α-Cyano-3-phenoxybenzyl Pyrethroids: Derivatizations at the Benzylic Position

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The benzylic position of α-cyano-3-phenoxybenzyl pyrethroids reacts readily with acetone to form 2-(3-phenoxybenzoyl)-2-propyl esters and with pentafluorobenzyl bromide to give pentafluorobenzyl compounds. Both additions occur via a benzyl anion intermediate. The pentafluorobenzyl derivatives of the pyrethroids fenvalerate, fenpropanate, cypermethrin, and decamethrin provide high electron-capture sensitivity potentially useful in residue analysis.

Many commercial and experimental pyrethroid insecticides (e.g., fenvalerate, fenpropanate, cypermethrin, and decamethrin; Figure 1) are esters of α-cyano-3-phenoxybenzyl alcohol or related cyanohydrins (Elliott, 1977; Elliott and Janes, 1978). The benzylic position bearing the cyano group is relatively acidic, undergoing rapid exchange with deuterium on mixing with alkaline D_2O (Roussel-Uclaf, 1978; Ruzo and Casida, 1977). This report describes reactions of α-cyanophenoxybenzyl pyrethroids with acetone and with pentafluorobenzyl bromide (PFB-Br) (Figure 2) that may be useful in residue analysis.

MATERIALS AND METHODS

Chromatography and Spectroscopy. For gas chromatography (GC), the Hewlett-Packard Model 5840A instrument was used with an SP-2100 wall-coated glass capillary column (0.25 mm i.d. × 30 m), helium as the carrier gas (40 cm/s) and a ^{63}Ni electron-capture detector (ECD). The operating conditions were as follows: split ratio 1/100; 300, 280, and 350 °C for the injector, column, and detector temperatures, respectively; make-up gas of 5% argon in methane (20 mL/min). An on-line computer provided the retention time (t_R) and peak area (sum of isomers) relative to mirex as the internal standard.

For GC coupled with mass spectrometry (MS), the Finnigan Model 4023 GC/MS/computer system was used with an SP-2100 glass capillary column as above. Unless indicated otherwise, all data are for the electron impact mode. Relative intensities are based on the most intense ion as 100% and on bromine-79. Proton nuclear magnetic resonance (NMR) spectra were recorded on the Brucker HXS-360 spectrometer with tetramethylsilane as the internal standard.

Condensation with Ketones. An acetone solution of 5 mM decamethrin was refluxed for 48 h in the presence of a suspension of Na_2CO_3. The product was isolated in 95% yield and >99% purity (GC/ECD) by filtration, evaporation to dryness, dissolving in ether, washing with water and then saturated NaCl, drying over anhydrous $MgSO_4$, and solvent evaporation.

Pentafluorobenzylation. For quantitative analysis, 1 mL of an aqueous solution which was 0.1 M in tetrabutylammonium hydrogen sulfate (Bu_4NHSO_4, a phase transfer catalyst) and 0.2 M in NaOH was added to 1 mL of methylene chloride containing the α-cyanophenoxybenzyl pyrethroid (up to 10 μg), mirex (amount estimated to be 0.2–5 times that of the pyrethroid), and PFB-Br (10 μL). The mixture was shaken vigorously at 25 °C for 15–20 min. The organic phase was recovered and evaporated to dryness, 1 mL of toluene was added and evaporated to dryness, and finally 1 mL of toluene was added to obtain the sample for analysis by GC/ECD.

For a larger scale reaction, 0.1 M Bu_4NHSO_4 in aqueous 0.2 M NaOH (10 mL) was added to a solution of decamethrin (50 mg) and PFB-Br (100 μL) in methylene chloride (10 mL). After shaking the mixture for 30 min at 25 °C and workup as above, the residue after toluene evaporation was dissolved in hexane and chromatographed on a silica gel column eluting with hexane (only PFB-Br and its degradation products), then with various ether in hexane mixtures. The fraction of highest purity was examined by GC/MS and NMR.

Table I. NMR Chemical Shifts (δ) of Methyl Groups and Benzylic Substituents of Decamethrin and Its α-Pentafluorobenzyl and Acetone Derivatives

substituent	compound: decamethrin	acetone derivative	pentafluorobenzyl derivative
	Solutions in Carbon Tetrachloride		
CH_3	1.27, 1.19	1.67, 1.66, 1.21, 0.87	1.22, 1.03
CHCN	6.32		
$CH_2C_6F_5$			3.40–3.50
	Solutions in Deuteriobenzene		
CH_3	0.86, 0.59	1.55, 1.52, 0.77, 0.75	0.94, 0.85, 0.68[a]
CHCN	5.94		
$CH_2C_6F_5$			3.04–3.16

[a] The δ 0.85 and 0.68 signals are for one isomer and the δ 0.94 and 0.68 signals for the other isomer in a ~2:1 ratio, respectively.

RESULTS AND DISCUSSION

Acetone Derivative of Decamethrin. The waxy solid has an elemental analysis consistent with $C_{24}H_{24}O_4Br_2$. Calcd: C, 53.75; H, 4.51; Br, 29.80. Found: C, 53.55; H, 4.43; Br, 28.89. This elemental composition is confirmed by positive ion chemical ionization MS (methane as the ionizing gas) with the observed base peak of m/e 535 $(M + 1)^+$. Electron impact MS gives m/e (relative intensity) 534 (0.5) and the same fragments from the acid moiety discussed later for PFB-decamethrin except that a major peak appears at m/e 279(42) corresponding to the acid moiety minus oxygen. NMR establishes that the CHCN proton is lost and two additional methyl groups are introduced (Table I). Thus, the product is an ester derived by loss of the elements of hydrogen cyanide and addition of those of acetone to the alcohol moiety. IR and MS evidence indicate that the product is the 2-(3-phenoxybenzoyl)-2-propyl ester (Figure 2). The IR ($CHCl_3$) establishes the presence of both ester and ketone carbonyl

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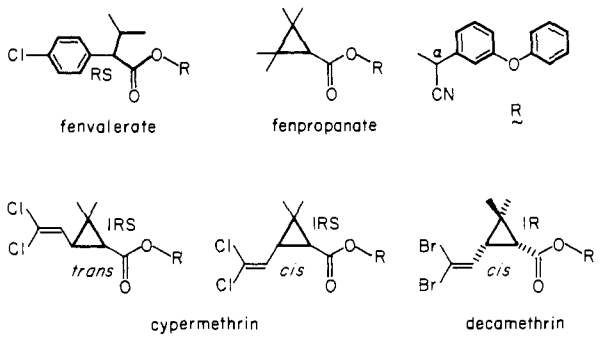


Figure 1. Structures of α-cyanophenoxybenzyl pyrethroids examined.

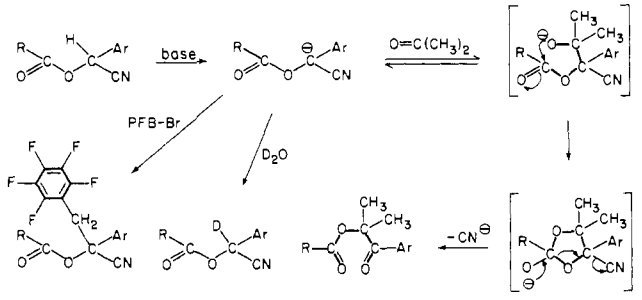
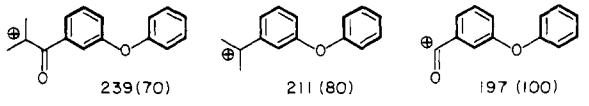


Figure 2. Derivatization of α-cyanophenoxybenzyl pyrethroids at the benzylic position. R is a portion of the acid moiety of the pyrethroid and Ar is 3-phenoxyphenyl or phenyl.

bands (1720 and 1685 cm^{-1}, respectively). Three major ions (MS) from the alcohol moiety also support the proposed



structure.

Analogous reactions appear to take place on refluxing *cis*-cypermethrin, *trans*-cypermethrin, fenvalerate, fenpropanate, and α-cyanobenzyl acetate in acetone with Na_2CO_3, each compound giving a single product evident by GC/ECD and TLC with suitable solvent systems. The acetone derivative of fenvalerate was also examined by MS, NMR, and IR, giving appropriate spectra in each case. The decamethrin–acetone and fenvalerate–acetone reactions proceed much faster on replacing suspended Na_2CO_3 by 1 mM potassium *tert*-butoxide, i.e., quantitative product formation within 15 min at 25 °C.

Relative to decamethrin, its acetone derivative is less stable under acidic and more stable under basic conditions. The acetone derivative does not react with PFB-Br. An important consequence of the acetone reaction is that it liberates cyanide for analysis by selective and sensitive procedures (Rand et al., 1976). It also indicates the need for caution in storing α-cyanophenoxybenzyl pyrethroids dissolved in acetone or other ketones.

Pentafluorobenzyl Derivatives. Reaction with PFB-Br yields two derivatives from each of fenvalerate, *cis*- and *trans*-cypermethrin and decamethrin and one from fenpropanate (Table II). When two derivatives are obtained, they are diastereomers with almost identical MS fragmentation patterns. The fenvalerate derivative is formed by pentafluorobenzylation, i.e., *m/e* (relative intensity) 599 (2) $(M)^+$. The other PFB-pyrethroids give no parent ion. The fragmentation pattern of PFB-decamethrin (Figure 3) suggests that pentafluorobenzylation occurs at the benzylic position (Figure 2). The base peak with all of the PFB pyrethroids is the ion from decarboxylation of the acid moiety and they all give identical

Table II. Retention Times of α-Cyanophenoxybenzyl Pyrethroids and Their α-Pentafluorobenzyl and Acetone Derivatives on an SP-2100 Capillary Column GC at 280 °C

	t_R, min[b]	
pyrethroid[a]	parent compd[c]	PFB deriv[c]
fenvalerate	5.07, 5.31	9.64, 10.75[d]
fenpropanate	2.64	4.40
cis-cypermethrin	4.11, 4.27	7.49, 8.17[e]
trans-cypermethrin	4.18, 4.27	7.83, 8.46[e]
decamethrin[f]	6.00	10.75, 10.98[e]

[a] Decamethrin is the 1*Rcis*, α*S* isomer. Other pyrethroids are not resolved. [b] Mirex gives t_R value of 3.22 min. [c] All products give appropriate GC/MS fragmentation patterns for the assigned structures, including very similar or identical spectra for each peak when two are indicated. [d] Relative area ~2:1 for the 9.64 and 10.75 min peaks, respectively. [e] Relative area ~1:1 for the two peaks. [f] The acetone derivative of decamethrin gives a single peak at t_R 6.27 min.

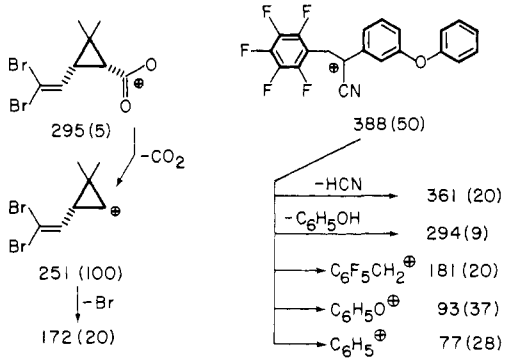


Figure 3. Mass spectral fragments from the pentafluorobenzyl derivative of decamethrin. No parent ion is observed. The data are *m/e* (relative intensity) with the appropriate ion clusters for the indicated numbers of bromine atoms. A portion of the *m/e* 93 ion may arise from loss of bromine from the *m/e* 172 ion. Additional fragment ions do not exceed 10% relative intensity.

fragments from the alcohol moiety. NMR spectral data on PFB-decamethrin (Table I) confirms the MS evidence that the PFB group is at the benzylic carbon, i.e., the C*H*CN is absent and the $CH_2C_6F_5$ is introduced.

The α*R* and α*S* diastereomers of PFB-decamethrin are distinguishable by NMR in C_6D_6 but not in CCl_4 (Table I). The ~2:1 isomer ratio indicated by the NMR signals of the methyl groups (Table I) is also evident from the signals of the cyclopropane ring protons and the peak ratios for total ion current on GC/MS with the higher t_R product predominating.

Pentafluorobenzylation as an Analytical Method. This is the same procedure commonly used for analysis of carboxylic acids, phenols, and sulfonamides (Ehrsson, 1971; Gyllenhaal and Ehrsson, 1975) but involves benzylic alkylation rather than N- or O-alkylation. More than 99% of the parent compound reacts with PFB-Br. The yield of PFB-decamethrin is >90% and its recovery is >98% using the isolated compound as the analytical standard. Each α-cyanophenoxybenzyl pyrethroid gives a unique set of products useful in GC/ECD recognition of the parent compound (Table II). The ECD response is lower for the parent pyrethroid than for an equal weight of mirex. However, on derivatization, fenvalerate, the cypermethrin isomers and decamethrin give a peak area of two–five-fold greater than that for a similar weight of mirex. This comparison is simplified for fenpropanate since it is a single peak before and after derivatization and its response relative to mirex is 3% as the parent compound and 30% as the PFB derivative.

Interfering ECD-sensitive peaks at short t_R, from side reactions of PFB-Br, can be removed on a short silica gel column since they elute with 5% toluene in hexane and the PFB-pyrethroid derivatives can be subsequently eluted with toluene (modified from Kováč and Anderle, 1978).

Pentafluorobenzylation provides a rapid and convenient method for introducing a highly ECD sensitive substituent into α-cyanophenoxybenzyl pyrethroids. These PFB derivatives may be useful in confirming the identity of residues analyzed by other methods and, with a suitable cleanup procedure, in enhancing the sensitivity of residue analysis.

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LITERATURE CITED

Ehrsson, H. *Acta Pharm. Suec.* **1971**, *8*, 113.
Elliott, M. *ACS Symp. Ser.* **1977**, *No. 42*, 1.
Elliott, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473.
Gyllenhaal, O.; Ehrsson, H. *J. Chromatogr.* **1975**, *107*, 327.
Kováč, P.; Anderle, D. In "Handbook of Derivatives for Chromatography"; Blau, K., King, G. S., Eds.; Heyden: Philadelphia, 1978; pp 201-233.
Rand, M. C.; Greenberg, A. E.; Taras, M. J., Eds. "Standard Methods for the Examination of Water and Wastewater", 14th ed.; American Public Health Association, Washington, DC, 1976; pp 361-387.
Roussel-Uclaf *French Patent* 2 375 161, 1978.
Ruzo, L. O.; Casida, J. E., unpublished results, 1977.

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Resolution, Absolute Configuration, and Acute and Delayed Neurotoxicity of the Chiral Isomers of *O*-Aryl *O*-Methyl Phenylphosphonothioate Analogues Related to Leptophos

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The chiral isomers of *O*-methyl phenylphosphonothioic acid, *O*-(4-bromo-2,5-dichlorophenyl) *O*-methyl phenylphosphonothioate (leptophos), and *O*-(2,5-dichlorophenyl) *O*-methyl phenylphosphonothioate (desbromoleptophos) were prepared and their toxicological properties were examined. The absolute configurations of the enantiomers of leptophos and desbromoleptophos were assigned by relating them to the configurations of the corresponding *O*-methyl phenylphosphonothioic acids. The absolute configuration of the (−)-α-methylbenzylammonium salt of (−)-*O*-methyl phenylphosphonothioic acid was established by X-ray diffraction analysis. Optical purity was assessed by chiral pseudo-contact lanthanide shift reagents and hydrolysis of the esters. The $(R)_p(+)$ isomers of leptophos and desbromoleptophos were more acutely toxic to the housefly and white mouse, while the $(S)_p(-)$ isomers were more delayed neurotoxic when administered intraperitoneally to the hen.

It is well known that chirality at the phosphorus atom of an organophosphorus ester often has a significant effect on the biological activity of the ester. The difference in toxicity of the enantiomers of chiral organophosphorus poisons has been attributed to differences in their ability to inhibit acetylcholinesterase and other esterases and to differences in their rates of metabolism in animals (Lee et al., 1978).

Recently, the effect of phosphorus chirality on the delayed neurotoxicity of the enantiomers of EPN [*O*-ethyl *O*-(*p*-nitrophenyl) phenylphosphonothioate] and the corresponding oxons was described (Ohkawa et al., 1977b; Abou-Donia et al., 1978). The dextrorotatory isomer was several-fold more acutely toxic to hens, houseflies, and the rice stem borer, while the levorotatory isomer was more delayed neurotoxic to hens. Such differences in the toxicological properties of the chiral isomers suggest that the active site associated with delayed neurotoxicity is stereochemically different from the site associated with acute toxicity, i.e., acetylcholinesterase. It has been hypothesized that organophosphorus induced delayed neurotoxicity is attributable to inhibition of an enzyme identified as neurotoxic esterase (Johnson, 1975).

O-(4-Bromo-2,5-dichlorophenyl) *O*-methyl phenylphosphonothioate (leptophos) and all the corresponding mono- and dichlorophenyl analogues also have been shown to cause delayed neurotoxicity (Hollingshaus et al., 1979). This paper is concerned with the resolution and determination of the absolute configuration of the chiral isomers of leptophos and desbromoleptophos and the toxicological properties of these compounds.

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MATERIALS AND METHODS

General. Optical rotations were determined with a

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