	0.4	0.4	0.4
29	2,5-diCl	A	0.06	0.1	<0.1
30	2,5-diCl	B			
31	2,6-diF	A	0.5	0.5	2.2
32	2,6-diF	B	1.2	0.7	1.8
33	2,4,5,6-tetraF	A	1.2	0.02	0.8
34	2,4,5,6-tetraF	B	2.1	1.4	1.3

0.04)]. The low activity of the 2,5-dichloro analogue (compound **29**) was consistent with the earlier finding that substitution other than fluorine in the 5-position of the biphenyl esters resulted in a dramatic loss of activity (Plummer et al., 1983).

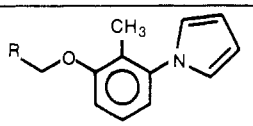
2-Methyl-3-(1*H*-pyrrol-1-yl)benzenemethanol was used in the preparation of a series of esters using common pyrethroid acid moieties. Insecticidal data for this series are collected in Table III. In general, none of these compounds is overall more active than compound **8**. Compounds **36**, **39**, and **41** are interesting for the fact that they are trans esters, all of which have excellent activity against MWB. Compound **38** is unique in this series for its excellent MBB activity. All the compounds had foliar activities lower than anticipated from the topical data. Only compounds **35** and **37** had significant acaricidal activity.

Since the effect of substitution on the "B" ring heterocyclic analogues generally parallels the results for the parent biphenyl esters, we suggest a common origin for the phenomena observed. It has been reported (Suzuki, 1959; Schmid and Brosa, 1972; Zaitsev and Khramova, 1974) that substitution of a methyl group in the 2-position of biphenyl increases the intraring twist angle from 20° to 53–58°. This increase in twist angle not only leads to a different steric relationship of the two aromatic rings that could affect the molecule's steric interaction at an active site but also results in a reduction in conjugation between the two aromatic rings (Zaitsev and Khramova, 1974) that could affect the electronic interaction of the molecule with the active site. Galasso and De Alti (1971) concluded from extended Huckel calculations and infrared evidence that 1-phenylpyrrole and 2-phenylthiophene have a preferred twist angle of ca. 40°, albeit in a shallow energy well, while 2-phenylfuran is nearly planar. The substitution of a methyl group in the 2-position of these heterocycles should also cause an increase in the twist angle. The shorter intraring bond distance of 1-phenylpyrrole (Galasso and De Alti, 1971) should lead to a somewhat larger twist angle than 2-methylbiphenyl. The larger 2-bromo group in the biphenyl ester (**21**) and the pyrrole ester (**22**) caused a significant loss of activity, a trend also noted for other large 2-substituents in the biphenyl series (Plummer et al., 1983). This evidence leads us to speculate that the activity and perhaps the spectrum of biphenyl and "B" ring heterocyclic analogues of biphenyl pyrethroid esters is dependent on the intraring twist angle of the alcohol. Further, we suggest that an optimum twist angle exists and that large groups in the 2-position (e.g., bromine) or a 2,2′-**11** or 2,2′,5′-substitution pattern (**9**, **10**) produce a twist angle that exceeds this optimum.

CONCLUSIONS

Substitution of a 2-methyl group on the "A" ring of pyrethroid esters of 3-heterocyclic benzyl alcohols generally results in an increase in activity and in some cases leads to pyrethroid esters with broader spectrum than other synthetic pyrethroids, e.g., permethrin. On the basis of data developed for a series of substituted 3-(1*H*-pyrrol-1-yl)benzenemethanol esters, it is concluded that substitution of other groups in other positions significantly reduces activity. An exception was compound **25**, a 2,6-dimethyl-3-(1*H*-pyrrol-1-yl)benzenemethanol ester, which equaled its 2-methyl analogoues, compound **8**, in overall activity. The insecticidal activity of these biphenyl analogues and the biphenyl pyrethroid esters themselves may

Table III. Insecticidal Activity of Esters of 2-Methyl-3-(1*H*-pyrrol-1-yl)benzenemethanol and Common Pyrethroid Acid Moieties



compound		topical relative potency (permethrin = 1.00)				
no.	R	SAW	TBW	CL	MBB	MWB
35	*cis*-3-(3-chloro-2,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate	0.2	0.5	0.4	0.2	1.5
36	*trans*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate	0.07	NT[a]	NT	0.2	4.2
37	(1*R*)-*cis*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate	0.8	3.0	2.3	0.9	8.4
38	*cis*-3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropanecarboxylate	0.2	1.2	2.6	6.7	3.0
39	*trans*-3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropanecarboxylate	0.05	NT	NT	0.5	4.7
40	*trans*-3-(2-methyl-1-propenyl)-2,2-dimethylcyclopropanecarboxylate	0.02	NT	NT	0.08	1.3
41	(1*R*)-*trans*-3-(cyclopentylidenemethyl)-2,2-dimethylcyclopropanecarboxylate	0.2	0.3	1.5	0.4	9.1
42	(1*R*)-*cis*-3-(1,2-dibromo-2.2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate	0.7	NT	NT	0.8	2.6
43	1-(4-chlorophenyl)-2-methylpropanecarboxylate	<0.01	NT	NT	0.06	0.24
44	2,2-dichloro-1-(4-ethoxyphenyl)cyclopropanecarboxylate	0.05	NT	NT	0.04	<0.1
45	2,2,3,3-tetramethylcyclopropanecarboxylate	0.02	NT	NT	0.2	1.1
46	2,2-dichloro-3,3-dimethylcyclopropanecarboxylate	<0.01	NT	NT	0.01	0.3

[a] NT = not tested.

be related to an optimal twist angle between the aromatic rings of the alcohol.

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Registry No. 1, 76351-21-8; **2**, 82657-04-3; **3**, 89929-76-0; **4**, 89929-75-9; **5**, 89929-71-5; **6**, 89929-69-1; **7**, 83141-15-5; **8**, 83141-13-3; **9**, 83141-21-3; **10**, 83141-20-2; **11**, 90740-88-8; **12**, 90762-68-8; **13**, 90740-89-9; **14**, 90740-90-2; **15**, 89929-79-3; **16**, 89929-78-2; **17**, 90740-91-3; **18**, 89929-81-7; **19**, 90740-92-4; **20**, 89929-81-7; **21**, 83141-27-9; **22**, 82657-09-8; **23**, 83141-33-7; **24**, 90740-93-5; **25**, 90740-94-6; **26**, 82657-06-5; **27**, 90820-82-9; **28**, 83322-09-2; **29**, 83141-35-9; **30**, 90740-95-7; **31**, 90740-96-8; **32**, 82657-05-4; **33**, 90740-97-9; **34**, 83169-69-1; **35**, 90740-98-0; **36**, 83141-16-6; **37**, 83198-50-9; **38**, 83141-17-7; **39**, 83141-26-8; **40**, 83153-50-8; **41**, 83141-38-2; **42**, 90740-99-1; **43**, 83141-37-1; **44**, 83141-39-3; **45**, 83141-36-0; **46**, 90741-00-7; 2-methyl-3-(thien-2-yl)benzenemethanol, 89929-88-4; 3-chloro-2-methylaniline, 87-60-5; 1-chloro-2-methyl-3-(thien-2-yl)benzene, 89634-69-5; 2-methyl-3-(thien-2-yl)benzoic acid, 89929-87-3; 1-chloro-2-methyl-3-(pyridin-2-yl)benzene, 4381-33-3; 1-chloro-2-methyl-3(pyridin-4-yl)benzene, 4381-38-8; 2-methyl-3-(pyridin-2-yl)benzenemethanol, 89930-07-4; 2-methyl-3-(pyridin-3-yl)benzenemethanol, 89930-04-1; 2-methyl-3-(furan-2-yl)benzenemethanol, 89929-94-2; (3-amino-2-methylphenyl)methyl acetate, 89929-96-4; [3-(furan-2-yl)-2-methylphenyl]methyl acetate, 89929-97-5; [2-methyl-3-(1-methyl-1*H*-pyrrol-2-yl)phenyl]methyl acetate, 90741-02-9; 2-methyl-3-(1-methyl-1*H*-pyrrol-2-yl)benzenemethanol, 90741-01-8; 2-methyl-3-(pyrazin-2-yl)benzenemethanol, 89929-98-6; 3-amino-2-methylbenzenemethanol pyranyl ether, 90762-69-9; 2-methyl-3-(imidazol-1-yl)benzenemethanol, 90741-03-0; (3-isothiocyanato-2-methylphenyl)methyl acetate, 90741-04-1; 1-aminocacetaldehyde diethyl acetal, 25740-42-5; *N*-(diethoxyethyl)-*N'*-[2-methyl-3-(acetoxymethyl)phenyl]thiourea, 90741-05-2; 2-methyl-3-(2-mercaptoimidazol-1-yl)benzenemethanol, 90741-06-3; 2-methyl-3-(1*H*-pyrrol-1-yl)benzenemethanol, 83140-97-0; 1-(3-chloro-2-methylphenyl)pyrrole, 83140-95-8; 2-methyl-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzenemethanol, 83141-01-9; 1-(3-chloro-2-methylphenyl)-2,5-dimethylpyrrole, 83140-99-2; 2,6-dichloro-3-(1*H*-pyrrol-1-yl)benzenemethanol, 83141-06-4; 2-bromo-3-(1*H*-pyrrol-1-yl)benzenemethanol, 83141-09-7; [2-bromo-3-(1*H*-pyrrol-1-yl)phenyl]methyl acetate, 83141-08-6; 2,6-difluoro-3-(1*H*-pyrrol-1-yl)benzenemethanol, 83153-49-5; 2,6-difluorobenzoic acid, 385-00-2; 2,6-difluoro-3-nitrobenzoic acid, 83141-10-0; 2,6-difluoro-3-(1*H*-pyrrol-1-yl)benzoic acid, 83141-12-2; 6-methyl-3-(1*H*-pyrrol-1-yl)benzenemethanol, 90741-07-4; 2,5-dichloro-3-(1*H*-pyrrol-1-yl)benzenemethanol, 90762-70-2; 2,3,4,6-tetrafluoro-3-(1*H*, 90741-08-5; 2,3,4,6-tetrafluoro-3-(1*H*-pyrrol-1-yl)benzoic acid, 90741-09-6; 2,6-dimethyl-3-(1*H*-pyrrol-1-yl)benzenemethanol, 90741-10-9; [2,6-dimethyl-3-(1*H*-pyrrol-1-yl)phenyl]methyl acetate, 90741-11-0.

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