Insecticidal 2-(Methylcarbamoyloxyphenyl)-1,3-dioxolanes, -oxathiolanes, and -dithiolanes

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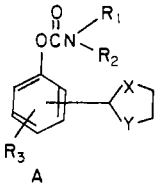
2-(2-Methylcarbamoyloxyphenyl)-1,3-dithiolane (1), -dioxolane (3), and -oxathiolane (2) were effective inhibitors of fly-head acetylcholinesterase and had activity against certain aphids, coleopterous pests, and the housefly. Analogs and homologs of these materials were of diminished activity; in particular, insecticidal activity is more drastically affected by structural changes than is acetylcholinesterase inhibition. *S*-oxidation of 1 also decreased activity. The parent phenol of 1 was relatively effective as an acetylcholinesterase inhibitor, $I_{50} = 5 \times 10^{-5}$. Carbamate 1 showed systemic activity against certain aphids by the soil drench method.

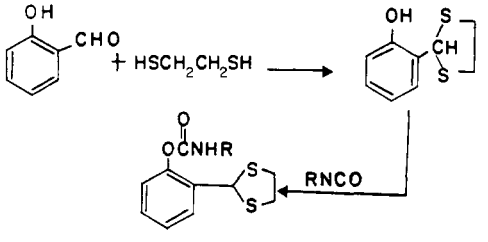
As part of a continuing program on the relationship between chemical structure and biological activity of esters of carbamic acids, the study of a series of compounds generalized by A was initiated. Carbamates



of this type had not been previously studied, although after this work was complete, patents generally disclosing this class of compounds were issued (Nikles *et al.*, 1966; Weil and Schlichting, 1966).

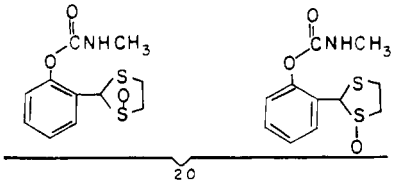
CHEMISTRY

The general synthetic procedure employed in this work is illustrated by Equation 1. In the preparation of the dimethylcarbamates, dimethylcarbamoyl chloride with an acid acceptor was used in the final step.



The preparations of the heterocyclic derivatives of *o*- and *p*-hydroxybenzaldehyde and acetophenone were relatively slow reactions; the dithiolane of *o*-hydroxyacetophenone was not obtained, although several approaches were investigated. This failure and the general sluggishness experienced in these reactions are compatible with the idea that these *o*- and *p*-hydroxy compounds may be considered vinylogous carboxylic acids.

The preparation of *S*-oxidation products of the dithiolane methylcarbamates gave generally predictable results. The oxidation of 2,2-diphenyl-1,3-dithiolane, a symmetrical molecule, has been studied in detail (Kuhn and Neugebauer, 1961; Otting and Neugebauer, 1962). Because of this symmetry, in each case except the disulfoxide, the oxidation products are monoisomeric. However, in the present work, the substitution at the 2-carbon is unsymmetrical and in every oxidation state except the disulfone more than one isomer should exist. This is exemplified by the monosulfoxide (Table I, 20) which was isolated in two fractions (a and b). Whether these fractions represent two different isomers or different mixtures of the two isomers is not certain.



The dithiolane oxidation states higher than the monosulfoxide (except the disulfone) appear to be best prepared stepwise. In the case of the disulfone (Table I, 21), it was necessary to use a large excess of oxidizing agent with a prolonged reaction period (200 hours) at room temperature. The product isolated after 100 hours was a mixture of equal parts of 21 and the corresponding sulfoxide-sulfone as shown by infrared studies. The disulfoxide, 33, is apparently a mixture of isomers while the monosulfoxide, 32, may be monoisomeric.

All attempts to prepare *S*-oxidation products of the oxathiolanes were unsuccessful.

SYNTHESIS

All melting points are uncorrected. The infrared spectra were obtained on either Baird Atomic AB-2 or 4-55 spectrophotometers using either 1% KBr plaques or capillary cells. NMR spectra were obtained on a Varian A-60 instrument using *D*-chloroform as solvent and tetra-

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methylsilane as an internal standard. With each of the compounds reported the spectra were compatible with the desired structure; no unusual spectral features were observed. Elemental analyses were performed at Union Carbide European Research Associates, Brussels, Belgium.

Most of the starting aldehydes are available commercially. The alkyl salicylaldehydes were prepared from the corresponding alkyl phenol using a modified Duff reaction (Liggett and Diehl, 1945) to give 2-hydroxy-4-methylbenzaldehyde, m.p. 57-8° [lit. m.p. 61° (Gross *et al.*, 1963)]; 2-hydroxy-5-methylbenzaldehyde, m.p. 56° [lit. m.p. 56° (Duff, 1941)]; and 2-hydroxy-4-isopropylbenzaldehyde, b.p. 77°/1 mm. This last material is apparently novel; the products prepared from it gave correct analyses.

The intermediate dioxolanes, dithiolanes, and oxathiolanes were prepared by the usual technique of refluxing a mixture of the carbonyl compound and excess dithiol, etc., in benzene or toluene containing a trace of *p*-toluenesulfonic acid or 85% phosphoric acid while removing water azeotropically. When the required water had been collected the reaction mixture, in most cases, was cooled and washed with aqueous sodium bicarbonate, and the organic layer was dried over sodium or magnesium sulfate. Filtration and subsequent concentration in vacuo gave the product as a residue. Since the infrared spectra of these residues usually indicated the absence of unreacted aldehydes, they could be used as such. In reactions involving ethylene glycol the method of Fieser *et al.* (1944) was employed.

Most of the heterocyclic phenols obtained by these reactions were novel compounds and are summarized in Table II. Several were not analyzed as such, as they possessed satisfactory infrared and NMR spectra and their methylcarbamates gave satisfactory analyses.

The carbamates (Table I) were prepared by dissolving the phenol in acetone or chloroform in a pressure bottle in the presence of a 5 to 10% excess of ethyl or methyl isocyanate with 2 to 3 drops of dibutyltin diacetate. After a reaction period varying from 2 to 48 hours the product was isolated by in vacuo concentration of the reaction mixture with subsequent agitation of the residue to induce crystallization. If solid, the carbamate was recrystallized from an appropriate solvent; if liquid, it was taken up in a water-insoluble solvent, thoroughly washed with water, dried, treated with charcoal, filtered, and concentrated in vacuo to a residue which was analyzed as product. The melting points and analytical data relative to these materials are presented in Table III.

The *S*-oxidation reactions were accomplished with peracetic acid (25% in ethyl acetate) in methylene chloride or ethyl acetate solvent. In the case of the mono- and disulfoxides (Table I, 20, 32, and 33) equivalent amounts of oxidant and substrate were employed and the reaction period varied from 2 to 24 hours. With the disulfone (Table I, 21) a large excess of peracid and a prolonged reaction period (~200 hours) were required. After the initial addition of the peracid at −5° to 0°C., the reactions were carried out at room temperature. The products were isolated by washing the reaction mixture with cold 5% potassium bicarbonate solution, drying the neutral organic layer, and finally concentrating in vacuo to a residue. Acetone was the most useful recrystallization solvent.

The following examples specifically illustrate the synthetic procedures employed in this work.

2-(2-Methylcarbamoyloxyphenyl)-1,3-dithiolane (1). A solution of 12.2 grams (0.1 mole) of salicylaldehyde and 10 grams (0.11 mole) of 1,2-ethanedithiol in 300 ml. of benzene plus 0.5 grams of *p*-toluenesulfonic acid was refluxed under azeotroping conditions until 1.7 ml. of water was collected. The cooled reaction mixture was washed with saturated sodium bicarbonate solution until neutral and then dried over sodium sulfate. Filtration and concentration in vacuo gave a residue (20 grams) whose infrared spectrum was in agreement with the expected dithiolane. This residue was dissolved in 125 ml. of chloroform in a pressure bottle, 6 grams (0.1 mole) of methyl isocyanate and 4 drops of dibutyltin diacetate were added, and the bottle was sealed. After standing overnight at room temperature the reaction mixture was concentrated in vacuo to give a residue which, upon crystallization from ethyl acetate, gave 1.

2-(2-Dimethylcarbamoyloxy-4,6-dichlorophenyl)-1,3-dioxolane (25). To a solution of 7 grams (0.03 mole) of 2-(2-hydroxy-4,6-dichlorophenyl)-1,3-dioxolane (m.p. 44–6°) in 100 ml. of acetone was added portionwise with stirring 4.16 grams (0.03 mole) of potassium carbonate. After stirring for 30 minutes at 30°, 6 grams (excess) of dimethylcarbamoyl chloride was added dropwise with stirring and the resulting mixture was stirred at room temperature overnight. The finely divided solid was collected on a filter and the filtrate concentrated in vacuo to give a residue which crystallized upon agitation. Recrystallization from isopropyl ether gave 25.

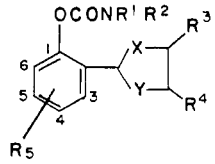
2-(2-Methylcarbamoyloxyphenyl)-1,3-dithiolane-1-monooxide (20a and b). A solution of 12.8 grams (0.05 mole) of 1 in 300 ml. of methylene chloride was cooled to 0° and treated dropwise with stirring with 15.5 grams (0.05 mole) of peracetic acid (25% in ethyl acetate). After addition was complete, the mixture was held at 0° for 2.5 hours and then washed with dilute potassium bicarbonate solution until no more effervescence was noted. After drying over sodium sulfate, the solution was concentrated in vacuo to a solid residue which was dissolved in 150 ml. of boiling acetone and the resulting hot solution was filtered by vacuum through charcoal and then by gravity. Chilling gave 20a (6.5 grams, m.p. 138–41.5°). Concentration of the filtrate to about 1/3 volume with a subsequent crystallization period at room temperature gave 20b, (4.0 grams, m.p. 121–25°). No effort was made to recover additional material. Infrared spectra were generally the same.

BIOLOGICAL ASPECTS

Cholinesterase (ChE) Inhibition. It appears that sulfide sulfur plays a special role. All of the dithiolanes are at least 10-fold more effective than their oxygen analogs: 1 *vs.* 3, 4 *vs.* 5, 15 *vs.* 13, 17 *vs.* 10, 19 *vs.* 9, 26 *vs.* 28, 37 *vs.* 38. Consistent with this, the two oxathiolanes (2 and 27) are intermediate in activity between the corresponding dithiolanes and dioxolanes. Since 2-cyclohexylphenyl methylcarbamate (39) is no less inhibitory than its oxygen analog (37), it is evident that the sulfur atom provides a unique increase in activity. Metcalf *et al.* (1965) have found a similar effect in alkylthiophenyl methylcarbamates. The sulfide form also appears to play an important role in ChE inhibition by simple *O*-(methylcarbamoyl)oximes

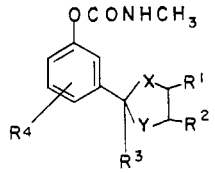
Table I. Biological Activity

Phenyl Carbamate Esters with Heterocyclic Ring in Ortho Position



No.	R^1	R^2	R^3	R^4	R^5	X	Y	LD_{50}, PPM[a] BA	AW	MBB	HF (+PB)[b]	AcChE I_{50}
1	CH_3	H	H	H	H	S	S	2	350	13	12 (3)	2×10^{-8}
2	CH_3	H	H	H	H	S	O	7	>500	100	20 (4)	1.8×10^{-7}
3	CH_3	H	H	H	H	O	O	8	230	~30	8 (2)	5×10^{-7}
4	CH_3	H	CH_3	H	H	S	S	10	>500	>100	22 (10)	4.5×10^{-8}
5	CH_3	H	CH_3	H	H	O	O	15	>500	50	15 (3)	8×10^{-7}
6	CH_3	H	CH_3	CH_3	H	O	O	~150	>500	30	25	3×10^{-7}
7	CH_3	H	CH_2Cl	H	H	O	O	i[c]	i	~90	35	3.5×10^{-7}
8	CH_3	H	C_2H_5	H	H	S	S	i	i	i	i	8×10^{-8}
9	CH_3	H	H	H	4-NO_2	O	O	i	i	i	>500 (>500)	2.0×10^{-4}
10	CH_3	H	H	H	4-Cl	O	O	i	i	~100	40 (3)	9×10^{-7}
11	CH_3	H	H	H	4,6-Cl_2	O	O	i	i	i	i	...
12	CH_3	H	H	H	6-CH_3O	O	O	i	i	i	>500 (>100)	2×10^{-4}
13	CH_3	H	H	H	4-CH_3	O	O	40	~500	i	12 (1.0)	7×10^{-7}
14	CH_3	H	H	H	5-CH_3	S	S	15	>500	i	30 (6)	2.5×10^{-8}
15	CH_3	H	H	H	4-CH_3	S	S	i	>500	12	350 (2)	1.6×10^{-8}
16	CH_3	H	H	H	5-(i-C_3H_7)	S	S	20	i	i	>500 (4)	8×10^{-9}
17	CH_3	H	H	H	4-Cl	S	S	i	>500	~50	>500 (2)	4.5×10^{-8}
18	CH_3	H	H	H	4,6-Cl_2	S	S	i	i	i	>500 (>500)	2.5×10^{-6}
19	CH_3	H	H	H	4-NO_2	S	S	i	i	i	>500 (>500)	5.0×10^{-5}
20a	CH_3	H	H	H	H	S-O	S	4	>500	~100	50	...
b	CH_3	H	H	H	H	S-O	S	3	>500	>100	60 (18)	4.0×10^{-7}
21	CH_3	H	H	H	H	SO_2	SO_2	i	i	i	i	...
22	CH_3	CH_3	H	H	H	S	S	2	>500	i	41 (8)	1×10^{-7}
23	C_2H_5	H	H	H	H	S	S	i	250	20	200 (16)	2×10^{-7}
24	CH_3	CH_3	H	H	4-Cl	O	O	i	i	i	150 (10)	2×10^{-6}
25	CH_3	CH_3	H	H	4,6-Cl_2	O	O	i	i	i	>500 (500)	4.5×10^{-4}

Phenyl Carbamate Esters with the Heterocyclic Ring in Meta Position



No.	R^1	R^2	R^3	R^4	X	Y	LD_{50} (PPM)[a] BA	AW	MBB	HF (+PB)[b]	AcChE I_{50}
26	H	H	H	H	S	S	>100	>500	>100	>500 (80)	7×10^{-7}
27	H	H	H	H	O	S	>100	>500	~150	85 (20)	2×10^{-6}
28	H	H	H	H	O	O	>100	~500	15	50 (8)	2×10^{-5}
29	H	H	CH_3	H	S	S	i[c]	i	i	100 (18)	2×10^{-7}
30	CH_3	CH_3	H	H	O	O	>100	>500	>100	65 (5)	4×10^{-6}
31	H	H	H	6-CH_3O	S	S	i	i	i	>500 (8)	4×10^{-7}
32	H	H	H	H	S-O	S	>100	>500	>100	190 (70)	1×10^{-5}
33	H	H	H	H	S-O	S-O	>100	>500	>100	375 (150)	1×10^{-6}

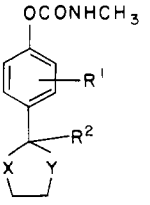
[a] BA, bean aphid, *Aphis fabae* Scop.; AW, southern armyworm, *Prodenia eridania* (Cram.); MBB, Mexican bean beetle, *Epilachna varivestis*, Muls.; HF, housefly, *Musca domestica*, Linn.
[b] PB, piperonylbutoxide. Values in parentheses represent synergized toxicities obtained in presence of 500 p.p.m. of piperonylbutoxide.

such as *S*-methyl *N*-[(methylcarbamoyl)oxy]thioacetimidate (Lannate, DuPont 1179).

That the effect of the sulfur atom is to increase the reversible complexing—i.e., to decrease the affinity constant, *Ka* (Main, 1964)—of the 1,3-dithiolan-2-ylphenyl carbamates with cholinesterase is suggested by the greater inhibitory action of 2-(2-hydroxyphenyl)-1,3-dithiolane over a 2-cyclohexylphenol. In fact, the former compound is the most active phenol that we have tested against the fly-head preparation, being more active than classical (3-hydroxyphenyl)trialkylammonium salts. Thus, the molar I_{50} for fly-head cholinesterase at 37°C., with 0.02*M*

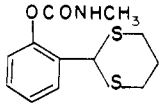
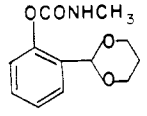
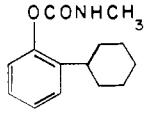
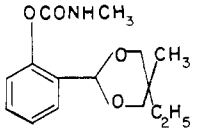
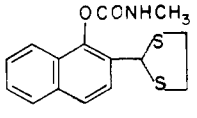
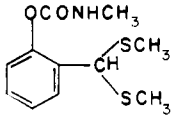
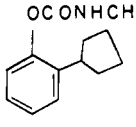
Table I. (*Continued*)

Phenyl Carbamate Esters with Heterocyclic Ring in Para Position



No.	R^1	R^2	X	Y	LD_{50} (PPM)[a] BA	AW	MBB	HF (+PB)[b]	AcChE I_{50}
34	H	H	S	S	>100	>500	>100	>500 (60)	5×10^{-6}
35	H	CH_3	S	S	i[c]	>500	i	>500 (35)	2×10^{-6}
36	2-CH_3O	H	S	S	i	i	i	>500 (40)	1.5×10^{-6}

Miscellaneous Phenyl Carbamate Esters

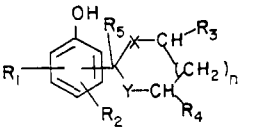
No.		LD_{50} (PPM)[a] BA	AW	MBB	HF (+PB)[b]	AcChE I_{50}
37		i[c]	i	~100	500(2)	2×10^{-8}
38		10	>500	70	17(2)	3×10^{-7}
39		i	i	i	i-(12)	2×10^{-7}
40		i	i	i	125(5)	4×10^{-7}
41		i	...	i	i	...
42[d]		12	~500	~100	113 (10)	6×10^{-8}
43		25	i	...	~500 (−)	1×10^{-7}

[c] i, inactive at highest dosage tested.
[d] W. J. Bartley, Union Carbide Corp.

acetyl choline as substrate was 1×10^{-3} for 2-cyclohexylphenol, 5×10^{-5} for 2-(2-hydroxyphenyl)-1,3-dithiolane, 7.5×10^{-4} for dimethylethyl(3-hydroxyphenyl)ammonium chloride, and 4.3×10^{-4} for (3-hydroxyphenyl)-triethylammonium iodide.

The size of the hetero ring does not appear to be critical, since the six-membered 37 and 38 are as inhibitory as their respective five-membered analogs (1 and 3). Even opening the five-membered dithiolane causes only a threefold drop in potency (42 *vs.* 1). This decrease in potency may result from introducing freedom of rotation of the methylthio groups.

Table II. Intermediate Heterocyclic Phenols Prepared



R^1	R^2	R^3	R^4	R^5	n	X	Y	Position of Heterocycle	M.P., °C. (B.P.°/Mm.)
H	H	H	H	H	1	O	O	2	(127–29/1.0)[a]
H	H	H	H	H	0	S	S	4	117–18[b]
H	H	H	H	H	0	O	S	3	(144–50/0.3)[c]
H	H	H	H	H	0	O	O	2	(110–11/1)[d]
H	H	H	CH_3	H	0	S	S	2	(147–52/1)
H	H	H	CH_3	H	0	O	O	2	(110–10.5/~1)[e]
H	H	CH_3	CH_3	H	0	O	O	2	53–55[f]
H	4-NO_2	H	H	H	0	O	O	2	~74–84
6-Cl	4-Cl	H	H	H	0	O	O	2	53–54
H	H	H	H	CH_3	0	S	S	4	80–81[g]
H	4-CH_3	H	H	H	0	O	O	2	59–60
H	4-CH_3	H	H	H	0	S	S	2	73–74[h]
H	4-Cl	H	H	H	0	S	S	2	61–62[i]
6-Cl	4-Cl	H	H	H	0	S	S	2	113–15
		H	H	H	0	S	S	2	96.5–101.5
2-CH_3O	H	H	H	H	0	S	S	4	90–91
2-CH_3O	H	H	H	H	0	S	S	5	55–56

[a] Linduska *et al.* (1946).
[b] Jones *et al.* (1954, 1955) report m.p. 119–20°C.
[c] Oxygen: Calcd. 17.6. Found, 18.06.
[d] Oxygen: Calcd. 28.89. Found, 29.11, 28.92.
[e] Fieser *et al.* (1944) report 155–56°/13 mm.
[f] Oxygen: Calcd. 24.71. Found, 24.83, 24.78.
[g] Oxygen: Calcd. 7.54. Found, 7.70, 7.66.
[h] Oxygen: Calcd. 7.54. Found, 7.42, 7.47.
[i] Anal.: Calcd., C, 46.44; H, 3.90. Found, C, 46.61, 46.59; H, 3.87, 3.99.

The position of the hetercyclic moiety also affects activity. Substitution by the heterocycle ortho to the carbamate function is superior to meta substitution (1 *vs.* 26, 3 *vs.* 28, 2 *vs.* 27, 20b *vs.* 32). The meta position in turn is superior to the para (26 *vs.* 24, 29 *vs.* 35, 31 *vs.* 36). A similar positional relationship is observed with alkoxy or alkylthio substituents of similar bulk (Metcalf *et al.*, 1965) and with the cyclohexyl group (Metcalf *et al.*, 1962).

Substituent effects have been studied in some detail. Alkyl substitution in the heterocycle does not change or only slightly reduces activity in the ortho series (4, 8, 5, 6, 7, and 40), but increases it in the other positions (29, 30, and 35). It appears that the unsubstituted ring provides for optimal complementarity with cholinesterase when in the ortho position. In contrast, the less satisfactory orientation and fit apparently associated with the meta and para positions can be improved by alkyl substitution.

With the exception of the 5-isopropyl analog (16), substitution of the phenyl ring did not improve the activity of the parent ortho compound 1. If the heterocyclic function is visualized as covering the anionic site of cholinesterase, the modest increase observed with 16 may result from nonspecific lipophilic-hydrophobic bonding of the isopropyl group or more effective binding for that statistical proportion of the molecules oriented at the enzyme surface with the 5-position of the phenyl adjacent to the anionic site.

Substitution of the phenyl ring with strong electron-withdrawing substituents such as —NO_2 markedly increases the lability of the methylcarbamate moiety. As a result, compounds such as 9 and 19 hydrolyze rapidly under the conditions of the Warburg method of cholinesterase assay (Fukuto *et al.*, 1967). Because of this complication the values obtained cannot be validly included in structure -I_{50} correlations. The inhibition for 9 and 19 approaches the I_{50} that one might expect for the phenol. The very marked loss of activity associated with substitution in both positions ortho to the carbamate function was anticipated. The generalization that optimal inhibition is usually obtained with monomethyl substitution of the carbamate nitrogen (Kolbezen *et al.*, 1954) is supported by the I_{50}'s of the dimethyl (22,) and the ethyl (23) homologs of 1.

Insecticidal Activity. The activity spectrum of the better compounds in Table I resembles that of a typical aryl methylcarbamate (Weiden and Moorefield, 1964). This comprises significant activity against the bean aphid and Mexican bean beetle and weak or no activity against the southern armyworm and the two-spotted spider mite. Housefly toxicity in the present series appears to be somewhat greater than might be anticipated, but the marked synergism shown by combination with piperonyl butoxide follows the usual pattern.

Examining individual compounds in Table I, the dithiolane (1) is the most active, followed by the dioxolane (3). As was the general case with cholinesterase inhibition, none of the structural modifications of either 1 or 3 im-

Table III. Analytical Results

No.	M.P., °C.	Analyses					
		Carbon		Hydrogen		Oxygen	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
1	142–43	51.76	51.74	5.13	5.30	5.49	5.26[a]
2	109–10	55.21	54.87	5.47	5.51	20.46	20.31
3	114.5–15.5	59.18	59.36	5.87	5.86	28.67	28.91
			59.21		5.91		28.98
4	101–02	53.50	53.30	5.61	5.64	5.20	5.38[a]
5	Residue	...	...	...	...	26.98	27.46
							27.29
6	96–102	62.14	62.11	6.82	7.13	25.47	25.38
7	Residue	...	...	...	...	23.56	23.52
							23.45
8	66–67.5	55.12	54.62	6.05	5.98	...	...
9	141–44	49.25	49.63	4.5	4.57	...	...
			49.36		4.59		
10	120–21	51.27	51.35	4.67	4.87	24.84	24.62
11	158–60	45.22	44.80	3.80	3.93	21.91	21.70
			44.73		3.73		21.74
12	128–29.5	56.91	56.91	5.97	6.19	31.59	31.93
			56.78		6.23		31.68
13	110–11	60.75	60.58	6.37	6.36	...	...
14	163–64.5	53.50	53.03	5.61	5.53	...	...
15	161–63.5	53.50	53.21	5.61	5.61	...	...
16	147–49	56.53	56.20	6.43	6.36	...	...
17	170–72	45.59	45.74	4.17	4.23	11.37	11.26
18	180–82	40.74	41.48	3.42	3.43	...	...
19	170.5–72	43.98	43.78	4.02	3.97	...	...
20a	138–41	48.30	48.61	4.83	4.97	17.68	17.50
20b	121–25[b]	...	...	...	...	...	...
21	213–14	41.37	41.55	4.10	4.13	30.06	29.85
							29.82
22	Residue	53.50	53.54	5.60	5.69	...	...
			53.27		5.76		
23	125–27	53.50	53.52	5.60	5.61	...	...
24	Residue	53.24	53.18	4.83	5.36	...	...
25	63.5–64.5	47.07	47.00	4.27	4.28	...	...
26	97–98	51.76	52.41	5.13	5.34	5.49	5.54[a]
			52.21		5.22		5.44
27	63–64.5	55.23	54.93	5.48	5.53	5.86	5.87[a]
28	76–77.5	59.18	59.30	5.87	5.95	28.67	28.74
			59.46		5.91		28.67
29	91.5–93.0	53.50	53.44	5.61	5.69	11.87	12.15
30	Residue	...	...	...	...	5.57	6.07[a]
							6.18
31	173–74	50.50	50.57	5.30	5.32	...	...
			50.38		5.18		
32	135.5–36.5	48.69	48.59	4.83	4.59	17.69	17.72
			48.78		4.67		17.92
33	140.5–62.5 (dec.)	46.00	45.67	4.56	4.66	22.69	22.69
34	90.5–92	51.76	51.79	5.13	5.20	...	...
35	120–21	53.50	53.37	5.61	5.67	...	...
			53.41		5.75		
36	173–74.5	50.50	50.57	5.30	5.32	...	...
			50.38		5.18		
37	151–52	53.53	53.24	5.62	5.77	...	...
			53.11		5.66		
38	130–31	60.75	60.86	6.37	6.55	26.98	26.69
			60.87		6.45		26.98
39	78–79.5	...	...	...	...	6.80	6.83
40	114–21	64.49	64.55	7.58	7.80	22.91	23.00
			64.51		7.93		23.20
41	181–84	58.99	59.06	4.95	4.92	...	...

[a] Nitrogen analysis.
[b] Infrared spectrum of 20a essentially the same as that of 20b.

proved their activity. The dioxolanes tend to be more active, both alone and in combination with piperonyl butoxide, than the dithiolanes of the same I_{50}'s. The effect of the alkyl substituents in 15 and 16 is not only to decrease toxicity but also to increase lipophilic-hydrophobic character. We suggest that this association is not accidental, but that the increased lipophilicity predisposes these compounds to more efficient degradation by microsomal oxidation (Gaudette and Brody, 1959).

Evaluation of Utility of 1. The superiority of 1 in the initial tests, its lack of phytotoxicity under both laboratory and field conditions, and its favorable mammalian toxicity (oral LD_{50} to male rats as a 1% suspension in corn oil is 160 mg. per kg.) suggested further evaluation.

Laboratory leaf-dip tests showed 1 to be good against alfalfa weevil, *Hypera postica* (Gyllenhal), larvae (LD_{50} 8 p.p.m.), but poor against the eastern tent caterpillar, *Malacosoma americanum* (Fabricius) ($LD_{50} \sim 50$ p.p.m.). Activity was fair in Petri dish residual film tests against the rice weevil, *Sitophilus oryzae* (Linnaeus), and the confused flour beetle, *Tribolium confusum* J. du Val. Compound 1 possesses some systemic activity, since by the soil drench method, it gave fair control of populations of bean aphids on nasturtiums, of pea aphids, *Acyrthosiphon pisum* (Harris), on broad beans, of chrysanthemum aphids, *Macrosiphoniella sanborni* (Gillette), and of Mexican bean beetles on bean plants.

In field screening tests with dilute aqueous sprays, 1 was rated good against Mexican bean beetle larvae at 1/4 pound per 100 gallons and alfalfa weevil larve at 1 pound per 100 gallons; fair at 1/4 pound per 100 gallons against apple aphids (*Aphis pomi* de Geer) and Colorado potato beetle, *Leptinotarsa decemlineata* (Say), and at 1 pound per acre against imported cabbage worm, *Pieris rapae* (Linnaeus), on collards; poor against *Heliothis* spp. larvae on late-planted corn at 2 pounds per acre; and completely ineffective at 1 pound per 1000 gallons against rosy apple aphids, *Dysathis plantaginea* (Passerini), and two-spotted spider mites on snap beans. Residual activity appears to be poor.

METHODS

Insect species, insecticidal tests, and I_{50} determinations have been described (Payne *et al.*, 1966). Piperonyl butoxide at 500 p.p.m. was incorporated with the toxicant in the fly bait to obtain the synergized toxicity. Instability under Warburg conditions was determined by varying the incubation of the carbamate with the enzyme over a period of several hours. Equivocal results regarding stability may be obtained if the parent phenol is unusually inhibitory.

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