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O-(α-Cyano-m-phenoxybenzyl) N-Alkyl- and N-Aralkylcarbamates and Related Pyrethroid-like Insecticides

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Structure–activity relationships are examined for the toxicity to houseflies of pyrethroid-like carbamates, esters, and related compounds lacking a cyclopropane ring. The isosteric tert-butyl α-bromoacetate and N-tert-butylcarbamate are effective acid moieties with α-cyano-m-phenoxybenzyl, m-phenoxybenzyl, and other pyrethroid alcohols and the oxidase inhibitor piperonyl butoxide strongly synergizes the toxicity in each case. The esterase inhibitor phenylsaligenin cyclic phosphonate is generally more effective in synergizing the carboxylic esters than the carbamates. Substituent effects on the activity of 15 O-(α-cyano-m-phenoxybenzyl) N-alkylcarbamates are shown by a modified Free–Wilson method to be related to the number of branches in the alkyl group in which α branching is favorable and β and γ branching are unfavorable for the activity. O-(α-Cyano-m-phenoxybenzyl) N-[(R)-α-methylbenzyl]carbamate is much more toxic than the S isomer. In a series of esters, amides, and ethers, critical features for activity are both the distance between the tert-butyl and m-phenoxyphenyl groups and the nature of the central linkage providing this distance.

Structural modifications of the chrysanthemate moiety of pyrethroids establish that the isobutenyl moiety and cyclopropane ring are not absolute requirements for insecticidal activity but the gem-dimethyl group or an equivalent substituent is essential (Barlow et al., 1971; Berteau and Casida, 1969; Elliott and Janes, 1978; Henrick et al., 1980; Matsui and Kitahara, 1967; Ohno et al., 1974). Further simplification of the pyrethroid acid moiety led to the tert-butyl acetate, but it has little activity (Elliott et al., 1983), possibly due in part to rapid hydrolysis of the ester linkage. Esteratic detoxification might be minimized or circumvented by increasing the steric bulk of the acid moiety or changing the nature of the central linkage, e.g. introducing a bromine atom in the α-position of the tert-butyl acetate (Kirino et al., 1983), modifying the carboxylic acid ester to a carbamic acid ester linkage (Berteau and Casida, 1969), or using a central linkage other than an ester (Berteau and Casida, 1969; Bull et al., 1980; Nakatani et al., 1982). The present structure–activity study applies these approaches to O-(α-cyano-m-phenoxybenzyl) N-alkyl and N-aralkylcarbamates and related pyrethroid-like insecticides.

MATERIALS AND METHODS

Chemicals. The compounds listed in Tables I–VI were synthesized by conventional methods. Carbamates were prepared by one of three procedures: (1) reaction of an isocyanate with an alcohol in tetrahydrofuran in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene as a catalyst; (2) reaction of an amine with a chloroformate (obtained

Table I. R_M Values and NMR Spectral Characteristics of Key Compounds

compd	$R_M{}^a$	^{1}H NMR, $\delta{}^b$
2	−0.05	1.04 (s, t-Bu), 2.34 (s, CH₂), 4.47 (s, Bz), 7.1–7.7 (m, Ar)
3	0.01	1.16 (s, t-Bu), 4.20 (s, CH), 4.46 (s, Bz), 7.1–7.7 (m, Ar)
4	−0.20	1.34 (s, t-Bu), 4.97 (br s, NH), 6.42 (s, Bz), 7.0–7.6 (m, Ar)
6	−0.13	1.32 (s, t-Bu), 4.76 (br s, NH), 5.03 (s, Bz), 6.9–7.4 (m, Ar)
8	−0.22	1.33 (s, t-Bu), 3.94 (s, Bz), 4.75 (br s, NH), 4.87 (s, CH₂-Fu), 7.2–7.4 (m, Ar)
10	−0.10	1.05 (s, t-Bu), 2.25 (s, CH₂), 5.19 (s, Bz)
12	−0.33	1.19 (s, t-Bu), 1.66 (m, CH₂-C), 2.26 (m, CH₂), 4.83 (br s, NH), 5.31 (s, CH₂-N)
14	−0.35	1.21 (s, t-Bu), 1.89 (s, Me), 2.13 and 2.67 (dd, CH₂-C), 2.79 and 2.82 (s, ring-CH₂), 4.8–4.9 (m, CH₂=), 4.98 (s, NH), 5.5–5.7 (m, CH=)
15	−0.40	2.81 (d, Me), 5.29 (d, NH), 6.40 (s, Bz), 7.0–7.5 (m, Ar)
26	−0.15	0.89 (s, t-Bu), 3.00 (d, CH₂), 5.02 (t, NH), 6.39 (s, Bz), 6.9–7.5 (m, Ar)
34	−0.29	2.97 (s, Me), 6.47 (s, Bz), 7.0–7.6 (m, Ar)
45	−0.21	1.66 (s, Me), 5.38 (s, NH), 6.29 (s, Bz), 7.0–7.5 (m, Ar)
49	0.05	1.03 (s, t-Bu), 2.26 (s, CH₂), 5.07 (s, Bz), 6.9–7.4 (m, Ar)
55	−0.02	1.43 (s, t-Bu), 3.48 (s, Bz), 6.9–7.4 (m, Ar)
61	−0.28	1.29 (s, t-Bu), 3.44 (s, Bz), 5.28 (br s, NH), 6.8–7.4 (m, Ar)
68	−0.07	0.94 (s, t-Bu), 3.11 (s, CH₂), 4.49 (s, Bz), 6.9–7.4 (m, Ar)

^{a} Values obtained from reversed-phase TLC developed with acetone–water (4:1) are the mean of at least three determinations with a standard deviation of less than 0.04. ^{b} Spectra were measured in deuteriochloroform with tetramethylsilane as the internal standard. Abbreviations are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad; Ar, aromatic; Bz, benzylic methylene or methine; Fu, furyl; Ph, phenyl.

from an alcohol and phosgene in benzene in the presence of triethylamine and used without purification); (3) reac-

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Table II. Toxicity of *tert*-Butyl Acetates and Their Carbamate Analogues to Houseflies by Topical Application

	t-Bu-X-COOR:	n^{22}D	LD$_{50}$, μg/g			
no.	X subst	(mp, °C)	alone	PSCP[a]	PB[a]	PB + PSCP[a]
			R = α-Cyano-m-phenoxybenzyl			
1	none	1.5349	>600	150	570	21
2	CH$_2$	1.5331	500	130	190	14
3	CHBr	1.5467	55	24	5.0	1.3
			5.0[b]	1.5[b]	4.0[b]	0.47[b]
4	NH	1.5349	24	17	1.5	1.1
			1.0[b]	0.95[b]	0.43[b]	0.40[b]
			R = m-Phenoxybenzyl			
5	CHBr	1.5515	>600	500	65	34
6	NH	1.5402	>600	>600	120	34
			R = 5-Benzyl-3-furylmethyl			
7	CHBr	1.5281	>600	500	64	40
8	NH	1.5208	120	100	45	15
			R = 2,3,4,5,6-Pentafluorobenzyl			
9	CHBr	1.4638	>600	75	450	29
10	NH	(99–101)	85	60	70	28
			R = (3,4,5,6-Tetrahydrophthalimido)methyl			
11	CHBr	1.5196	>600	>600	>600	87
12	NH	(97–99)	>600	>600	420	270
			R = Allethronyl			
13	CHBr	1.5098	>600	>600	>600	270
14	NH	1.4808	160	140	60	39

[a] PSCP or PB or a mixture thereof, each at 500 μg/g, applied 1 h before the candidate insecticide. [b] Injection.

Table III. Toxicity of O-(α-Cyano-m-phenoxybenzyl) N-Alkylcarbamates to Houseflies by Topical Application

		n^{22}D	LD$_{50}$, μg/g		no. of branches		pLD$_{50}$[a]	
no.	subst	(mp, °C)	alone	PB[b]	α	β + γ	obsd	calcd[c]
15	Me	1.5534	>600	65	0	0	6.6[d]	7.3
16	Et	(51–53)	390	6.0	0	0	7.7	7.3
17	n-Pr	1.5523	>600	20	0	0	7.2	7.3
18	i-Pr	(89–90)	410	4.1	1	0	7.9	7.9
19	allyl	1.5448	430	17	0	0	7.3	7.3
20	n-Bu	1.5383	>600	28	0	0	7.1	7.3
21	i-Bu	(63–64)	>600	29	0	1	7.1	6.8
4	t-Bu	1.5349	24	1.5	2	0	8.3	8.4
23	n-Pent	(62–63)	>600	31	0	0	7.0	7.3
24	i-Pent	(41–43)	>600	45	0	1	6.9	6.8
25	2-MeBu	1.5318	>600	80	0	1	6.6	6.8
26	neopent	1.5342	>600	170	0	2	6.3	6.3
27	1-EtPr	(61–63)	170	3.6	1	0	8.0	7.9
28	1,2-Me$_2$Pr	1.5326	>600	13	1	1	7.4	7.3
29	t-Pent	1.5402	45	1.4	2	0	8.4	8.4
30	c-Pr	(96–97)	>600	9.0	1	0	7.5[d]	7.9
31	c-Bu	(69–70)	>600	320	1	0	6.0[d]	7.9
32	c-Pent	(62–63)	>600	490	1	0	5.8[d]	7.9
33	c-Hex	(87–88)	>600	>600	1	0	<5.7[d]	7.9

[a] pLD$_{50}$ is the negative logarithm of the LD$_{50}$ dose (mol/g) for the candidate insecticide applied 1 h after PB at 500 μg/g. [b] PB at 500 μg/g applied 1 h before the candidate insecticide. [c] By eq 3. [d] Not included in the correlation.

Table IV. Toxicity of O-(α-Cyano-m-phenoxybenzyl) N,N-Dialkylcarbamates to Houseflies by Topical Application

	dialkyl subst		n^{22}D	LD$_{50}$, μg/g	
no.				alone	PB[a]
34	Me	Me	1.5529	280	130
35	Me	n-Bu	1.5373	>600	170
36	Et	Et	1.5354	270	6.0
37	Et	n-Bu	1.5332	520	8.8
38	n-Pr	n-Pr	1.5355	470	53

[a] PB at 500 μg/g applied 1 h before the candidate insecticide.

tion of a carbamoyl chloride with an alcohol in the presence of pyridine. (*R*)-(*d*)-α-Methylbenzyl isocyanate and its (*S*)-(*l*) isomer (Aldrich Chemical Co., Milwaukee, WI) were

Table V. Toxicity of O-(α-Cyano-m-phenoxybenzyl) N-Alkylcarbamates to Houseflies by Topical Application

		n^{22}D	LD$_{50}$, μg/g	
no.	aralkyl subst[a]	(mp, °C)	alone	PB[b]
39	PhCH$_2$	1.5576	>600	>600
40	Ph(Me)CH racemic	(98–100)	130	1.5
41	Ph(Me)CH R form	(90–92)	46	1.0
42	Ph(Me)CH S-form	(96–99)	>600	28
43	Ph(Et)CH	1.5652	76	1.4
44	Ph(i-Pr)CH	1.5657	>600	35
45	Ph(Me)$_2$C	1.5728	31	0.55
46	Ph$_2$CH	1.5936	>600	>600
47	PhCH$_2$CH$_2$	1.5703	>600	440
48	α-Nap(Me)CH	1.5956	>600	>600

[a] Ph and α-Nap denote phenyl and α-naphthyl, respectively. [b] PB at 500 μg/g applied 1 h before the candidate insecticide.

Table VI. Toxicity of Esters, Amides, Carbamates, Ethers, and Related Compounds Having Both tert-Butyl and m-Phenoxyphenyl Groups to Houseflies by Topical Application

no.	t-Bu–X–Ph–O–Ph: X subst	$n^{22}{}_D$ (mp, °C)	LD$_{50}$,^{a} µg/g PB	LD$_{50}$,^{a} µg/g PB + PSCP
	Esters and Reversed Esters			
49	CH$_2$COOCH$_2$	1.5330	>600	260
50	CH$_2$COO	1.5318	>600	550
51	COOCH$_2$	1.5345	>600	55
52	COO	1.5340	>600	>600
53	CH$_2$OCOCH$_2$	1.5336	>600	>600
54	CH$_2$OCO	1.5376	>600	470
55	OCOCH$_2$	1.5362	19	8
56	OCO	1.5540	>600	>600
	Amides and Reversed Amides			
57	CH$_2$CONHCH$_2$	(65–66)	>600	>600
58	CONHCH$_2$	(53–54)	>600	120
59	CH$_2$NHCOCH$_2$	(64–65)	>600	550
60	CH$_2$NHCO	(98–99)	260	55
61	NHCOCH$_2$	(110–111)	130	29
62	NHCO	(113–114)	>600	>600
	Carbamates and Urea			
63	NHCOON=CH	(62–64)	>600	>600
6	NHCOOCH$_2$	1.5402	120	34
64	NHCOO	1.5810	>600	>600
65	NHCONHCH$_2$	(143–144)	>600	>600
	Ethers^b			
66	CH$_2$CH$_2$OCH$_2$CH$_2$	1.5114	>600	>600
67	CH$_2$CH$_2$OCH$_2$	1.5328	320	78
68	CH$_2$OCH$_2$	1.5380	13	8
69	CH$_2$O	1.5867	>600	>600
70	OCH$_2$	1.5817	>600	>600
	Amines and Imine			
71	CH$_2$NHCH$_2$	1.5130	>600	>600
72	NHCH$_2$	1.5478	>600	>600
73	CH$_2$N=CH	1.5469	>600	>600

^{a} PSCP or PB or a mixture thereof, each at 500 µg/g, applied 1 h before the candidate insecticide. LD$_{50}$ values for compounds 49–73 are each >600 µg/g alone or with PSCP except as follows [compound no., LD$_{50}$ alone (LD$_{50}$ with PSCP)]: 55, 220 (140); 68, 98 (39). ^{b} The related ether 2-(p-ethoxyphenyl)-2-methylpropyl m-phenoxyphenyl ether (MTI-500) (Nakatani et al., 1982) gives LD$_{50}$ values (µg/g) of 1.2 alone, 0.85 with PSCP, 0.12 with PB, and 0.06 with both PB and PSCP.

used to prepare the N-[(R)-(d)-α-methylbenzyl]carbamate (41) [[α]$^{22}{}_D$ +20.8° (c 1.0, CHCl$_3$)] and its S isomer (42) [[α]$^{22}{}_D$ −20.9° (c 1.0, CHCl$_3$)], respectively. Esters and amides were synthesized by reaction of an acid chloride with an alcohol and amine, respectively, in the presence of triethylamine. Ethers were obtained by treating an alkyl or aralkyl halide with a sodium or potassium alcoholate or phenolate. Imine 73 (obtained from the corresponding amine and aldehyde) was reduced to amine 71 with sodium borohydride in ethanol, and an analogous procedure gave amine 72. Urea 65 was prepared from the appropriate amine and isocyanate. Compounds were purified either by preparative thin-layer chromatography (TLC) on silica gel, developing with chloroform, or by recrystallization from appropriate solvents.

The structure of each product was confirmed by its 300-MHz ^{1}H nuclear magnetic resonance (NMR) spectrum recorded with a Bruker WM-300 wide-bore spectrometer; data for key compounds are given in Table I. Optical rotations were measured with a cell path length of 100 mm (cell capacity 1 mL) by using a Perkin-Elmer 241 polarimeter. Melting points determined on a micro hot stage are not corrected.

R_M values. Each compound was chromatographed on a reversed-phase TLC plate (0.20 mm, LKC18F; Whatman,

Clifton, NJ) with acetone–water (4:1) for development and UV visualization to determine the R_M value calculated according to the equation, $R_M = \log[1/(R_f - 1)]$ (Boyce and Milborrow, 1965).

Bioassays. Adult female houseflies (*Musca domestica* L., SCR strain; ~20 mg each) were treated with the test compound applied topically in 0.5 µL of acetone to the ventrum of the abdomen or injected in 0.2 µL of methoxytriglycol into the mesothorax. In synergized toxicity studies, the flies were treated topically on the abdomen as above with piperonyl butoxide (PB) or phenylsaligenin cyclic phosphonate (PSCP) or a mixture thereof each at 500 µg/g 1 h before application of the candidate insecticide either topically or by injection. Mortality determinations for the treated houseflies, held in batches of 10 with sugar and water at 25 °C, were made after 24 h. The reported LD$_{50}$ values, the doses required for 50% mortality, were estimated using log dose–probit mortality analysis and were reproducible within 2-fold in repeated tests. LD$_{50}$ values for commercial pyrethroids under these test conditions are 0.1 and 0.02 µg/g for (1R,trans,α-RS)-cyphenothrin alone and with PB, respectively, and 14 and 0.32 µg/g for (1R,trans,α-S)-allethrin alone and with PB, respectively.

Miticidal activity was examined by spraying the test compound in water–acetone (3:1) onto only one leaf of bean plants at the two-leaf stage at a rate of 2 mL per leaf where the top of the plant was cut off and the stem was surrounded by lanolin to confine the mites (*Tetranychus urticae* Koch). After drying, more than 100 mites were released on the treated leaf surface and the number of mites on the back side of the treated and untreated leaves was checked separately after 24 h.

Correlation Analysis. Structure–activity relationships of the O-(α-cyano-m-phenoxybenzyl) N-alkylcarbamates were analyzed by a modified Free–Wilson method (Fujita and Ban, 1971) according to eq 1, where pLD$_{50}$ is the negative logarithm of the dose (mol/g) required for 50% mortality on synergism with PB and $B_α$ and $B_{β+γ}$ are the numbers of branches at the α and the β plus γ positions of the alkyl groups, respectively. The levels of significance of the correlations were examined by the t- and F-tests.

$$pLD_{50} = aB_α + bB_{β+γ} + \text{constant} \quad (1)$$

RESULTS

R_M **Values.** R_M values (standard deviations <0.04) of the commercial pyrethroids are 0.10–0.13 for four α-cyano-m-phenoxybenzyl compounds (cyphenothrin, cypermethrin, fenvalerate, fluvalinate) and 0.22 for a m-phenoxybenzyl ester (permethrin). The most insecticidal compounds prepared for this study possess lower R_M values than those of the commercial pyrethroids (Table I).

Comparison of tert-Butyl Acetates and Their Carbamate Analogues with Various Alcohol Moieties (Compounds 1–14) (Table II). The α-cyano-m-phenoxybenzyl esters (1–4) are of increasing potency on topical application to houseflies in the sequence t-BuCOOR < t-BuCH$_2$COOR < t-BuCH(Br)COOR < t-BuNHCOOR. PB greatly increases the effectiveness of 1–4 and PSCP of 1–3, indicating the importance of oxidase detoxification for all compounds and of esterase detoxification for the carboxylic acid esters. The toxicity of 3 and 4 without PB is increased >10-fold on injection vs. topical application, a difference from the method of administration overcome in the most part by synergism with PB.

tert-Butyl α-bromoacetates or N-tert-butylcarbamates of other alcohols (5–14) are much less effective than the α-cyano-m-phenoxybenzyl esters (3 and 4). In comparing

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the *tert*-butyl α-bromoacetates with the *N-tert*-butylcarbamates, the carboxylic esters are equitoxic or more effective in the phenoxybenzyl and (tetrahydrophthalimido)methyl series and the carbamic esters in the (benzylfuryl)methyl, pentafluorobenzyl, and allethronyl series.

Importance of α-Branched N-Alkyl Substituent of Carbamates (Compounds 4, 15–33) (Table III). The importance of branching in the carbamate N-alkyl moieties was examined in the α-cyano-*m*-phenoxybenzyl series since this alcohol confers the highest activity and with PB, which minimizes detoxification and enhances potency. Analyses of the structure–activity relationships by the Hansch–Fujita method (Hansch and Fujita, 1964) using various physicochemical substituent parameters including hydrophobic π, electronic σ*, and steric E_s^c (Hansch and Leo, 1979) gave no significant correlation. It is apparent that N-alkyl substituents conferring an LD$_{50}$ of 5 μg/g or less are compounds with one or two α branches but no β or γ branches, i.e., *i*-Pr, *sec*-Bu, *t*-Bu, 1-EtPr and *t*-Pent. The methyl derivative (15) having no β-carbon atom shows the least activity in the series of *n*-alkyl derivatives with up to five carbon atoms. The N-cycloalkylcarbamates, except the cyclopropyl analogue, are much less toxic than their noncyclic analogues. The data were therefore analyzed by the modified Free–Wilson method (Fujita and Ban, 1971) according to eq 1 to yield eq 2 for all derivatives excluding methyl and cycloalkyl derivatives. In this and the following equation, *n* is the number of data points used in the correlation, *s* is the standard deviation, *r* is the correlation coefficient, F_{ν_1,ν_2} is the *F* value of the correlation where $\nu_1 = m$ and $\nu_2 = n - m - 1$, *m* is the number of independent variables, and figures in parentheses are the 95% confidence intervals of the corresponding coefficients.

$$pLD_{50} = 0.56 \ (\pm0.17)B_\alpha - 0.47 \ (\pm0.20)B_{\beta+\gamma} + 7.30 \ (\pm0.18) \quad (2)$$

$$n = 15, s = 0.20, r = 0.95, F_{2,12} = 60$$

$$pLD_{50} = 0.52 \ (\pm0.10)(B_\alpha - B_{\beta+\gamma}) + 7.34 \ (\pm0.11) \quad (3)$$

$$n = 15, s = 0.20, r = 0.95, F_{1,13} = 124$$

Since the magnitude of the coefficient of the B_α term in eq 2 is similar to that of $B_{\beta+\gamma}$, the two terms are combined to derive eq 3. Adding terms for π, R_M determined by reversed-phase TLC, σ*, or E_s^c singly or together to eq 3 afforded no significant improvement of the correlation. According to eq 3, one branching at the α-position of the alkyl group increases the activity about 3-fold whereas one branching at the β- and γ-position decreases the potency by the same magnitude. The weak activity of the methyl (15) or cycloalkyl derivatives (31–33) except for the cyclopropyl compound (30) is not correctly predicted by eq 3 (Figure 1).

Activity of N,N-Dialkyl- and N-Aralkylcarbamates (Compounds 34–38) (Tables IV and V). The activity of the N,N-dimethyl- (34), -diethyl- (36), and -di-*n*-propyl- (38) carbamates is similar to or identical with that of the corresponding N-monoalkylcarbamates (15–17). The activity of the N-(*n*-butyl)-N-methyl- (35) and N-(*n*-butyl)-N-ethyl- (37) carbamates is quite different from that of the N-(*n*-butyl) derivative (20) but close to that of the N-methyl (15) and N-ethyl (16) derivatives, respectively.

The N-benzylcarbamate (39) is completely inactive even with PB. Introduction of a methyl (40), ethyl (43), isopropyl (44), or dimethyl group (45) at the α-position of the benzyl moiety greatly increases the potency whereas a phenyl group (46) does not improve the activity. The *R*
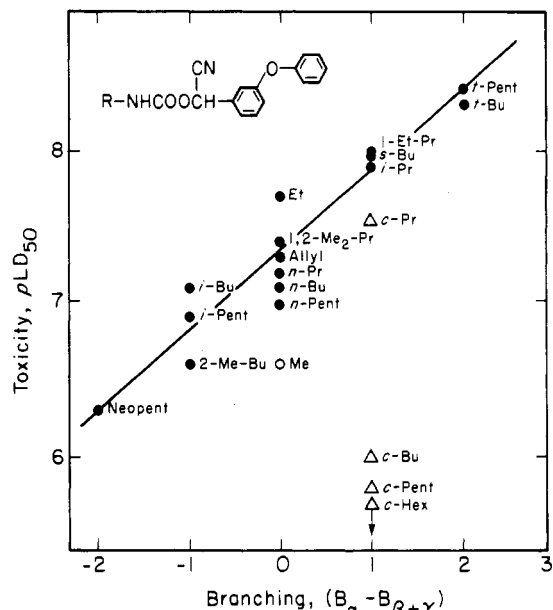

Figure 1. Relationship between branching of the alkyl group and the toxicity of O-(α-cyano-*m*-phenoxybenzyl) N-alkylcarbamates. The numbers of branches are indicated as B_α and $B_{\beta+\gamma}$ for the α- and β+γ-positions, respectively. pLD$_{50}$ is the negative logarithm of the LD$_{50}$ dose (mol/g) for houseflies treated topically with the carbamate and PB. An *r* value of 0.95 is obtained for the C$_2$–C$_5$ alkyl or allyl compounds (●) according to eq 3. Methyl (○) and cycloalkyl (△) derivatives are not included in this correlation.

isomer (41) of 40 possesses much higher activity than the *S* isomer (42). β-Phenylethyl (47) and 1-(α-naphthyl)ethyl (48) derivatives are almost inactive.

Effect of Central Linkage on the Activity of *tert*-Butyl Phenoxyphenyl Derivatives (Compounds 6, 49–73) (Table VI). All compounds with a two-atom bridge between the *tert*-butyl and *m*-phenoxyphenyl groups are inactive, i.e., **52, 56, 62, 69, 70,** and **72**. Those with a five-atom central linkage are also inactive, i.e. **63** and **66**. Esters and reversed esters with a four-atom bridge are inactive or slightly active, i.e. **49** and **53**. Active analogues are obtained when there is a three-atom central linkage and compounds in which the ester group is not bonded directly with the benzene ring (i.e., ester **51** and reversed ester **55**) are more potent with those whose ester group is bonded directly (i.e., **50** and **54**). Reversed amides **60** and **61** with a three-atom bridge are more effective than the other amides and reversed amides with a three- or four-atom linkage, i.e., **57–59.** Carbamate **6** with the four-atom central linkage is active, but the corresponding urea **65** and carbamate **64** with the three-atom bridge are completely inactive. Ether **68** with the three-atom central linkage is more potent than ether **67** with the four-atom bridge. Amine **71** and imine **73** are inactive.

Miticidal Activity. The *tert*-butyl α-bromoacetate (3) and cypermethrin each kill all the mites at 0.1% (a.i.), reduce the population at 0.01%, and are ineffective at 0.001%. In both cases but not in the controls all surviving mites move to an untreated leaf. Compounds **4, 14, 45,** and **68** are not miticidal at 0.1% (a.i.).

DISCUSSION

Lipophilicity is important for high pyrethroid activity (Briggs et al., 1976; Elliott and Janes, 1978). R_M values on reversed-phase TLC are a useful guide to lipophilicity (Boyce and Milborrow, 1965). The pyrethroid-like compounds considered in the present study are only moder-
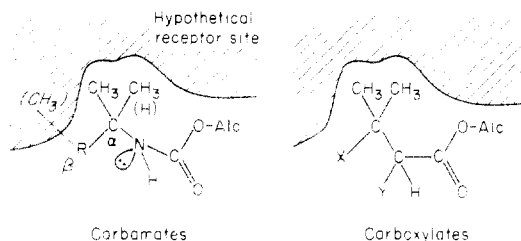
Figure 2. Hypothetical pyrethroid receptor site illustrating the advantage of α branching and the disadvantage of β branching of the N-alkyl- and N-aralkylcarbamates. R is hydrogen, alkyl, or aryl, and Alc is α-cyano-m-phenoxybenzyl. In the carboxylates X and Y are hydrogen and the p-chlorophenyl group of fenvalerate and constitute the cyclopropane ring of cypermethrin. In the carbamates the lone pair on nitrogen is shown equivalent to Y.

ately active and are much less lipophilic than the most potent commercial compounds.

Oxidase and esterase detoxification of pyrethroids can be evaluated in part by the degree of synergism by PB and PSCP, respectively (Casida, 1983). PB synergism is important with all of the pyrethroid-like compounds except for the pentafluorobenzyl esters, which apparently are not subject to rapid oxidative detoxification. It therefore appears that oxidases attack most of the alcohol moieties to a greater degree than the *tert*-butyl substituent of the acid moieties. The toxicity of one of the most potent compounds in this study, i.e., 4, may be limited primarily by oxidase detoxification during penetration, i.e. within the integument, since the ~20-fold LD_{50} difference for topical vs. injected treatments is largely overcome by topically applied PB. PSCP is a relatively poor synergist except in the presence of PB in which case is synergizes the toxicity of the carbamates examined by less than 4-fold and of the carboxylic esters considered by up to 27-fold. This is consistent with expectations since carbamates are often resistant to esteratic cleavage in houseflies (Shrivastava et al., 1969).

The novel compounds in this study are of considerably lower potency than the commercial pyrethroids and may therefore differ from them in their distribution and metabolic profiles. Nevertheless, structure–activity relationships of the O-(α-cyano-m-phenoxybenzyl) N-alkyl- and N-aralkylcarbamates provide a useful supplement to findings from other series (Elliott and Janes, 1977, 1978; Hopfinger et al., 1984) in defining the topography of the pyrethroid receptor site (Figure 2). α branching of the carbamates positions one or two methyl groups equivalent to the *gem*-dimethyl group of fenvalerate and cypermethrin. The essential methyl group of the preferred [(R)-α-methylbenzyl]carbamate (41) may be equivalent to the methyl group cis to the ester moiety, which is most important for the less flexible chrysanthemates (Sugiyama et al., 1974). The (α,α-dimethylbenzyl)carbamate is about twice as active as the α-methylbenzyl analogue due perhaps to increasing the opportunity for a suitably positioned methyl group to interact with the receptor or to the involvement of a *gem*-dimethyl group for optimal action. α branching in these compounds and other carbamates may also restrict the conformation of the alkyl groups facilitating receptor fit. In the N,N-dialkylcarbamate series it appears to be the smaller alkyl group that interacts with the active site. The steric bulk of the cyclopropyl group is as small as that of the ethyl group. However, the other cyclic derivatives having more than three carbon atoms may be unfavorable for fit because the flexibility of the alkyl chain is limited by the cyclic form. The methyl substituent may be too small to fit well. The detrimental

effect of β or γ branching in the N-alkylcarbamate type and of the naphthyl group of the α-naphthylethyl derivative indicates that the receptor cavity for the methyl or alkyl substituent is of small size. Lipophilicity of the N-alkyl substituent plays little role relative to the branching and steric effects.

The central linkage influences the action of the pyrethroid in several ways in addition to its effect on biodegradability. The dipole moment and polarizability appear to be important (Brown and Casida, 1984). It also serves as a flexible spacing group, in the present study establishing a critical distance between the *tert*-butyl and m-phenoxyphenyl moiety (or equivalent substituent in other pyrethroids).

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Registry No. 1, 98991-83-4; 2, 85889-59-4; 3, 98991-84-5; 4, 98991-85-6; 5, 98991-86-7; 6, 98991-87-8; 7, 98991-88-9; 8, 98991-89-0; 9, 99016-54-3; 10, 98991-90-3; 11, 98991-91-4; 12, 98991-92-5; 13, 98991-93-6; 14, 98991-94-7; 15, 98991-95-8; 16, 98991-96-9; 17, 98991-97-0; 18, 98991-98-1; 19, 98991-99-2; 20, 98992-00-8; 21, 98992-01-9; 22, 98992-02-0; 23, 98992-03-1; 24, 98992-04-2; 25, 98992-05-3; 26, 98992-06-4; 27, 98992-07-5; 28, 98992-08-6; 29, 98992-09-7; 30, 98992-10-0; 31, 98992-11-1; 32, 98992-12-2; 33, 98992-13-3; 34, 98992-14-4; 35, 98992-15-5; 36, 98992-16-6; 37, 98992-17-7; 38, 98992-18-8; 39, 98992-19-9; 40, 98992-20-2; 43, 98992-21-3; 44, 98992-22-4; 45, 98992-23-5; 46, 98992-24-6; 47, 98992-25-7; 48, 78445-38-2; 49, 98992-26-8; 50, 98992-27-9; 51, 98992-28-0; 52, 98992-29-1; 53, 98992-30-4; 54, 98992-31-5; 55, 98992-32-6; 56, 98992-33-7; 57, 98992-34-8; 58, 98992-35-9; 59, 98992-36-0; 60, 98992-37-1; 61, 98992-38-2; 62, 65261-11-2; 63, 98992-39-3; 64, 98992-40-6; 65, 98992-41-7; 66, 98992-42-8; 67, 64930-88-7; 68, 64930-73-0; 69, 98992-43-9; 70, 64930-85-4; 71, 98992-44-0; 72, 98992-45-1; 73, 98992-46-2.

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Alkaline Hydrolysis of Quinolyl *N,N*-Dimethylthiocarbamates

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O-8-(5-Z-quinolyl) *N,N*-dimethylthiocarbamates 1 (Z = NO$_2$, Cl, and H) were synthesized from the reaction of the 5-Z-8-quinolynol and *N,N*-dimethylthiocarbamoyl chloride. The kinetics of the hydrolysis in alkaline solution at several temperatures was measured. The observed rates are comparable to those of phenyl derivatives. The activation parameters and the Hammett relationship fit into a mechanism Bac2 for the hydrolysis, with rate-determining attack of the OH nucleophile on the C=S double bond.

INTRODUCTION

Esters of carbamic and thiocarbamic acid have gained a great economical importance during the last few years. Due to their generally low toxicity for warm-blooded animals, their short stability in the soil, and their relatively harmless decomposition products this type of compound is used today more and more as replacement for organochlorides, mercury, and arsenic compounds (Corbett, 1974; Schlagbauer and Schlagbauer, 1972).

We have synthesized several *N,N*-dimethylthio-carbamates of substituted quinolines with potential biological activity and report here a study of their alkaline hydrolysis, since hydrolysis is one of the most important mechanisms for the transformation and degradation of carbamates (Bastide et al., 1980).

RESULT AND DISCUSSION

The alkaline hydrolysis of O-8-(5-Z-quinolyl) *N,N*-di-methylthiocarbamates (1) in 4:1 (v/v) water–dioxane leads quantitatively to 5-Z-8-hydroxiquinoline 2 (eq 1) as determined by UV–vis spectroscopy and the isolation of 2.
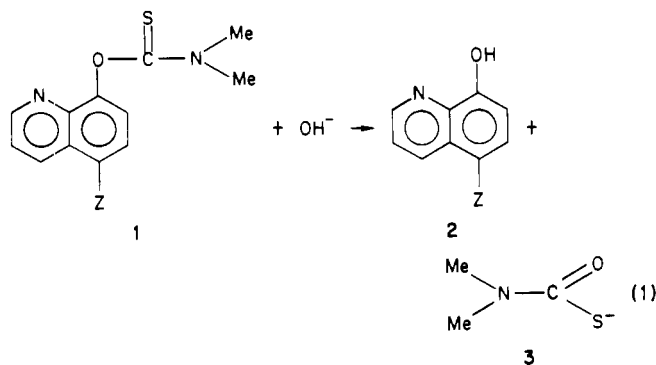
N,N-Dimethylthiocarbamate **3** could not be isolated because this product decomposes during the workup with acidic condition (Ewing et al., 1980).

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Table I. Dependence of Observed Rate Constants k_{obsd} on the Temperature and NaOH Concentration for the Hydrolysis of 1 in Water–Dioxane 4:1 (v/v) and Ionic Strength 1 M

OH⁻, M	$10^6 k_{obsd}$, s⁻¹ (Z = NO$_2$)[a]		$10^6 k_{obsd}$, s⁻¹ (Z = H)[b]	$10^6 k_{obsd}$, s⁻¹ (Z = Cl)[b]	
0.010	1.65[c]	2.90[d]			
0.053	3.17[c]	9.40[d]			
0.097	5.26[c]	11.70[d]			15.20[e]
0.189	5.93[c]	23.5[d]			
0.208			14.60[e]		18.20[e]
0.288	6.67[c]	26.7[d]			27.50[e]
0.417			3.37[d] 27.00[e]	5.50[d]	
0.508	14.70[c]	46.7[d]			
0.625			5.10[d] 45.50[c]	8.80[d]	74.30[e]
0.834			7.36[d] 56.50[e]	12.60[d]	101.00[e]
1.016	21.81[c]	93.8[d]			110.20[e]
1.042			9.40[d] 67.30[e]	14.93[d]	

[a] [substrate]$_o$ = 1·10⁻⁵ M. [b] [substrate]$_o$ = 1–2 × 10⁻⁴. [c] *T* = 30 °C. [d] *T* = 45 °C. [e] *T* = 60 °C.

Table II. Second-Order Rate Constants and Activation Parameters for the Hydrolysis of 1

	$10^5 k_{OH}$, M⁻¹ s⁻¹	$\Delta H^{\ddagger}$,[a] kcal/mol	$-\Delta S^{\ddagger}$,[a] eu
Z = NO$_2$	1.99[b]	17.1	21.3
	8.78[a]		
Z = Cl	1.50[a]	28.3	10.8
	11.50[c]		
Z = H	0.97[a]	29.0	10.2
	6.47[c]		

[a] *T* = 45 °C. [b] *T* = 30 °C. [c] *T* = 60 °C.

Repetitive scanning of the UV–vis spectra during the alkaline hydrolysis give perfect isosbestic points at λ 270 and 320 nm (Z = H), λ 290 and 380 (Z = NO$_2$), and λ 270 and 340 (Z = Cl), indicating a simple 1:1 reaction.

The observed pseudo-first-order rate constant k_{obsd} depends linearly on the OH⁻ concentration in the range studied. Similar results were obtained at two temperatures for each compound studied. The data are summarized on Table I. From the slopes of the linear plot (not shown) we calculated the second-order rate constants k_{OH}. These values, together with the activation parameters are summarized on Table II.

Two mechanisms have been suggested for the hydrolysis of carbamic and thiocarbamic esters (Williams, 1972; Mindl et al., 1980): the ElcB and the Bac2 mechanisms. The