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Pyrethroid-like Carbamates Having Insecticidal Activity

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Carbamate esters have been synthesized from 21 carbamic acids that are nitrogen isoteres of the acid moieties of fenvalerate- and fluvalinate-like pyrethroids. These acid moieties were derived, in the main, from *N*-isopropylaniline and α-(substituted)benzylamine derivatives. The alcohol portions of the carbamate esters were various appropriate pyrethroid alcohols. Preliminary insecticidal activity studies on pyrethroid-susceptible houseflies were conducted; some of the carbamate esters exhibited high toxicity. Conclusions regarding insecticidal activity with respect to the structure and stereochemistry of the carbamate esters have been made. Thus, the *N*-isopropyl substituent decreases insecticidal activity in the benzylamine-derived series of compounds, while the *N*-isopropyl substituent enhances activity in the aniline-derived series of compounds. Also, certain substituents on the phenyl groups of both series, and alkyl substituents on the benzylic carbon of the benzylamine series, can greatly affect insecticidal potency of the carbamate esters.

During the past several years, stereochemical requirements for both acid and alcohol moieties of active pyrethroids have been studied extensively and configurational characteristics have been determined in an effort to relate structure and bioactivity (Anderson et al., 1985; Burt and Goodchild, 1977; Elliott, 1977, 1980; Elliott and Janes, 1978; Plummer et al., 1984; Norton et al., 1985). The configuration at certain chiral centers must be properly oriented for a biological receptor. With stereoisomers of pyrethroid esters, e.g., cypermethrin and decamethrin, the *R* configurations (α-carbon) of the acid moieties are more active than are the *S* isomers (Burt et al., 1974; Elliott et al., 1974, 1978). Similarly, with fenvalerate and related acids, the first potent "pyrethroid" without the cyclopropane ring (Ohno et al., 1974), the (*R*)-isopropyl acetates are much less active than their *S* enantiomers (Miyakado et al., 1975). Again, with fluvalinate, the *R* enantiomer of the α-carbon of the acid moiety shows a higher insecticidal activity than does the *S* enantiomer (Anderson et al., 1985). However, the stereochemical structure in this chiral carbon of fulvalinate is equivalent to that of fenvalerate and the conventional cyclopropanecarboxylate pyrethroids, indicating a similar biological receptor for those structures.

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There has been some work reporting the elimination of certain chiral centers in the acid moieties. With a nitrogen atom in the cyclopropane ring, forming the aziridine group, the carbamic acid esters derived therefrom gave pyrethroid-like compounds but had decreased insecticidal activity (Berteau and Casida, 1969; Sheppard and Norton, 1980). Later reports showed that carbamates bearing the *N*-*tert*-butyl, *N*-benzyl, and *N*-(α-substituted)benzyl groups had some insecticidal activity when esterified with pyrethroid alcohols. (Kirino and Casida, 1985).

It has been reported that the bioactivity of fenvalerate-related pyrethroids is quite sensitive to structural modifications (Ohno et al., 1974, 1976; Elliott et al., 1980). The substitution of a nitrogen atom for the α-carbon atom of the fenvalerate acid moiety would result in the loss of the chiral center of this acid. In the resulting fenvalerate isostere, substituents attached to the nitrogen atom, via a rapid inversion process (Andose et al., 1970), could assume either the *R* or *S* configuration, adapting to a stereospecific receptor site.

In those cases where methylene or substituted methylene has been inserted between a phenyl group and a carbamate function (Kirino and Casida, 1985), the esters with pyrethroid alcohols have produced compounds with intermediate levels of insecticidal activity. These products would closely resemble the stereochemistry of fluvalinate if an isopropyl group were attached to the car-

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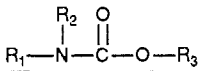
Table I. Physical Data for the Synthetic Carbamate Esters



no.	R_1[a]	R_2	phys state (mp, °C)	IR carbonyl str, cm^{-1}	^1H NMR, δ[b]
			R_3 = 3-Phenoxybenzyl		
I	3,4-$(OCH_2O)C_6H_3$	H	(85–86)	1710	5.15 (s, Bz), 5.93 (s, OCH_2O), 6.75–7.45 (m, Ar)
II	C_6H_5	*i*-Pr	oil	1690	1.13 (d, Me), 4.62 (m, CH), 5.12 (s, Bz), 6.8–7.45 (m, Ar)
III	4-ClC_6H_4	*i*-Pr	(54–55)	1695	1.18 (d, Me), 4.66 (m, CH), 5.17 (s, Bz), 7.00–7.47 (m, Ar)
IV	4-$CH_3OC_6H_4$	*i*-Pr	(59–61)	1675	1.09 (d, Me), 3.81 (s, CH_3O), 4.60 (m, CH), 5.09 (s, Bz), 6.85–7.38 (m, Ar)
V	4-$CH_3C_6H_4$	*i*-Pr	oil	1695	1.12 (d, Me), 2.39 (s, CH_3-Ar), 4.60 (m, CH), 5.03 (s, Bz), 6.96–7.45 (m, Ar)
VI	3-$CH_3OC_6H_4$	*i*-Pr	oil	1695	1.12 (d, Me), 3.77 (s, CH_3O), 4.58 (m, CH), 5.09 (s, Bz), 6.64–7.40 (m, Ar)
VII	3,4-$(OCH_2O)C_6H_3$	*i*-Pr	oil	1695	1.17 (d, Me), 4.62 (m, CH), 5.16 (s, Bz), 5.94 (s, OCH_2O), 6.56–7.45 (m, Ar)
VIII	3,5-$(CH_3O)_2C_6H_3$	*i*-Pr	oil	1695	1.13 (d, Me), 3.75 (s, CH_3O), 4.54 (m, CH), 5.10 (s, Bz), 6.85–7.40 (m, Ar)
IX	3,4,5-$(CH_3O)_3C_6H_2$	*i*-Pr	(69–70)	1675	1.14 (d, Me), 3.80 and 3.86 (d, CH_3O), 4.57 (m, CH), 5.12 (s, Bz), 6.88–7.40 (m, Ar)
			R_3 = 2,3,4,5,6-Pentafluorobenzyl		
X	3,4-$(OCH_2O)C_6H_3$	*i*-Pr	(88–89)	1695	1.09 (d, Me), 4.53 (m, CH), 5.17 (s, Bz), 5.99 (s, OCH_2O), 6.50–6.85 (m, Ar)
			R_3 = α-Cyano-3-phenoxybenzyl		
XI	3,4-$(OCH_2O)C_6H_3$	*i*-Pr	oil	1705	1.15 (d, Me), 4.51 (m, CH), 6.00 (s, OCH_2O), 6.00 (s, OCH_2O), 6.35 (s, Bz-CN), 6.70–7.50 (m, Ar)
XII	4-ClC_6H_4	*i*-Pr	oil	1705	1.14 (d, Me), 4.53 (m, CH), 6.37 (s, Bz-CN), 6.80–7.50 (m, Ar)
XIII	4-$ClC_6H_4CH_2$	*i*-Pr	oil	1700	1.14 (d, Me), 3.46 (s, Bz), 4.39 (m, CH), 6.38 (s, Bz-CN), 6.90–7.45 (m, Ar)
XIV	(*RS*)-$C_6H_5(CH_3)CH$[a]	*i*-Pr	oil	1700	1.22 (d, Me), 1.56 (d, Bz-CH_3), 3.46 (d, Bz), 4.26 (m, CH), 6.39 (s, Bz-CN), 6.90–7.50 (m, Ar)
XV	(*R*)-$C_6H_5(CH_3)CH$[a]	*i*-Pr	oil	1700	
XVII	4-$ClC_6H_4CH_2$	H	(75–77)	1720	4.25 (d, Bz), 5.30 (d, NH), 6.30 (s, Bz-CN), 6.85–7.35 (m, Ar)
XVIII	4-$ClC_6H_4(CH_3)CH$	H	oil	1715	1.28 (d, Me), 4.58 (m, Bz), 5.22 (d, NH), 6.10 (s, Bz-CN), 6.55–7.45 (m, Ar)
XIX	4-$ClC_6H_4(C_2H_5)CH$	H	oil	1715	0.88 (t, Me), 1.77 (m, CH_2), 4.38 (m, Bz), 5.30 (d, NH), 6.15 (s, Bz-CN), 6.60–7.40 (m, Ar)
XX	4-$CH_3OC_6H_4(C_2H_5)CH$	H	oil	1715	0.87 (t, Me), 1.68 (m, CH_2), 3.80 (s, MeO), 4.35 (m, Bz), 5.18 (d, NH), 6.10 (s, Bz-CN), 6.38–7.32 (m, Ar)
XXI	4-$ClC_6H_4(C_3H_5)CH$	H	oil	1715	0.28 (d, CH_2), 2.15 (m, CH), 4.30 (m, Bz), 5.20 (d, NH), 6.12 (s, Bz-CN), 6.60–7.45 (m, Ar)
XXII	4-$BrC_6H_4(CH_3)_2C$	H	oil	1720	1.52 (s, Me), 5.15 (s, NH), 6.10 (s, Bz-CN), 6.65–7.40 (m, Ar)

[a] *RS* prefix designates racemic mixture. *R* prefix designates *R* configuration. [b] Spectra were measured in $CDCl_3$ with TMS as an internal standard. Abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; Ar, aromatic; Bz, benzylic methylene or methine.

bamate nitrogen atom. Such compounds could provide additional structural and stereochemical information that could be utilized for the better understanding of structure–activity relationships of the pyrethroid-like insecticides.

We report the synthesis and preliminary insecticidal toxicity data that relate to a structural and stereochemical study of pyrethroid-like carbamates. These carbamates were obtained from the coupling of *N*-isopropylaniline, *N*-isopropylbenzylamine, or α-(substituted)benzylamine derivatives with various chloroformates prepared from appropriate pyrethroid alcohols.

EXPERIMENTAL SECTION

Infrared spectra were measured on a Perkin-Elmer 1330 spectrometer. The structures of products were confirmed by ^1H nuclear magnetic resonance spectra employing either the Hitachi Perkin-Elmer R24-B or the Varian VXR-300 FT-NMR spectrometer; data are presented with δ values in Table I. Melting points are uncorrected. Elemental analyses (C,H) were performed on novel compounds by Midwest Microlabs, Indianapolis, IN, and were within ±0.4% of the theoretical values. (*R*)-(+)-α-Methylbenzylamine and (*RS*)-(±)-α-methylbenzylamine racemic mixture (Aldrich Chemical Co., Milwaukee WI) were individually used to prepare the *N*-[(*R*)-(+)-α-methylbenzyl]-*N*-isopropyl carbamate (XV) and its *RS* counterpart (XIV). For column chromatography, silica gel (60–300 mesh, Fisher Scientific Co.) was used. Radial thin-layer chromatography was carried out by using a Harrison Model Chromatotron provided with a 2-mm silica gel rotor. For thin-layer chromatography, silica gel plates from Eastman Kodak Co. were employed.

General Procedure for the Preparation of Chloroformates. Pyrethroid alcohol (20 mmol) and *N*,*N*-dimethylaniline (26 mmol) were dissolved in 50 mL of dry ether. Phosgene (80 mmol) was condensed into 200 mL of dry ether at 0 °C. The pyrethroid alcohol solution was then slowly added to the phosgene solution. The mixture was maintained at 0 °C for 3 h and then stirred for 3 h (in the hood!) at room temperature. The solvent was removed in vacuo. The residue was then taken up in 100 mL of ether and extracted with water, 3% hydrochloric acid, and finally saturated sodium chloride solution. After drying, the ether was removed to give an oil which, based upon silica gel thin-layer chromatography and NMR analysis, was sufficiently pure to use in subsequent condensations with appropriate amines. The yield was typically about 90%.

3-Phenoxybenzyl chloroformate: yield 95%; NMR ($CDCl_3$) δ 6 .5–7.4 (9 H, m), 5.1 (2 H, s); IR, 1770 cm^{-1} (C=O).

Pentafluorobenzyl chloroformate: yield 81%; NMR ($CDCl_3$) δ 5.2 (2 H, s); IR, 1780 cm^{-1} (C=O).

α-Cyano-3-phenoxybenzyl Chloroformate. 3-Phenoxybenzyl cyanohydrin was prepared by the method of Ruzo et al. (1977). The chloroformate was prepared according to the general procedure (above). Data: yield 85%; NMR ($CDCl_3$) δ 6.1 (1 H, s), 6.6–7.4 (9 H, m); IR, 1770 (C=O), 2240 cm^{-1} (CN).

General Procedure for the Preparation of *N*-Isopropyl Derivatives. The method employed was similar to that reported

earlier (Schellenberg, 1963). Glacial acetic acid (5 mL) 2.5 g of sodium acetate trihydrate, 10 mL of water, and 5 mL of acetone were placed in a stirring flask at 0 °C. Sodium borohydride (4.0 g) was added in 30-mg portions over a 20-min period to a stirred solution of the aniline or benzylamine derivative (20.2 mmol) in 5 mL of ethanol and the temperature kept under 10 °C. The mixture was made alkaline with sodium hydroxide and then extracted with 2 × 100 mL of ether, and the ether was washed with 2 × 50 mL of water. The ether solution was then evaporated to dryness. The residue was purified by chromatography on silica gel (eluted with hexane–ethyl acetate, 12:1, v/v). The yield ranged from 40 to 70% after purification.

General Procedure for the Preparation of α-Alkylbenzylamine Derivatives. α-Alkylbenzylamine derivatives were prepared by a modification of the procedure of Borch et al. (1971). α-Substituted phenyl ketone (10 mmol), ammonium acetate (100 mmol), and sodium cyanoborohydride (8 mmol) in 30 mL of absolute methanol were stirred 48 h at 25 °C. Concentrated HCl was added to pH 2, and the methanol was removed in vacuo. The residue was taken up in 10 mL of water and extracted with 3 × 20 mL portions of ether. The aqueous phase was brought to pH 10–11 with solid KOH, saturated with NaCl, and extracted with 5 × 15 mL portions of ether. The combined extracts were dried with magnesium sulfate and evaporated in vacuo to give an oil that, based on NMR analysis, was sufficiently pure to use in subsequent condensations with appropriate chloroformates. The yield ranged from 60 to 74%.

α,α-Dimethyl-4-bromobenzylamine Preparation. The method employed for the preparation of α,α-dimethyl-4-bromobenzylamine was that reported by Kovacic et al. (1968).

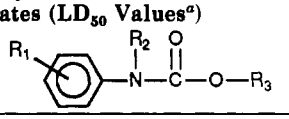
General Procedure for the Preparation of Carbamate Esters of *N*-Isopropylaniline, *N*-Isopropylbenzylamine, and α-Alkylbenzylamine Derivatives. A solution of the appropriate chloroformate (5 mmol) in 10 mL of anhydrous benzene was added dropwise to a stirred solution of the *N*-isopropylaniline, *N*-isopropylbenzylamine, or α-alkylbenzylamine derivative (10 mmol) in 5 mL of anhydrous benzene. The solution was maintained at 0 °C for 3 h under nitrogen. Stirring was continued overnight at room temperature. The precipitated hydrochloride salt was filtered, and the benzene was removed in vacuo. The residue was purified by radial chromatography on silica gel (developed with hexane–ether, 12:1, v/v). If the pure product was a solid, it was recrystallized from petroleum ether. The yield ranged from 48 to 85% after purification. Physical data for the carbamate esters are given in Table I.

Biological Evaluation. Four-day-old female houseflies (F58 WTII strain, about 25 mg each) were anesthetized and arranged on a screen, ventral side up. One microliter of sample (0.000 025%–1.0% in acetone) was applied to the abdomen. In synergized toxicity studies, the houseflies were dosed with 400 ppm of piperonyl butoxide (PB) applied to the abdomen, and 1 h later 1 μL of the carbamate sample was applied. With each compound studied, 10 flies were employed in each test and all tests were conducted at least in duplicate. Mortality was recorded after 24 h, and average percent mortality was determined. Controls, acetone only or synergist (PB) only, were included in each toxicity study. The LD_{50} values, the dose required for 50% mortality, were determined by Probit analyses (Finney, 1971). Fenvalerate and fluvalinate were employed in the evaluations as reference insecticides. In the instances where compounds exhibited low housefly toxicities, LD_{50} values were not determined.

RESULTS AND DISCUSSION

The insecticidal activity of pyrethroids has been shown to be very sensitive to structural and stereochemical variations at certain key regions of the molecule (Elliott, 1977; Elliott and Janes, 1978; Norton et al., 1985). This is particularly true in pyrethroids structurally related to fenvalerate and fluvalinate (Elliott, 1977; Henrick et al., 1980). In the present study, structural and stereochemical sensitives relating to the latter two insecticides have been examined further. Thus, carbon atom chiral centers bearing the isopropyl group have been replaced with a nitrogen atom. Such substitutions in the acid moiety were made in an effort to determine whether these compounds (carbamates), which may undergo nitrogen inversion (Rauk et al., 1970), and thus assume either *R* or *S* configurations, act as effective pyrethroid-like insecticides.

Table II. Housefly Toxicities of Substituted *N*-Phenylcarbamates (LD_{50} Values[a])



no.	R_1	R_2	LD_{50},[b] μg/g unsynergized	LD_{50},[b] μg/g synergized[c]
	R_3 = 3-Phenoxybenzyl			
I	3,4-(OCH_2O)	H	>400	
II	H	*i*-Pr	>400	
III	4-Cl	*i*-Pr	>400	
IV	4-CH_3O	*i*-Pr	>40[d]	
V	4-CH_3	*i*-Pr	>400	
VI	3-CH_3O	*i*-Pr	>400	
VII	3,4-(OCH_2O)	*i*-Pr	27	
VIII	3,5-$(CH_3O)_2$	*i*-Pr	>400	
IX	3,4,5-$(CH_3O)_3$	*i*-Pr	>400	
permethrin			0.9[e]	
	R_3 = 2,3,4,5,6-Pentafluorobenzyl			
X	3,4-(OCH_2O)	*i*-Pr	7	0.25
	R_3 = α-Cyano-3-phenoxybenzyl			
XI	3,4-(OCH_2O)	*i*-Pr	>40[d]	
XII	4-Cl	*i*-Pr	>40[d]	
fenvalerate			1.1[f]	

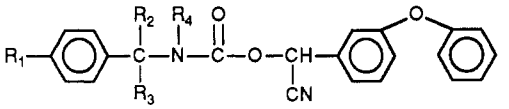
[a] 24-h mortality for pyrethrin-susceptible female houseflies (F 58 WTII). LD_{50} values were obtained by Probit analysis of the percent kill data (Finney, 1971); see Biological Evaluation for further details. [b] LD_{50} values were determined only on those compounds exhibiting 100% kill at 80 ppm or lower. [c] Synergist, piperonyl butoxide, 400 ppm. See Biological Evaluation for further details. [d] Compounds IV, XI, and XII gave 10%, 10%, and 25% kills, respectively, at the 40 ppm level. [e] Henrick et al. (1980). [f] Compounds of the fenvalerate series have been reported to be synergized 4–7-fold by piperonyl butoxide (Fujimoto et al., 1977).

The compounds prepared fall into two major categories: Carbamate esters derived from (1) *N*-isopropylaniline derivatives and (2) *N*-isopropylbenzylamine derivatives. The alcohols employed were among the most effective of those utilized in other pyrethroid esters. Preliminary insecticidal activities for these compounds against pyrethroid-susceptible female houseflies are shown in Tables II and III.

The first category is that in which the compounds of interest are carbamates derived mainly from *N*-isopropylaniline derivatives (Table II). Among compounds I–IX, in which the alcohol group is 3-phenoxybenzyl alcohol, only the one having an *N*-isopropyl and also a 3,4-methylenedioxy group (compound VII) has any appreciable housefly toxicity. It should be noted that compound I, which has a 3,4-methylenedioxy substituent, but no *N*-isopropyl substituent, shows very low toxicity (LD_{50} > 400 ppm). Further, compound II, which has the *N*-isopropyl group but does not have an R_1 substitution on the phenyl ring, is of equally low toxicity.

Compound X, which has a carbamic acid moiety identical with that of compound VII but is esterified to pentafluorobenzyl alcohol, has the highest toxicity of the compounds tested in this series. When synergized with piperonyl butoxide, its housefly toxicity is enhanced 28-fold. With certain other pyrethroid acids, the use of the pentafluorobenzyl alcohol substituent has been reported to give significant insecticidal activities (Holan et al., 1984). Compounds XI and XII, having the same carbamic acid

Table III. Housefly Toxicities of Substituted *N*-Benzylcarbamates (LD_{50} Values[a])



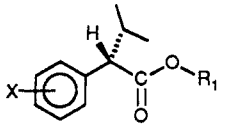
no.	R_1	R_2	R_3	R_4	LD_{50},[b] μg/g unsynergized	LD_{50},[b] μg/g synergized[c]
XIII	4-Cl	H	H	*i*-Pr	>160	40
XIV	H	CH_3 (racemic)	H	*i*-Pr	>160	
XV	H	CH_3 (*R*)	H	*i*-Pr	>160	
XVI	H	H	H	H	>600[d]	>600[d]
XVII	4-Cl	H	H	H	24	3.0
XVIII	4-Cl	CH_3	H	H	>40	
XIX	4-Cl	Et	H	H	26	
XX	4-CH_3O	Et	H	H	35	
XXI	4-Cl	c-Pr	H	H	18	0.15
XXII	4-Br	CH_3	CH_3	H	3.5	0.012
fluvalinate					4.0[e]	

[a] 24-h mortality for pyrethrin-susceptible female houseflies (F58 WTII). LD_{50} values were obtained by Probit analysis of the percent kill data (Finney, 1971); see Biological Evaluation for further details. [b] LD_{50} values were determined only on those compounds exhibiting 100% kill at 80 ppm or lower. [c] Synergist, piperonyl butoxide, 400 ppm. See Biological Evaluation for further details. [d] Kirino and Casida (1985). [e] Fluvalinate is synergized 7X by piperonyl butoxide (1:10) in *Musca domestica* (Henrick, 1981).

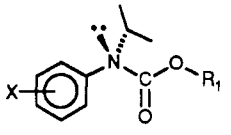
moiety as in compounds VII and III, respectively, but esterified to α-cyano-3-phenoxybenzyl alcohol, did not exhibit anticipated enhancement of housefly toxicity.

The second category of compounds studied is the α-cyano-3-phenoxybenzyl esters of benzylamine derivatives (compounds XIII–XXII). Housefly toxicity data for these compounds are shown in Table III. Compounds XVII and XIX–XXII show reasonably good potencies against houseflies; compound XXII has a toxicity that is considerably greater than any of the other compounds studied in this series.

The insecticidal activities of the compounds synthesized in the present study give some insight into the requisite structural and steric features required for bioactivity. While the relatively high toxicities of some of the compounds tested do not prove a pyrethroid-like mode of bioactivity, it is tempting to propose that a mimicry of such activity is involved. It is apparent, when one constructs appropriate Dreiding molecular models, that the steric similarities of the carbamate esters of aniline derivatives and fenvalerate-like pyrethroids are quite great (structures **a** and **b**).



a, (*S*)-fenvalerate derivatives



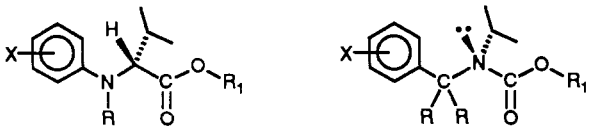
b, fenvalerate-like aniline carbamates

Further, because of possible inversions about the nitrogen atom of the carbamate esters, which negate the chirality of the α-position, one may envision a ready steric fit to the appropriate insect binding site. That such a ready fit does not apparently occur (based on lower activities as compared with fenvalerate) suggests that the conformation envisioned is not actually produced. One explanation is that there is actually coplanarity of the groups about the >NC(O)— functionality of the carbamate esters. Studies involving carbamates in the solid state (Bracher and Small, 1967) and in solution (Keith and Alford, 1970) by X-ray crystallography and proton NMR, respectively, indicate that there is indeed some double-bond character in the N–C linkage, similar to that found in amides. The consequence of this is restricted rotation and coplanarity of N-substituted groups. An isopropyl group attached to an sp^2-hybridized nitrogen, as in the aniline-derived carbamates of this study, is thus held in a steric position that is significantly different from that in which the attachment is to an sp^3-hybridized atom. The *N*-isopropyl substituent appears to be important in these carbamates in conferring bioactivity (compound I compared to compound VII). An inability of the *N*-isopropyl group to assume a "best fit" alignment for interacting with the insect binding site may be the explanation for the generally lower insecticidal activities of these carbamates as compared with the activities of fenvalerate derivatives (Ohno et al., 1976). Other explanations of the lower activities of the aniline derivatives as compared with fenvalerate-like pyrethroids cannot be ruled out. For example, differences in metabolism or differences in pharmacokinetic behavior could also be involved.

Several compounds were synthesized that are carbamate esters of benzylamine derivatives (compounds XIII–XXII). Compound XVI is placed in Table III for comparative purposes; biological data for this compound are literature values (Kirino and Casida, 1985). The insecticidal data of Table III show that (1) the isopropyl group on the carbamate nitrogen is not necessary for bioactivity, (2) the *p*-halo group significantly enhances the insecticidal potency, and (3) a single methyl or ethyl group substitution of the β-position of the carbamic acid moiety does not further enhance bioactivity of compounds containing a *p*-halo group. Studies by others (Kirino and Casida, 1985) have shown that alkyl substituents (particularly the dimethyl substitution) on the benzylic carbon atom may significantly enhance insecticidal activity of carbamates derived from non-halo-substituted benzylamine. The halogen compounds XXI and XXII, having the benzylic substituents cyclopropyl and dimethyl, respectively, do show enhanced activity. Compound XXII, when unsynergized, has a housefly toxicity comparable to that of fluvalinate (Henrick et al., 1980). This compound is significantly synergized by piperonyl butoxide (~300×), and its housefly toxicity exceeds that reported for synergized fenvalerate (Fujimoto et al., 1977). Comparable pronounced enhancements of toxicities by the presence of synergists have been reported for other carbamates, particularly for those in which the carbamate nitrogen atom is monosubstituted (Berteau and Casida, 1969; Kirino and Casida, 1985; Wilkinson, 1967).

It would appear that the suggested explanation for the housefly toxicity patterns of the aniline-derived carbamates (planarity about the carbamate grouping) is also valid

for the benzylamine-derived carbamates. The steric properties of the benzylamine carbamates appear strikingly similar to those of the fluvalinate pyrethroids, if one assumes an sp^3-hybridized carbamate nitrogen atom (structures **c** and **d**). On the other hand, planarity about the



c, (*R*)-fluvalinate derivatives **d**, fluvalinate-like benzylamine carbamates

R = H, alkyl

carbamate function, induced by an sp^2-hybridized nitrogen atom, introduces a different geometry. Stereo models show that the bulky isopropyl group, when attached to the carbamate nitrogen, is thrust into a very different spacial region when there is double-bond character associated with the carbamate N–C grouping. Such a steric orientation could explain why compound XVII, which has an unsubstituted carbamate nitrogen atom, exhibits much greater insect toxicity than the isopropyl group substituted compound XIII.

An additional interesting product of these observations results when planarity about the carbamate group is imposed on benzylamine carbamate molecular models. For example, the Drieding molecular model of the carbamic acid portion of compound XXII, which has *gem*-dimethyl substituents on the benzylic carbon atom, can conform to a steric shape similar to that of the molecular model for cyclopropane ring containing pyrethroid acids. Such a comparison of molecular shape is less apparent when planarity is not imposed on the carbamate functionality. This finding suggests that various alkyl substitutions on the benzylic carbon, coupled with appropriate substituents on the phenyl group of the benzylamine moiety, could result in compounds having enhanced pyrethroid-like properties. Syntheses following these guidelines should be undertaken.

Registry No. I, 123312-02-7; II, 123312-03-8; II *N*-isopropylaniline precursor, 768-52-5; III, 123312-04-9; III *N*-isopropylaniline precursor, 770-40-1; IV, 123312-05-0; IV *N*-isopropylaniline precursor, 16495-67-3; V, 123312-06-1; V *N*-isopropylaniline precursor, 10436-75-6; VI, 123312-07-2; VI *N*-isopropylaniline precursor, 31143-05-2; VII, 123312-08-3; VII *N*-isopropylaniline precursor, 10368-14-6; VIII, 123312-09-4; VIII *N*-isopropylaniline precursor, 108103-33-9; IX, 123312-10-7; IX *N*-isopropylaniline precursor, 100252-56-0; X, 123312-11-8; XI, 123312-12-9; XII, 123312-13-0; XIII, 123312-14-1; XIII *N*-isopropylbenzylamine precursor, 40066-21-5; XIV, 123312-15-2; XIV *N*-isopropylbenzylamine precursor, 19302-16-0; XV *N*-isopropylbenzylamine precursor, 87861-38-9; XVI, 98992-19-9; XVII, 123312-16-3; XVII *N*-isopropylbenzylamine precursor, 40066-21-5; XVIII, 123312-17-4; XVIII benzylamine precursor, 6299-02-1; XIX, 123312-18-5; XIX benzylamine precursor, 74788-46-8; XX, 123312-19-6; XX benzylamine precursor, 83948-35-0; XXI, 123312-20-9; XXI benzylamine precursor, 123312-22-1; XXII, 123312-21-0; XXII benzylamine precursor, 17797-12-5; permethrin, 52645-53-1; fluvalinate, 69409-94-5; (3-phenoxybenzyl) chloroformate, 75541-99-0; (2,3,4,5,6-pentafluorobenzyl) chloroformate, 53526-74-2; (α-cyano-3-phenoxybenzyl) chloroformate, 108505-17-5.

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Hydrolytic Degradation of Desmedipham

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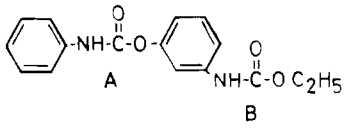
The alkaline hydrolysis of desmedipham into aniline and ethyl *N*-(3-hydroxyphenyl)carbamate was studied for hydroxide ion concentrations ranging from 10^{-6} to 3 N. The positive activation entropy and the fact that desmedipham fits well into a Brønsted plot log $k_{OH} = f(pK_a)$ obtained for the hydrolysis of alkyl and aryl *N*-phenylcarbamates with a slope value β of −1.15 supported an E1cB reaction scheme for desmedipham hydrolysis.

Phenmedipham and desmedipham are postemergence herbicides of the bis(carbamate) family with two carbamate functions, A and B (Trebst et al., 1968), and are sprayed on sugar beets to control certain broadleaf and grass weeds.



Desmedipham, ethyl [3-[[(phenylamino)carbonyl]oxy]phenyl]carbamate, a phenmedipham analogue, has been developed for the control of redroot pigweed (*Amaranthus retroflexus* L.), which is a problem weed in sugar beet crops and is resistant to phenmedipham (Schweizer and Weatherspoon, 1971; Laufersweiler and Gates, 1972; Sullivan and Fagala, 1977). In sugar beets (Knowles and Sonawane, 1972) and the rat (Sonowane and Knowles, 1971) the hydrolysis of desmedipham to ethyl *N*-(3-hydroxyphenyl)carbamate and subsequently to *m*-aminophenol is one of the main pathways of in vivo bis(carbamate) metabolism. In soils, desmedipham is also converted by microorganisms to ethyl *N*-(3-hydroxyphenyl)carbamate (Knowles and Benezet, 1981).

The only data in the literature concerning desmedipham stability in aqueous media are the values of the half-life measured at pH 7 ($t_{1/2} \simeq 14$ h) and pH 9 ($t_{1/2} \simeq 20$ min) at 26 °C (Röder et al., 1978).

In alkaline media, the hydrolytic breakdown of phenmedipham into methyl *N*-(3-hydroxyphenyl)carbamate and *m*-toluidine via *N*-(*m*-tolylcarbamic acid) follows an E1cB reaction scheme and involves the formation of *m*-tolyl isocyanate, which may lead to carbamylation reactions in biochemical systems (Bergon et al., 1985). To determine whether there is formation of phenyl isocyanate during the hydrolysis of desmedipham, we carried out a kinetic study of this reaction to identify its mechanism.

EXPERIMENTAL SECTION

Apparatus. A Unicam SP 1800 recording spectrophotometer fitted to an SP 1805 program controller and a thermostated multiple cell compartment or, for the more rapid reactions ($t_{1/2} < 10$ s), a Durrum D-110 stopped-flow spectrophotometer were used for all spectroscopic measurements. Optical density changes after mixing were recorded on a Gould storage oscilloscope (Model OS 4000).

The pH measurements were carried out on a Radiometer PHM 64 pH meter equipped with a Radiometer GK 2321 C electrode.

Synthesis of Desmedipham. Ethyl chloroformate (0.025 mol) was added dropwise at room temperature to 3-aminophenol (0.05 mol) dissolved in dry tetrahydrofuran (50 mL). The mixture was stirred for 2 h and the precipitated hydrochloride of 3-aminophenol was filtered off on cooling. The filtrate was evaporated to dryness to give ethyl *N*-(3-hydroxyphenyl)-carbamate, mp 94 °C (lit. mp 94–95 °C (Schering A.-G.)).

This carbamate was converted to desmedipham by reacting with phenyl isocyanate in dry benzene with a catalytic quantity of triethylamine and refluxing for 30 min; mp 120 °C (lit. mp 120 °C (Röder et al., 1978)).

pK_a Measurement. The ultraviolet spectra of the carbamate in aqueous media show an increase with the pH in the region 290–300 nm. In 1 N NaOH, the maximum observed at 295 nm is consistent with the formation of a phenolate ion (Scott, 1964). The pK_a was obtained from the intercept of the graph log $(D - D_{AH})/(D_{A^-} - D) = f(pH)$ where D_{A^-}, D_{AH}, and D are the optical densities of the phenolate ion in 0.05 N NaOH, of the nonionized carbamate in 1 N HCl, and of the mixture of the two species in buffer solutions ranging from pH 8.68 to 10.24.

The pK_a value of ethyl *N*-(3-hydroxyphenyl)carbamate is 9.77 (25 °C; μ 1.00, KCl).

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