Synthesis and Biological Evaluation of New Pyrethroids Having Halogen, Keto, or Nitro Group-Containing Substituents

Ming-Kuan Chyan and Scott J. Norton*

Division of Biochemistry, Box 5218, University of North Texas, Denton, Texas 76203-0218

Thirteen pyrethroid esters, most of which contain strong electron-withdrawing groups (e.g., halomethylketo and nitro groups) in the side chain of the cyclopropane acid moiety, have been synthesized. The synthesis involved the reaction of various active methylene compounds with 3-formyl-2,2-dimethylcyclopropanecarboxylic esters of known pyrethroid alcohols. Rather than the usually employed Wittig reaction for these syntheses, the novel pyrethroid acid moieties were prepared by amino acid-catalyzed Knoevenagel condensations under mild conditions. Preliminary toxicity studies of the pyrethroid esters, against several insect and one mite species, were conducted. Two of these compounds had good repellent activity against the twospotted spider mite (*Tetranychus urticae*) at 100 ppm, and six of them had medium insecticidal activity against either black bean aphid (*Aphis fabae*) or western potato leafhopper (*Empoasca abrupta*) at 10 ppm.

Keywords: *Insecticides; pyrethroids; halomethyl ketones*

INTRODUCTION

Synthetic pyrethroids have attracted great attention because of their high insecticidal activity, low mammalian toxicity, and low environmental persistence (Carter, 1989). Inside the molecule, the side chains of the cyclopropane-containing acid moieties of these esters play an important role in determining insecticidal activity, detoxification processes, and oxidative degradation processes (Ando et al., 1994; Elliott, 1989). Thus, replacement of the *gem*-dimethyl groups in the vinyl side chain of pyrethrin I with halogens greatly increases the insecticidal activity and photostability (Brown et al., 1973). In the past, a number of synthetic pyrethroids containing monohalo or dihalo side chains have been synthesized and used as effective insecticides (Elliott, 1989; Norton et al., 1976).

As a part of our continuing interest in pyrethroid insecticides, we have synthesized several novel pyrethroid-related compounds that contain strong electron-withdrawing groups in the acid moiety of the final pyrethroid ester. The syntheses of these pyrethroids were accomplished by amino acid-catalyzed Knoevenagel condensations of various active methylene compounds with 3-formyl-2,2-dimethylcyclopropanecarboxylates. Preliminary insect and mite toxicity data on the new pyrethroids are presented.

EXPERIMENTAL PROCEDURES

General. Nuclear magnetic resonance spectra were obtained on a Varian Gemini 200 NMR spectrometer in $CDCl_3$, and the chemical shifts are in parts per million using tetramethylsilane as internal standard. Elemental analyses of selected compounds (see Appendix) were performed by Atlantic Microlab, Norcross, GA; analyses were within ±0.4% of theory. Thin-layer chromatography was performed with precoated TLC (silica gel adsorbent sheets 13181 with fluorescent indicator) from Eastman Kodak Co. Preparative thin-layer chromatography was carried out on a Harrison Chromatotron, using the glass rotor coated to a 2-mm thickness with 55 g of silica gel PF-254 with $CaSO_4 \cdot {}^1/_2H_2O$ (EM Science, Inc.). Silica gel (60–200 mesh) from J. T. Baker Inc., heated in an open beaker for 24 h at 110 °C, was used for column chromatography. The solvent systems used for TLC were as follows (v/v): A, 1:19 ethyl acetate/*n*-hexane; B, 1:9 ethyl acetate/*n*-hexane; C, 1:1 ethyl acetate/*n*-hexane. Methyl (±)-*cis,trans*-3-(dimethoxymethyl)-2,2-dimethylcyclopropanecarboxylate and 4-cyclopentene-1,3-dione were purchased from Aldrich Chemical Co., Inc. 3-Phenoxybenzyl alcohol and 3-phenoxybenzaldehyde were kindly supplied by Hardwicke Chemical Co. 1-Bromo-3-trifluoro-2-propanone, 1-chloro-3-trifluoro-2-propanone, 1-bromo-3-trichloro-2-propanone, and 1,3,3,3-tetrachloro-2-propanone were prepared according to the procedure of Shapiro et al. (1973). Bromonitromethane was synthesized according to the procedure of Fishwick et al. (1986). 1,2,3,4-Tetrachloro-1,3-cyclopentadiene and 4,5-dichloro-4-cyclopentene-1,3-dione were prepared following the procedure of Roedig and Hörnig (1955). 4,5-Dibromo-4-cyclopentene-1,3-dione and 4,5-diiodo-4-cyclopentene-1,3-dione were synthesized according to the method of Roedig and Ziegler (1961).

Organic Syntheses. *Methyl (±)-cis,trans-3-Formyl-2,2-dimethylcyclopropanecarboxylate.* The compound was prepared from methyl (±)-*cis,trans*-3-(dimethoxymethyl)-2,2-dimethylcyclopropanecarboxylate according to the method of Ortiz de Montellano and Dinizo (1978). The yield was 86%: TLC (solvent B) $R_f = 0.46$; ^{1}H NMR 9.59 (d, 1 H, $J = 3.1$ Hz, CHO), 3.71 (s, 3 H, CO_2CH_3), 2.47 (m, 2 H, ring CH), 1.35, 1.31 (2 × s, 6 H, ring CH_3) ppm.

(±)-cis,trans-3-Formyl-2,2-dimethylcyclopropanecarboxylic Acid. The procedure was the same as in an earlier paper (Matsui et al., 1962). The yield was 90%: TLC (solvent C) $R_f = 0.48$; ^{1}H NMR 9.60 (d, 1 H, $J = 3.3$ Hz, CHO), 2.51 (dd, 1 H, $J = 3.3$, 5.5 Hz, ring CH), 2.47 (d, 1 H, $J = 5.5$ Hz, ring CH), 1.39, 1.33 (2 × s, 6 H, ring CH_3) ppm.

3-Phenoxybenzyl (±)-cis,trans-3-Formyl-2,2-dimethylcyclopropanecarboxylate. One gram (7.03 mmol) of (±)-*cis,trans*-3-formyl-2,2-dimethylcyclopropanecarboxylic acid, 1.69 g (8.44 mmol) of 3-phenoxybenzyl alcohol, and 1.60 g (7.75 mmol) of dicyclohexylcarbodiimide were dissolved in 25 mL of anhydrous ether at 0 °C, and then 0.10 g (0.84 mmol) of *N,N*-dimethyl-4-aminopyridine was added to the reaction mixture in one portion. The reaction mixture was stirred in an ice bath for 2 h and then at room temperature for 16 h. A few drops of glacial acetic acid were added to the reaction mixture, which was then stirred for an additional 30 min. Column chromatography (solvent A) and preparative Chromatotron chromatography (solvent B) were utilized for the purification. A pure colorless oil, 2.01 g (88%), was recovered after solvent was

* Author to whom correspondence should be addressed [e-mail norton@cas1.unt.edu; fax (817) 565-4136].

0021-8561/95/1443-2286$09.00/0

removed *in vacuo*: TLC (solvent B) R_f = 0.47; ^{1}H NMR 9.58 (t, 1 H, J = 1.7 Hz, CHO), 7.40–6.95 (m, 9 H, Ar-H), 5.10 (s, 2 H, CO_2CH_2), 2.50 (d, 2 H, J = 1.7 Hz, ring CH), 1.33, 1.30 (2 × s, 6 H, ring CH_3) ppm.

α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-Formyl-2,2-dimethylcyclopropanecarboxylate. 3-Phenoxybenzylcyanohydrin was prepared according to the method of Ruzo et al. (1977). The esterification procedure described above was used, and the yield was 83%: TLC (solvent B) R_f = 0.32; ^{1}H NMR 9.64, 9.61 (2 × d, 1 H, J = 3.0, 3.0 Hz, CHO), 7.45–7.00 (m, 9 H, Ar-H), 6.36, 6.35 (2 × s, 1 H, CHCN), 2.54 (m, 2 H, ring CH), 1.39, 1.32, 1.31, 1.28 (4 × s, 6 H, ring CH_3) ppm.

General Procedure for the Knoevenagel Condensation To Prepare Pyrethroid Esters. A procedure reported for amino acid-catalyzed Knoevenagel reaction was modified for this condensation (Franklin, 1953). The (±)-*cis,trans*-3-formyl-2,2-dimethylcyclopropanecarboxylate (1.0 mmol), active methylene compound (1.1 mmol), amino acid catalyst (e.g., β-alanine or 6-aminohexanoic acid) (0.1 mmol), and glacial acetic acid (0.6 mL) in anhydrous benzene (10 mL) were placed in a 25-mL, single-neck flask. A small Dean-Stark trap, a condenser, and a calcium chloride drying tube were attached to the flask. The reaction mixture was brought to reflux with vigorous stirring for 3 h and then cooled to room temperature. Purification was accomplished by column chromatography (solvent A) followed by preparative silica gel chromatography using a Chromatotron radial chromatographic system, with solvent B, to give the desired pure product.

*α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-[(E,Z)-2-Chloro-3-(chloromethyl)-3-oxo-1-propenyl]-2,2-dimethylcyclopropanecarboxylate (**1**).* The yield was 49%: TLC (solvent B) R_f = 0.27; ^{1}H NMR 7.45–7.01 (m, 9 H, Ar-H), 6.81, 6.76 (2 × d, 1 H, J = 9.7, 9.7 Hz, vinylic CH), 6.39, 6.37 (2 × s, 1 H, CHCN), 4.56, 4.53 (2 × s, 2 H, $ClCH_2CO$), 2.56 (dd, 1 H, J = 5.2, 9.7 Hz, ring CH), 1.97 (2 × d, 1 H, J = 5.2, 5.2 Hz, ring CH), 1.40, 1.32, 1.31, 1.28 (4 × s, 6 H, ring CH_3) ppm.

*α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-[(E,Z)-2-Chloro-3-(chloromethyl)-3-oxo-2-(1-ethoxy-1-oxo)-1-propenyl]-2,2-dimethylcyclopropanecarboxylate (**2**).* The yield was 38%: TLC (solvent B) R_f = 0.12; ^{1}H NMR 7.45–7.00 (m, 9 H, Ar-H), 6.86–6.75 (m, 1 H, vinylic CH), 6.41, 6.38, 6.37, 6.35 (4 × s, 1 H, CHCN), 4.47–4.22 (m, 4 H, CH_2Cl and CO_2CH_2), 2.89, 2.52 (2 × m, 1 H, ring CH), 1.99 (m, 1 H, ring CH), 1.41–1.26 (m, 9 H, ring CH_3 and ethoxy CH_3) ppm.

*α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-[(E,Z)-2-Bromo-3-(trifluoromethyl)-3-oxo-1-propenyl]-2,2-dimethylcyclopropanecarboxylate (**3**).* The yield was 65%: TLC (solvent B) R_f = 0.18; ^{1}H NMR 7.45–7.01 (m, 10 H, Ar-H and vinylic CH), 6.41, 6.39 (2 × s, 1 H, CHCN), 2.72 (dd, 1 H, J = 5.1, 9.2 Hz, ring CH), 2.13, 2.11 (2 × d, 1 H, J = 5.1, 5.1 Hz, ring CH), 1.44, 1.35 (2 × s, 6 H, ring CH_3) ppm.

*α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-[(E,Z)-2-Chloro-3-(trifluoromethyl)-3-oxo-1-propenyl]-2,2-dimethylcyclopropanecarboxylate (**4**).* The yield was 32%: TLC (solvent B) R_f = 0.33; ^{1}H NMR 7.46–7.01 (m, 9 H, Ar-H), 6.86, 6.84 (2 × d, 1 H, J = 9.5, 9.5 Hz, vinylic CH), 6.41, 6.38 (2 × s, 1 H, CHCN), 2.74 (dd, 1 H, J = 5.1, 9.5 Hz, ring CH), 2.11, 2.09 (2 × d, 1 H, J = 5.1, 5.1 Hz, ring CH), 1.44, 1.34 (2 × s, 6 H, ring CH_3) ppm.

*3-Phenoxybenzyl (±)-cis,trans-3-[(E,Z)-2-Chloro-3-(trichloromethyl)-3-oxo-1-propenyl]-2,2-dimethylcyclopropanecarboxylate (**5**).* The yield was 44%: TLC (solvent B) R_f = 0.61; ^{1}H NMR 7.39–6.95 (m, 9 H, Ar-H), 7.19 (d, 1 H, J = 9.6 Hz, vinylic CH), 5.13 (s, 2 H, CO_2CH_2), 2.67 (dd, 1 H, J = 5.2, 9.6 Hz, ring CH), 2.04 (d, 1 H, J = 5.2 Hz, ring CH), 1.37, 1.29 (2 × s, 6 H, ring CH_3) ppm.

*α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-[(E,Z)-2-Bromo-3-(trichloromethyl)-3-oxo-1-propenyl]-2,2-dimethylcyclopropanecarboxylate (**6**).* The yield was 61%: TLC (solvent B) R_f = 0.43; ^{1}H NMR 7.46–7.01 (m, 10 H, Ar-H and vinylic CH), 6.41, 6.39 (2 × s, 1 H, CHCN), 2.67 (dd, 1 H, J = 5.2, 8.9 Hz, ring CH), 2.05, 2.03 (2 × d, 1 H, J = 5.2, 5.2 Hz, ring CH), 1.43, 1.34, 1.33, 1.29 (4 × s, 6 H, ring CH_3) ppm.

*α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-[(E,Z)-2-Nitroethenyl]-2,2-dimethylcyclopropanecarboxylate (**7**).* The yield was 76%: TLC (solvent B) R_f = 0.37; ^{1}H NMR 7.46–6.89 (m, 9 H, Ar-H), 7.14 (d, 1 H, J = 13.1 Hz, vinylic CH), 6.95 (dd, 1 H, J = 10.3, 13.1 Hz, vinylic CH), 6.37, 6.36 (2 × s, 1 H, CHCN), 2.25 (dd, 1 H, J = 5.1, 10.3 Hz, ring CH), 1.99, 1.98 (2 × d, 1 H, J = 5.1, 5.1 Hz, ring CH), 1.37, 1.34, 1.30, 1.28 (4 × s, 6 H, ring CH_3) ppm.

*α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-[(E,Z)-2-Bromo-2-nitroethenyl]-2,2-dimethylcyclopropanecarboxylate (**8**).* The yield was 66%: TLC (solvent B) R_f = 0.44; ^{1}H NMR 7.38 (d, 1 H, J = 9.8 Hz, vinylic CH), 7.45–7.01 (m, 9 H, Ar-H), 6.40, 6.38 (2 × s, 1 H, CHCN), 2.41 (dd, 1 H, J = 5.1, 9.8 Hz, ring CH), 2.06, 2.05 (2 × d, 1 H, J = 5.1, 5.1 Hz, ring CH), 1.42, 1.36, 1.32 (3 × s, 6 H, ring CH_3) ppm.

*α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-(2,3,4,5-Tetrachloro-2,4-cyclopentadien-1-ylidenemethyl)-2,2-dimethylcyclopropanecarboxylate (**9**).* The yield was 81%: TLC (solvent B) R_f = 0.54; ^{1}H NMR 7.45–7.00 (m, 9 H, Ar-H), 6.40, 6.39 (2 × s, 1 H, CHCN), 6.34, 6.32 (2 × d, 1 H, J = 10.5, 10.5 Hz, vinylic CH), 3.39 (dd, 1 H, J = 5.1, 10.5 Hz, ring CH), 2.05, 2.04 (2 × d, 1 H, J = 5.1, 5.1 Hz, ring CH), 1.43, 1.36, 1.35, 1.32 (4 × s, 6 H, ring CH_3) ppm.

*α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-(2,5-dioxo-3-Cyclopenten-1-ylidenemethyl)-2,2-dimethylcyclopropanecarboxylate (**10**).* The yield was 52%: TLC (solvent B) R_f = 0.13; ^{1}H NMR 7.45–7.00 (m, 11 H, Ar-H and vinylic CH), 6.63, 6.62 (2 × d, 1 H, J = 11.3, 11.3 Hz, vinylic CH), 6.42, 6.37 (2 × s, 1 H, CHCN), 3.61 (dd, 1 H, J = 5.1, 11.3 Hz, ring CH), 2.07, 2.06 (2 × d, 1 H, J = 5.1, 5.1 Hz, ring CH), 1.43, 1.37, 1.34, 1.32 (4 × s, 6 H, ring CH_3) ppm.

*α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-(3,4-Dichloro-2,5-dioxo-3-cyclopenten-1-ylidenemethyl)-2,2-dimethylcyclopropanecarboxylate (**11**).* The yield was 48%: TLC (solvent B) R_f = 0.32; ^{1}H NMR 7.44–7.00 (m, 9 H, Ar-H), 6.75, 6.73 (2 × d, 1 H, J = 11.4, 11.4 Hz, vinylic CH), 6.42, 6.38 (2 × s, 1 H, CHCN), 3.59 (dd, 1 H, J = 5.0, 11.4 Hz, ring CH), 2.15, 2.14 (2 × d, 1 H, J = 5.0, 5.0 Hz, ring CH), 1.44, 1.38, 1.35, 1.34 (4 × s, 6 H, ring CH_3) ppm.

*α-Cyano-3-phenoxybenzyl (±)-cis,trans-3-(3,4-Dibromo-2,5-dioxo-3-cyclopenten-1-ylidenemethyl)-2,2-dimethylcyclopropanecarboxylate (**12**).* The yield was 33%: TLC (solvent B) R_f = 0.23; ^{1}H NMR 7.44–7.00 (m, 9 H, Ar-H), 6.72, 6.70 (2 × d, 1 H, J = 11.4, 11.4 Hz, vinylic CH), 6.42, 6.38 (2 × s, 1 H, CHCN), 3.60 (dd, 1 H, J = 5.1, 11.4 Hz, ring CH), 2.15, 2.14 (2 × d, 1 H, J = 5.1, 5.1 Hz, ring CH), 1.44, 1.38, 1.35, 1.34 (4 × s, 6 H, ring CH_3) ppm.

*3-Phenoxybenzyl (±)-cis,trans-3-(3,4-Diiodo-2,5-dioxo-3-cyclopenten-1-ylidenemethyl)-2,2-dimethylcyclopropanecarboxylate (**13**).* The yield was 32%: TLC (solvent B) R_f = 0.23; ^{1}H NMR 7.40–6.93 (m, 9 H, Ar-H), 6.77, 6.64 (2 × d, 1 H, J = 11.6, 11.6 Hz, vinylic CH), 5.11 (s, 2 H, CO_2CH_2), 3.57 (dd, 1 H, J = 5.1, 11.6 Hz, ring CH), 2.15, 2.15 (2 × d, 1 H, J = 5.1, 5.1 Hz, ring CH), 1.38, 1.34 (2 × s, 6 H, ring CH_3) ppm.

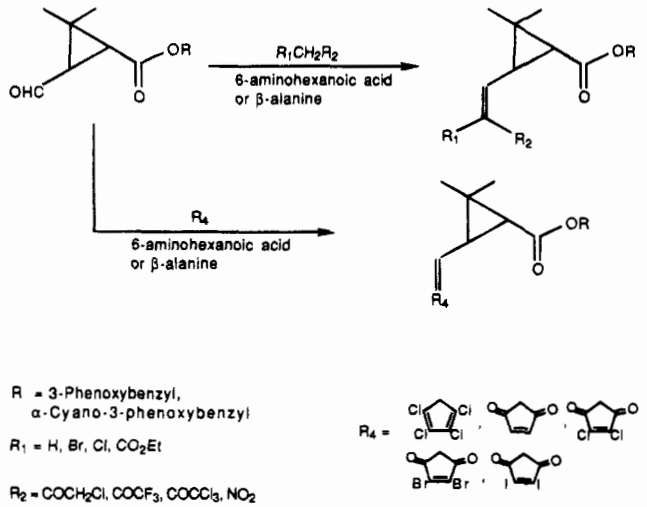
Biological Evaluation. Biolgical testing of selected compounds, as 34:66 mixtures of their *cis/trans* isomers relating to the cyclopropane ring, was carried out by the Agricultural Research Center, American Cyanamid, Princeton, NJ. Compounds that caused >75% mortality in the primary screen target species were elevated to secondary screen for evaluation at lower rates and against additional species. The compounds were tested at dosage rates of 10 and 100 ppm active ingredient in acetone/water (1:1). Some details of the secondary screen methods are given below.

Test 1: Spodoptera eridania (Southern Armyworm; 2nd Instar), Lima Bean Leaf Dip Assay. Test compounds were dissolved at the two dosage concentrations in acetone/water. Leaves were removed from the plant, dipped into the solutions, and allowed to dry at room temperature. Ten larvae were placed on each leaf, and larval mortality was observed after 7 days.

Test 2: Tetranychus urticae (Twospotted Spider Mite), Lima Bean Plant Dip. Testing was similar to that for test 1, except leaves on the whole plant (seedlings, two leaves) were dipped into the test solutions. Larval mortality was determined after 3 days.

Test 3: Aphis fabae (Black Bean Aphid; Mixed Stages), Nasturtium Foliar Treatment. Single plants (seedling stage) were sprayed, using an atomizer, with 50% acetone/water solutions of each test compound. Each plant tested had been

Scheme 1



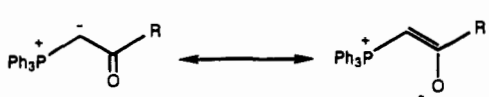
previously infected with 10–50 aphids of mixed stages, and aphid mortality was measured after 3 days.

Test 4: Empoasca abrupta (Western Potato Leafhopper; Adults), Lima Bean Leaf Dip. Testing was as described for test 1, except treated leaves were placed in closed Petri dishes containing 5–20 adults; mortality was determined after 3 days.

Test 5: Heliothis virescens (Tobacco Budworm; 2nd Instar), Cotton Leaf Dip. Testing was as described for test 1, except cotton leaves were used; larval mortality was measured after 5 days.

RESULTS AND DISCUSSION

The low pK_a values associated with active methylene compounds (e.g., CH_3COCH_2Cl, 17; CH_3NO_2, 10.2) containing halomethylketo or nitro groups allow ready condensation with aliphatic aldehydes in amino acid-catalyzed Knoevenagel-type reactions (Franklin, 1953). On the other hand, the Wittig reaction fails for such condensations because the presence of strong electron-withdrawing groups in the alpha position of phosphorus ylides spreads the negative charge on the carbon by resonance and results in reduced nucleophilicity of the ylide as shown below.



The even more acidic compound 4-cyclopentene-1,3-dione (pK_a = 6) is polymerized easily in basic solution (DePuy and Zaweski, 1959), yet condenses with the cyclopropane aldehyde in an amino acid-catalyzed Knoevenagel reaction to give a reasonable yield of product. Although the active methylene compounds dihalocyclopentene-3,5-diones have been shown to condense with aromatic aldehydes easily, with or without catalyst (Roedig and Ziegler, 1961), we found that such is not the case with the aliphatic cyclopropane aldehyde employed in the present study. The employment of amino acids for catalysis of the Knoevenagel reaction in the present study represents, to our knowledge, the first such usage for the synthesis of pyrethroid acids from cyclopropane aldehydes (see Scheme 1). Both β-alanine and 6-aminohexanoic acid were employed as catalysts; the condensation yields were comparable with either amino acid.

A major reason for synthesizing many of the compounds presented herein relates to earlier synthetic studies, in which the *gem*-dimethyl groups on the vinylic side chain of chrysanthemic acid were replaced by halogens. Some of the resulting halopyrethroid acids are now used in commercially successful pyrethroid esters (Brown et al., 1973; Elliott, 1989). In several of the new pyrethroid acids synthesized in the present study, the products have one of the methyls of chrysanthemic acid replaced by halogen, while the other methyl is replaced by reactive halomethyl ketone groups (**1**, **2**, **5**, **6**). It was considered that these reactive halomethyl ketone functionalities, in the final pyrethroid esters, could serve as insect binding site-directed, electrophilic reagents, resulting in covalent bond formation with nucleophilic protein side chains at or near the pyrethroid binding site. Additionally, with most of the compounds synthesized in this study, it is possible that the very electron-deficient cyclopropane vinyl side chains are susceptible to Michael-type reactions (March, 1992a).

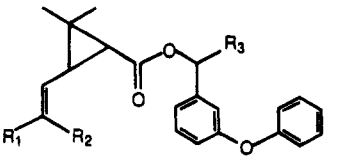
Compounds **7** and **8** explore the effects on insect toxicity of an alternate electron-withdrawing group, the nitro group, substituted on the vinylic side chain of the pyrethroid acid, in the presence and absence of a *gem*-bromo substituent. It was previously found that when two bromine atoms are substituted for the *gem*-dimethyls of the side chain of chrysanthemic acid, the result is the most potent pyrethroid acid yet synthesized (Brown et al., 1973; Elliott, 1989). It has also been shown that replacement of the *gem*-dimethyls of the side chain of chrysanthemic acid with a chlorine atom and a trifluoro group results in a significant increase in insecticidal activity of the final ester (Jutsum et al., 1984).

Compounds **9**–**13** were synthesized to explore the insecticidal/miticidal effects of halogen-substituted cyclopentenedione or cyclopentadiene substituents on the vinylic side chain of pyrethroid acids. Esters of these acids have structures similar to K-Othrin, a potent pyrethroid containing cyclopentane substituents on the vinylic side chain of the acid moiety (Lhoste et al., 1969). Compounds **11**–**13** have a dual halomethyl ketone substitution on the vinylic group of the cyclopropane ring. The halogens, however, are substituted on the olefinic carbons of the cyclopentenedione moiety and should not be reactive for S_N2-type nucleophilic substitution. It is possible, however, that an addition–elimination process, on an electron-deficient olefinic carbon of the cyclopentenedione moiety, could result in a substitution at that site (March, 1992b). Compound **10** was synthesized to serve as the parent structure for measuring the effects of halogen atom substitutions on the cyclopentenedione ring.

The results of insecticidal/miticidal screening studies for southern armyworm (SAW), tobacco budworm (TBW), twospotted spider mite (TSM), black bean aphid, (BBA) and western potato leafhopper (WPLH), are summarized in Tables 1 and 2. Bifenthrin was employed in the evaluations as reference insecticide (Plummer et al., 1983). Limited insect mortality activities are found in the concentration range 10–100 ppm, for compounds **6** (WPLH), **7** (WPLH), **8** (TBW, BBA), **9** (TBW, WPLH), **10** (WPLH), and **13** (WPLH). Further, compounds **3** and **5** have repellent effects against the twospotted spider mite in the same concentration range.

It is difficult to make generalizations concerning structure–activity relationships of the new pyrethroids bearing the dihalocyclopentenedione group (**11**–**13**). The anticipated high insecticidal/miticidal activities were not found, possibly due to the relatively low lipophilicity of

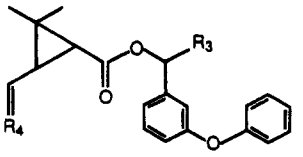
Table 1. Insecticidal/Miticidal Activity of Synthetic Pyrethroids

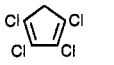
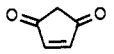
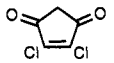
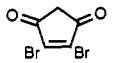
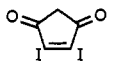


compd	R_1	R_2	R_3	ppm	% mortality SAW[a]	TBW[a]	TSM[a]	BBA[a]	WPLH[a]
1	Cl	$COCH_2Cl$	CN	100	0	0	0	0	–[c]
				10	0	0	0	0	0
2	CO_2Et	$COCH_2Cl$	CN	100	0	0	0	0	–
				10	0	0	0	0	0
3	Br	$COCF_3$	CN	100	0	0	R80[b]	0	–
				10	0	0	0	0	0
4	Cl	$COCF_3$	CN	100	0	0	0	0	–
				10	0	0	0	0	0
5	Cl	$COCCl_3$	H	100	0	0	R90[b]	0	–
				10	0	0	0	0	0
6	Br	$COCCl_3$	CN	100	0	0	0	0	–
				10	0	0	0	0	30
7	H	NO_2	CN	100	0	0	0	–	–
				10	0	0	0	0	30
8	Br	NO_2	CN	100	0	30	0	50	–
				10	0	0	0	0	0
bifenthrin[d]				10	100	100	100	90	100
				1	100	80	0	90	–

[a] SAW, southern armyworm; TBW, tobacco budworm; TSM, twospotted spider mite; BBA, black bean aphid; WPLH, western potato leafhopper. [b] R, repellent effect. [c] –, no data. [d] The data presented are from American Cyanamid, NJ.

Table 2. Insecticidal/Miticidal Activity of Synthetic Pyrethroids



compd	R_4	R_3	ppm	% mortality SAW[a]	TBW[a]	TSM[a]	BBA[a]	WPLH[a]
9		CN	100	0	50	0	0	–[b]
			10	0	0	0	0	30
10		CN	100	0	0	0	0	–
			10	0	0	0	0	30
11		CN	100	0	0	0	0	–
			10	0	0	0	0	0
12		CN	100	0	0	0	0	–
			10	0	0	0	0	0
13		H	100	0	0	0	0	–
			10	0	0	0	0	50
bifenthrin[c]			10	100	100	100	90	100
			1	100	80	0	90	–

[a] SAW, southern armyworm; TBW, tobacco budworm; TSM, twospotted spider mite; BBA, black bean aphid; WPLH, western potato leafhopper. [b] –, no data. [c] The data presented are from American Cyanamid, NJ.

these compounds. The moderate insecticidal/miticidal activities of the esters of the halomethyl ketone pyrethroid acids synthesized were also surprising, since the acid moieties are sterically similar to the natural acid pyrethric acid. The highest activity was found with compound **13** against western potato leafhopper (50% mortality at 10 ppm). The alcohol moiety of compound **13** is the 3-phenoxybenzyl group. It may be that toxicity can be significantly enhanced if the usually far more potent α-cyano-3-phenoxybenzyl alcohol were utilized in the formation of the final pyrethroid ester (Elliott, 1977).

The biological testing program also did not provide for determining the effects of synergists on the pyrethroid toxicities. It is possible, however, that the bioactivity of compounds of the type synthesized herein would not be significantly enhanced by added synergists (Cochran, 1994). Finally, none of the pyrethroid products synthesized in this study was resolved into pure stereoisomers; insecticidal and miticidal activities would most probably have been significantly enhanced with the utilization of pure preparations of the most active isomers (Elliott, 1977).

APPENDIX

Elemental Analysis Data. *Compound* ***3****,* $C_{24}H_{19}BrF_3NO_4$. Theory: C, 55.18; H, 3.67. Found: C, 55.40; H, 3.76.

Compound ***8****,* $C_{22}H_{19}BrN_2O_5$. Theory: C, 56.06; H, 4.06. Found: C, 56.12; H, 4.09.

Compound ***9****,* $C_{26}H_{19}Cl_4NO_3$. Theory: C, 58.34; H, 3.58. Found: C, 58.59; H, 3.72.

Compound ***10****,* $C_{26}H_{21}NO_5$. Theory: C, 73.06; H, 4.95. Found: 72.67; H, 5.36.

LITERATURE CITED

Ando, T.; Koseki, N.; Yasuhara, I.; Kasuga, K.; Matsuo, N.; Ishiwatari, T. Insecticidal activity of new fluorinated pyrethroids and their stability toward chemical oxidation and photoreaction. *Pestic. Sci.* **1994**, *40*, 307–312.

Brown, D. G.; Bodenstein, O. F.; Norton, S. J. New potent pyrethroid, bromethrin. *J. Agric. Food Chem.* **1973**, *21*, 767–769.

Carter, S. W. A review of the use of synthetic pyrethroids in public health and vector pest control. *Pestic. Sci.* **1989**, *27*, 361–374.

Cochran, D. G. Effects of three synergists on pyrethroid resistance in the german cockroach (Dictyoptera: Blattellidae). *J. Econ. Entomol.* **1994**, *87*, 879–884.

DePuy, C. H.; Zaweski, E. F. Cyclopentene-3,5-dione. I. Synthesis and properties. *J. Am. Chem. Soc.* **1959**, *81*, 4920–4924.

Elliott, M. *Synthetic Pyrethroids*; Elliott, M., Ed.; ACS Symposium Series 42; American Chemical Society: Washington, DC, 1977; pp 1–28.

Elliott, M. The pyrethroids: early discovery, recent advances and the future. *Pestic. Sci.* **1989**, *27*, 337–351.

Fishwick, B. R.; Rowles, D. K.; Stirling, C. J. M. bromonitromethane—a versatile electrophile. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1171–1179.

Franklin, S. P. Amino acid catalysis of the Knoevenagel reaction. *J. Org. Chem.* **1953**, *18*, 928–933.

Jutsum, A. R.; Collins, M. D.; Perrin, R. M.; Evans, D. D.; Davies, R. A. H.; Ruscoe, C. N. E. pp321—a novel pyrethroid insecticide. *Proc. Br. Crop Prot. Conf. Pests Dis.* **1984**, 421–428.

Lhoste, J.; Martel, J.; Rauch, F. New insecticide: 5-benzyl-3-furylmethyl *D-trans*-ethanochrysanthemate. *Proc. Br. Insectic. Fungic. Conf. 5th* **1969**, *2*, 554–557.

March, J. Addition to carbon-carbon multiple bonds. In *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; Wiley: New York, 1992a; pp 763–770.

March, J. Nucleophilic substitution at a vinylic carbon. In *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; Wiley: New York, 1992b; pp 335–337.

Matsui, M.; Yamada, Y.; Nonyama, M. Studies of chrysanthemic acid. Part VI. Synthesis of 2,2-dimethyl-3-(2′-cyano-1′-propenyl)cyclopropanecarboxylic acids and their allethrolone esters. *Agric. Biol. Chem.* **1962**, *26*, 351–354.

Norton, S. J.; Bodenstein, O. F.; Brown, D. G. Halopyrethroids: structure-activity relationships. *Bochu Kagaku* **1976**, *41*, 1–7.

Ortiz de Montellano, P. R.; Dinizo, S. E. Based-catalyzed isomerization of *cis*- and *trans*-2,2-dimethyl-3-formylcyclopropanecarboxylates. Nature of the base-stable *cis* intermediate. *J. Org. Chem.* **1978**, *43*, 4323–4328.

Plummer, E. L.; Cardis, A. B.; Martinez, A. J.; VanSaun, W. A.; Palmere, R. M.; Pincus, D. S.; Stewart, R. R. Pyrethroid insecticides derived from substituted biphenyl-3-ylmethanols. *Pestic. Sci.* **1983**, *14*, 560–570.

Roedig, A.; Hörnig, L. 1,2,3,4-Tetrachloro-1,3-cyclopentadiene. *Chem. Ber.* **1955**, *88*, 2003–2011.

Roedig, A.; Ziegler, H. Investigation of 1,2-dihalocyclopentene-3,5-diones. Condensation with aldehydes, coupling, halogenation, and halogen-exchange reactions. *Chem. Ber.* **1961**, *94*, 1800–1813.

Ruzo, L. O.; Holmstead, R. L.; Casida, J. E. Pyrethroid photochemistry: decamethrin. *J. Agric. Food Chem.* **1977**, *25*, 1385–1394.

Shapiro, B. L.; Lin, H. L.; Johnston, M. D., Jr. NMR studies and rotational isomerism in fluoroacetones. I. Trifluoroacetones. *J. Magn. Reson.* **1973**, *9*, 305–325.

Received for review December 5, 1994. Revised manuscript received May 8, 1995. Accepted May 18, 1995.[⊗] This work was supported, in large part, by a research grant from Active Organics of Dallas, TX.

JF940681F

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1995.