Sugar, Glyceryl, and (Pyridylalkoxy)sulfinyl Derivatives of Methylcarbamate Insecticides

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A series of sugar, glyceryl, and (pyridinealkoxy)sulfinyl derivatives of methylcarbamate esters were prepared and examined for insecticidal and anticholinesterase activity and for mouse toxicity. Several of the derivatives showed good insecticidal activity, and on a mole basis some showed higher activity than the parent methylcarbamate. Overall, the derivatives exhibited poorer anticholinesterase activity and were less toxic to mice than the methylcarbamate. The sulfinylated derivatives were readily hydrolyzed or solvolyzed to the methylcarbamate, indicating that the parent methylcarbamate is released in biological systems and is responsible for intoxication.

A previous paper from this laboratory (Fahmy and Fukuto, 1981) described the reaction between insecticidal methylcarbamate esters and thionyl chloride to give the corresponding *N*-(chlorosulfinyl)-*N*-methylcarbamate intermediates. These intermediates proved to be useful for the synthesis of a large variety of new N-derivatized methylcarbamate esters, many of these derivatives having favorable properties of selectivity, i.e., high insecticidal activity and reduced mammalian toxicity.

Because of their versatile nature, the chlorosulfinyl intermediates were examined further for the synthesis of derivatives of different physical properties to determine the effect of the polarity of the molecule on insecticidal activity and plant systemic activity. This report is concerned with the synthesis and insecticidal evaluation of a series of (oxysulfinyl)methylcarbamates containing hydrophilic moieties such as pyridinealkanols, glycerols, and derivatized sugar molecules.

MATERIALS AND METHODS

Chemicals. The methylcarbamate insecticides which were derivatized in this study, i.e., *S*-methyl *N*-[methylcarbamoyl)oxy]thioacetimidate (methomyl), 3-methylphenyl methylcarbamate (tsumacide), 3-isopropylphenyl methylcarbamate (MIP), *S*-methyl *N*-[(methylcarbamoyl)oxy]-2-(*N'*,*N'*-dimethylamino)-2-oxoethanamidothioate (oxamyl), and 2-isopropoxyphenyl methylcarbamate (propoxur) were obtained from their respective manufacturers or were prepared by conventional methods. 2,2-Dimethyl-1,3-dioxolane-4-methanol, 1,2,5,6-di-*O*-isopropylidene-D-glucose, and the various pyridinealkanols were obtained from the Aldrich Chemical Co. 2-Phenyl-5-hydroxy-1,3-dioxolane, 3-(allyloxy)-1,2-propanediol, 2-(allyloxy)-1,3-propanediol, and 3-(benzyloxy)-1,2-propanediol were prepared according to Hibbert and Carter (1929). 1,2,4,5-Di-*O*-isopropylidene-D-fructose and 2,3,4,5-di-*O*-isopropylidene-D-fructose were prepared according to Brady (1970).

Synthesis. The chlorosulfinyl intermediates were prepared by reaction of the appropriate methylcarbamate and an equimolar amount of thionyl chloride and pyridine in tetrahydrofuran (Fahmy and Fukuto, 1981). The resulting (chlorosulfinyl)methylcarbamate was reacted in situ with the respective alkanol or sugar derivative in the presence of pyridine or triethylamine. Solid products were purified by recrystallization from hexane–ethyl acetate and liquid products by silicic acid column chromatography (Mallinckrodt CC-7) or preparative thin-layer chromatography (TLC) (E. Merck 60PE-254) using benzene or ethyl acetate as the solvents. Typical examples of synthesis are given below.

^{1}H NMR spectra were recorded in a Varian EM-390 spectrometer with tetramethylsilane as an internal standard.

Synthesis of *S*-Methyl *N*-[(2-Pyridylmethoxy)sulfinyl]-*N*-[(methylcarbamoyl)oxy]thioacetimidate (1). A mixture of freshly distilled thionyl chloride (1.25 g, 0.0105 mol) and 2 mL of anhydrous tetrahydrofuran (THF) was added dropwise with stirring to an ice-chilled solution of methomyl (1.62 g, 0.01 mol) and pyridine (0.987 g, 0.013 mol) in 10 mL of anhydrous THF. After stirring for 5 h at room temperature, 0.987 g pyridine was added, the mixture was chilled and 2-pyridinemethanol (1.09 g, 0.01 mol) was added dropwise. The mixture was stirred for an additional 1 h at room temperature, 100 mL of ether was added, and the organic phase was washed twice with water and dried over anhydrous sodium sulfate. Removal of the solvent gave 2.65 g of crude product as a light brown solid. Recrystallization from hexane–ethyl acetate (3:1) gave 1.59 g (50%) of colorless needles: mp 65–66 °C; ^{1}H NMR ($CDCl_3$) δ 8.58 (1 H, d, J = 5 Hz, 6'-H), 7.2–7.9 (3 H, m, pyridine protons), 5.12 (2 H, s, OCH_2), 2.98 (3 H, s, NCH_3) 2.38 (3 H, s, $CH_3C{=}N$), 2.28 (3 H, s, SCH_3).

Synthesis of *N*,*N''*-Tris[(1,2,3-propyltrioxy)sulfinyl]tris[*S*-methyl *N*-[(methylcarbamoyl)oxy]thioacetimidate] (21). A mixture of thionyl chloride (1.25 g, 0.0105 mol) and 2 mL of THF was added dropwise with stirring to an ice-chilled solution of *S*-methyl *N*-(methylcarbamoyl)thioacetimidate (1.62 g, 0.01 mol) and pyridine (0.987 g, 0.013 mol) in 10 mL of THF. After the mixture was stirred for 5 h at room temperature, 0.987 g of pyridine was added, the mixture was chilled, and 0.31 g of glycerol in 2 mL of dimethylformamide (DMF) was added dropwise. The mixture was stirred for another 1 h at room temperature and 70 mL of dichloromethane and 30 mL of ice water were added with vigorous stirring. The organic layer was removed, dried over magnesium sulfate, and concentrated under reduced pressure to give 2.3 g of a yellow oil. Purification was by silica gel column chromatography using benzene–ethyl acetate (10:1) and ethyl acetate as eluting solvents. The final product (0.78 g, 35%) was a light yellow oil which solidified to an amorphous solid upon standing: mp 65–70 °C; ^{1}H NMR ($CDCl_3$) δ

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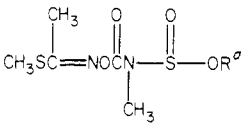
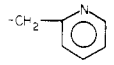
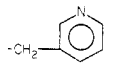
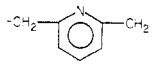
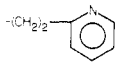
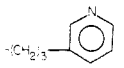
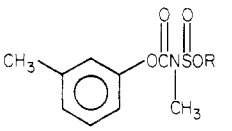
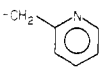
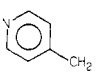
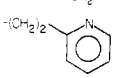
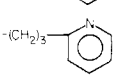
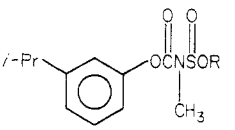
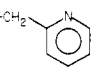
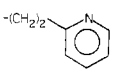
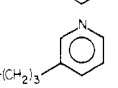
Table I. Physical and Toxicological Properties of *N*-[(Pyridylalkoxy)sulfinyl]-*N*-methylcarbamates

compound no.	compound R	n^{24}D (or mp, °C)	analysis calcd	analysis found	housefly LD_{50} μg/g	housefly LD_{50} μmol/g	mouse oral LD_{50}, mg/kg
	 methomyl						
1		(65-66)	C: 41.63 H: 4.76	41.28 4.39	7.0	0.022	85
2		(85-87)	C: 41.63 H: 4.76	42.30 5.44	5.8	0.018	96
3		1.5485	C: 36.75 H: 4.54	36.47 4.42	65	0.124	170
4		1.5523	C: 43.79 H: 5.17	44.85 5.54	10.8	0.032	232
5		1.5250	C: 45.20 H: 5.54	45.86 6.07	11	0.032	280
6	methomyl				3.7	0.023	10
	 tsumacide						
7		1.5560	C: 56.24 H: 5.03	56.40 5.24	235	0.73	750
8		1.5505	C: 56.24 H: 5.03	56.34 5.71	>500	>1.56	>1000
9		1.5500	C: 57.47 H: 5.43	58.25 5.75	200-400	0.60-1.20	870
10		1.5500	C: 58.60 H: 5.79	58.56 6.09	>500	>1.44	750-1000
11	tsumacide				390	2.36	268
	 MIP						
12		1.5430	C: 58.60 H: 5.79	59.36 5.65	111.5	0.32	105
13		1.5440	C: 59.65 H: 6.12	60.34 6.19	168	0.46	130
14		1.5420	C: 60.62 H: 6.43	60.71 6.21	205	0.55	100
15	MIP				41	0.21	16

[a] The sulfinyl sulfur atom is attached to the methylcarbamate nitrogen atom.

4.5–4.8 (1 H, q, J = 5 Hz, CH_2CHCH_2), 3.8–4.3 (4 H, m, CH_2CHCH_2), 3.0 (9 H, s, NCH_3), 2.4 (9 H, s, CH_3-C), 2.28 (9 H, s, SCH_3).

Synthesis of *S*-Methyl *N*-[(1,2,5,6-Di-*O*-isopropylidene-3-*O*-glucofuranosyl)sulfinyl]-*N*-[(methylcarbamoyl)oxy]thioacetimidate (24). To a chilled solution of *S*-methyl *N*-(chlorosulfinyl)-*N*-[(methylcarbamoyl)oxy]thioacetimidate (0.01 mol) in 10 mL of THF, prepared as described above, was added dropwise with stirring 1,2,5,6-di-*O*-isopropylidene-α-glucose (2.6 g, 0.01 mol) in 5 mL of THF. The mixture was stirred for 40 min at room temperature and the product was worked up as described above to give 3.12 g of a brown solid. Recrystallization from hexane–ethyl acetate gave colorless prisms (1.06 g, 23%): mp 141 °C; ^{1}H NMR ($CDCl_3$) δ 5.88 (1 H, d, 1′-H), 4.77 (1 H, d, 3′-H), 4.58 (1 H, d, 2′-H), 3.8–4.4 (4 H, m, 4′,5′,6′-H), 3.07 (3 H, s, NCH_3), 2.40 (3 H, s, CCH_3), 2.27 (3 H, s, SCH_3), 1.50, 1.40, 1.30, 1.27 (12 H, s, isopropylidene-CH_3).

Structures of all derivatized methylcarbamates which were prepared are given in Tables I and II, along with their elemental analyses and physical properties.

Biological Activity. Housefly toxicity was determined with a susceptible (NAIDM) strain of houseflies, *Musca domestica*, according to usual procedures (Metcalf and March, 1949). Mammalian toxicity was determined orally with Swiss white mice by using propylene glycol or corn oil as the carrier (Hollingworth et al., 1967).

The systemic insecticidal activity against the green peach aphid, *Myzus pericae*, was evaluated as follows. A 10% wettable powder of each compound was prepared and appropriate amounts were dissolved in water to make a final concentration of 25 and 100 ppm. To 30 mL of each solution in a 30-mL amber glass bottle was placed a leaf petiole of the field mustard plant, *Brassica Rapa* var. *pervidis*. The leaf was infested with 40–60 aphids and the petiole was held in place by a wad of cotton inserted in the neck of the bottle. The bottle was placed in a cardboard carton and the carton was placed in a vinyl cylinder containing a nylon cap. Mortality was determined every 24 h up to 72 h after treatment.

In the test against the tobacco cutworm, *Sphodoptera litura*, aqueous solutions containing each toxicant at 100 and 500 ppm and the emulsifying agent Shingramin (0.03%) were prepared. A cabbage leaf was dipped into each of these solutions for 30 s and placed in a paper cup of 8-cm diameter. Ten tobacco cutworms (third instar) were released on the leaf and mortality was determined 72 h later. Two leaves were used for each concentration.

Evaluation against the resistant strain of green rice leafhopper, *Nephotettix cincticeps* (last instar larvae of the Shinwa strain), and brown plant hopper, *Nilaparvata lugens*, was made according to Fujita et al. (1975). Mortality was determined 3 days after treatment.

Bimolecular rate constants (k_i) for the inhibition of housefly-head and bovine erythrocyte acetylcholinesterase (AChE) (Sigma Chemical Co.) were determined at 30 °C, pH 7.6, by using the colorimetric method of Ellman et al. (1961). Procedures for the determination of k_i values (Wustner and Fukuto, 1973) and preparation of housfly-head AChE (Fukuto and Metcalf, 1956) were previously described.

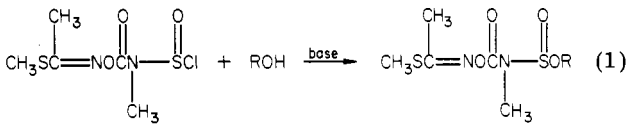
Hydrolysis and Methanolysis. Analysis of products from the acid-catalyzed hydrolysis of the sulfinyloxy methylcarbamate derivatives was carried out according to the following example for the hydrolysis of 3-benzyloxy-1,2-propanedioxysulfinylbis-(3-methylphenyl methylcarbamate) (**36**). To a solution of **36** (0.604 g, 0.001 mol) in 4 mL of dioxane–water (1:1) was added 2 drops of 6 M hydrochloric acid and the mixture was stirred for 3 h at room temperature. The mixture was extracted with two 10-mL portions of ether, and removal of the ether after drying gave a yellow oil which was analyzed by TLC using benzene–ethyl acetate (4:1) as the solvent. The following compounds, in order of decreasing R_f values, were observed: (1) 0.15 g (29%) of 3-hydroxy-1,2-propanedioxysulfinylbis(3-methylphenyl methylcarbamate) [n_D^{24} 1.5330; ^{1}H NMR ($CDCl_3$) δ 6.8–7.4 (8 H, m, Ar), 4.0–5.2 (5 H, m, CH_2CHCH_2), 3.10 (6 H, s, NCH_3), 2.30 (6 H, s, CH_3), 1.97 [1 H, s, OH (exchangeable with D_2O)]]; (2) 0.09 g (27%) of 3-methylphenyl methylcarbamate (mp 76 °C); (3) trace 3-(benzyloxy)-1,2-propanediol.

The analysis of methanolysis products was carried out according to the following example for the methanolysis of 3-methylphenyl *N*-(2,2-dimethyl-1,3-dioxolan-5-ylmethoxysulfinyl)-*N*-methylcarbamate (**34**). A solution of 0.343 g (0.001 mol) of **34** and 2 mL of methanol was heated at reflux temperature for 3 h. Removal of the methanol gave a yellow oil (0.3 g) which upon distillation gave 0.085 g (64%) of 1,2-di-*O*-isopropylidene glycerol, bp 84–85 °C (0.4 mmHg). The undistillable residue was 3-methylphenyl methylcarbamate, 0.165 g (100%), mp 74 °C. These compounds were spectroscopically (NMR) identical with authentic compounds.

The rate of breakdown of two selected oxysulfinyl methylcarbamates (**17** and **34**) to give the parent carbamates in acidic solution and in methanol was monitored at short time intervals over a period of 40 min (acid hydrolysis) and 270 min (methanolysis). The reaction conditions were the same as described above. The relative amounts of each component were determined by means of a Hitachi 635-T type high-pressure liquid chromatograph (HPLC), equipped with an UV detector (254 nm) and 5 × 50 cm glass column packed with Hitachi 3010. Carrier solvent [mixture of methanol, acetic acid, and water (94:1:5)] was introduced at a rate of 1.5 mL/min. The temperature of the column was 50 °C. The sulfinyloxy methylcarbamates used in this experiment were found to be stable in the HPLC column. Only the peak attributable to the parent methylcarbamate was detected on the HPLC chromatogram as the breakdown product for either **17** or **34**.

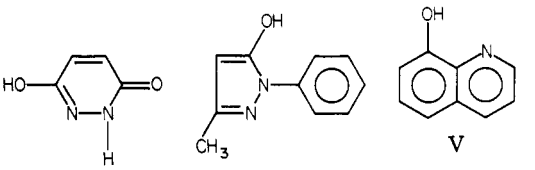
RESULTS

Synthesis. An earlier paper from this laboratory described the reaction between an *N*-(chlorosulfinyl)-*N*-methylcarbamate (e.g., I in eq 1) and a simple alcohol or



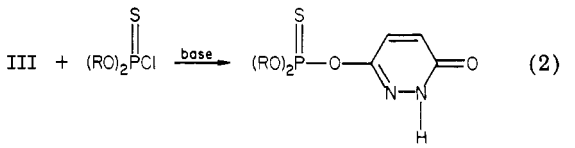
I II, R = alkyl or aryl

phenol to give in good yield the corresponding *N*-[(alkyloxy)sulfinyl- or *N*-[(aryloxy)sulfinyl]-*N*-methylcarbamate. In the present study, this reaction was initially applied to compounds containing both a hydroxy and nitrogen heterocyclic moiety in an attempt to introduce a basic group in the molecule. Reaction with nitrogen heterocycles containing an aromatic hydroxyl group, e.g., compounds such as maleic hydrazide (III), 1-phenyl-3-



III IV V

methyl-5-hydroxypyrazole (IV), and 8-hydroxyquinoline (V), failed to give the expected product under a variety of reaction conditions. III has been shown to react readily with *O,O*-dialkyl phosphorochloridothioates to give the corresponding pyridazinyl phosphorothioates (VI) (Jojima and Takeshiba, 1974) (eq 2).



VI

In contrast to the aromatic hydroxy heterocycles, the *N*-(chlorosulfinyl)-*N*-methylcarbamates reacted smoothly with the pyridinealkanols to give the corresponding (pyridylalkoxy)sulfinyl derivatives in yields varying from 16–76%. Methylcarbamate insecticides which were converted to the (pyridiylalkoxy)sulfinyl derivatives were methomyl, tsumacide, and MIP (see Table I). The (py-

Table II. Physical and Toxicological Properties of Glycerol and Sugar Sulfinyl Derivatives of Methylcarbamate Insecticides

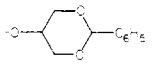
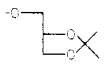
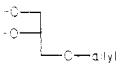
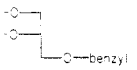
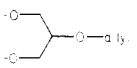
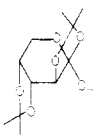
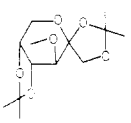
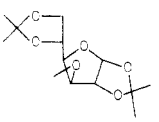
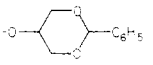
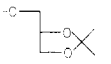
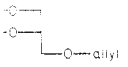
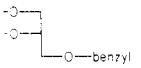
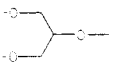
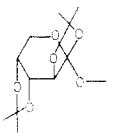
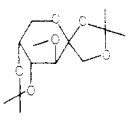
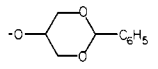
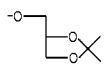
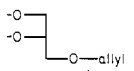
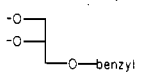
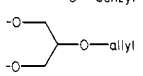
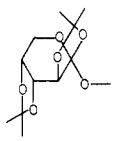
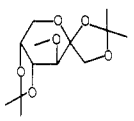
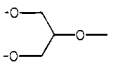
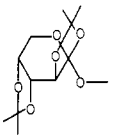
compound no.	R	n	$n^{24}D$ (or mp, °C)	analysis calcd	analysis found	housefly LD_{50} µg/g	housefly LD_{50} µmol/g	mouse oral LD_{50}, mg/kg
				(methomyl—S(=O)—)$_n$R[a]				
16		1	(93.5)	C: 46.38 H: 5.19	46.71 5.43	650	1.67	85
17		1	(72-74)	C: 38.81 H: 5.92	39.10 6.10	7.0	0.021	84
18		2	1.5323	C: 35.03 H: 5.14	35.87 5.45	40	0.073	50-80
19		2	1.5540	C: 40.12 H: 5.05	40.40 5.49	<50	<0.084	50-100
		2	1.5352	C: 35.03 H: 5.14	36.08 5.74	6.5	0.012	88
21		3	(65-70)	C: 32.04 H: 4.76	31.78 4.90	>500	>0.74	50-100
22		1	1.4992	C: 43.58 H: 6.02	43.84 6.54	50	0.11	500
23		1	1.4998	C: 43.58 H: 6.02	43.08 6.60	115	0.25	1000
24		1	(141)	C: 43.58 H: 6.02	43.83 6.15			>1000
6	methomyl					3.7	0.023	10
				$[(CH_3)_2NCC(=O)=NOCNS(CH_3)(=O)-]_nR$				
				oxamyl				
25		1	1.5492	C: 45.83 H: 5.20	45.95 5.80	160.5	0.36	25
26		1	1.5183	C: 39.29 H: 5.83	39.51 5.90	2.6	0.0064	31
27		2	1.5408	C: 36.24 H: 5.17	36.26 5.46			12.5-25
28		2	1.5450	C: 40.44 H: 5.09	40.55 5.50	11	0.015	12.5-25
29		3	(70-74)	C: 32.46 H: 4.65	32.88 4.26	500	0.56	
30		1	1.5040	C: 43.42 H: 5.95	43.76 6.16	20	0.038	44
31		1	(55-57)	C: 43.42 H: 5.95	43.55 6.18	97.5	0.19	50
32	oxamyl					3.6	0.016	3.7

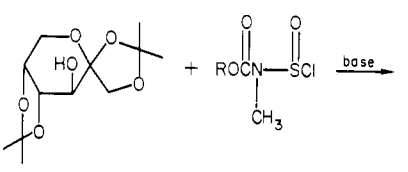
Table II (*Continued*)

compound no.	R	n	$n^{24}D$ (or mp, °C)	analysis calcd	analysis found	housefly LD_{50} μg/g	housefly LD_{50} μmol/g	mouse oral LD_{50}, mg/kg
				(tsumacide—S(=O)—)$_n$R				
33		1	1.5506	C: 58.30 H: 5.41	58.61 5.77	>500	>1.28	>1000
34		1	1.5115	C: 52.47 H: 6.16	52.16 6.18	>500	>1.46	>1000
35		2	1.5323	C: 51.97 H: 5.45	51.88 5.54	>500	>0.90	>1000
36		2	1.5482	C: 55.62 H: 5.33	55.63 5.77	>500	>0.83	>1000
37		2	1.5370	C: 51.97 H: 5.45	52.00 5.83	>500	>0.90	>1000
38		1	1.4974	C: 53.49 H: 6.20	54.22 7.11	>500	>1.06	>1000
39			1.5088	C: 53.49 H: 6.20	53.70 6.40	>500	>1.06	>1000
11	tsumacide					390	2.36	268
				i-PrO, OCN(CH$_3$)—S(=O)—)$_n$R				
	propoxur							
40		3	1.5370	C: 50.40 H: 5.52	50.84 6.16	>500	>0.58	>1000
41		1	1.5032	C: 53.58 H: 6.45	53.81 6.78	>500	>0.97	>1000
42	propoxur					22	0.105	24

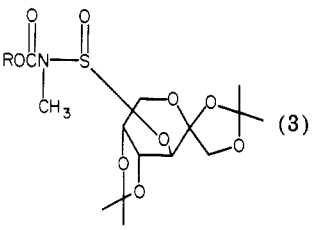
[a] The sulfinyl sulfur atom is attached to the methylcarbamate nitrogen atom. See Table I for structures of methomyl, tsumacide, and MIP.

ridylalkoxy)sulfinyl derivatives of oxamyl were highly unstable, and although the products were formed, they decomposed during the purification process. In general, 2-pyridinemethanol gave better yields of products compared to the 3- and 4-pyridinemethanols. Further, the longer chain pyridinealkanols also gave better yields than those of the shorter chain analogues.

The reaction between the *N*-(chlorosulfinyl)-*N*-methylcarbamate intermediate and a variety of polyhydroxy compounds, where the hydroxy groups were unprotected or partially protected, was explored. These compounds were synthesized for the purpose of attaching a highly polar moiety to the methylcarbamate insecticide or a group which conceivably would be converted into a highly polar moiety. The reaction between the protected or unprotected glycerols with the *N*-chlorosulfinyl intermediate gave the desired products in good yields. However, sugars such as glucose and fructose, owing to their poor solubility in organic solvents, did not react with the *N*-chlorosulfinyl intermediate. In contrast, protected sugars such as 1,2,4,5-di-*O*-isopropylidene-α-D-fructose (VII) were soluble in organic solvents and readily reacted with the *N*-(chlorosulfinyl)-*N*-methylcarbamates to give the corresponding product in good yield (eq 3). The glycerol and sugar derivatives which were prepared are listed in Table II.



VII



(3)

Table III. Toxicity of Representative Oxysulfinyl Methylcarbamates to Some Agriculturally Important Insects

	% mortality								
	green peach aphid (systemic), ppm		tobacco cutworm, ppm				green rice leafhopper, kg/10 are		brown planthopper, kg/10 are	
compound	100	25	500	100	20	4	7.05	1.41	7.05	1.41
				Methomyl Derivatives						
1	22.4	1	65	5			10		27.3	
2			100	85	15	0	100	15	90.9	
3							100	100	100	100
4							100	95.2	100	95.8
5							100	85.7	100	72.7
16	100	87.8	100	100	90	80	100	0	80	
17	47.7	7.0	100	100	55	10	100	59.1	100	87.0
18	41.9	0	100	95	45	5	100	9.1	100	39.1
19	100	5.1	100	100	90	40	100	45.5	100	56.5
20	100	100	100	100	15	5	100	8.7	100	72.7
22							90.9		40	
23							100	4.3	27.3	
methomyl	100	100	100	100	100	15				
				Tsumacide Derivatives						
7	100	38.8	50	5			100	52.4	100	100
8	52.2	9.5	20	0			100	19	100	100
9							100	90.5	100	100
10							100	39.1	100	90
33	0	0	60	20			100	59.1	100	100
34	3.1	0	25	10			100	31.8	100	100
35	54.5	0	15	0			100	23.0	100	100
36							45.5		100	19
37	23.4	6	5	15			100	31.8	100	100
38							90		100	40.9
39							90		100	77.3
				Oxamyl Derivatives						
25	100	100	20				72.7		72.7	
26	100	100	5				80		80	
27	100	100	0				100		90	
				Propoxur Derivatives						
40							70		100	70.8
41							36.4		100	100

Toxicological Properties. Data for the toxicity of the various sulfinyloxy derivatives of the methylcarbamate insecticides to the housefly are given in Tables I and II and to other agriculturally important insects in Table III. Where available, analogous data for the parent methylcarbamate are included for comparison.

On a weight basis, the *N*-[(pyridylalkoxy)sulfinyl]-*N*-methylcarbamates (Table I) were generally slightly less toxic to the housefly than the parent methylcarbamates. However, several of the (pyridylalkoxy)sulfinyl derivatives of methomyl were highly toxic to house flies; on a micromole basis, **2** appeared slightly more effective against the housefly than methomyl. As in the case of previous examples of sulfinyl derivatives of toxic methylcarbamate insecticides, the (pyridylalkoxy) sulfinyl derivatives were all substantially less toxic to the white mouse compared to the parent methylcarbamate.

The toxicity of the protected glycerol- and sugar-oxysulfinyl derivatives of methomyl and oxamyl to houseflies was variable. For example, **17**, **20**, **26**, and **28** were highly toxic to houseflies, each revealing activity comparable to or greater than that of the parent methylcarbamate when differences in molecular weights are taken into account. The tris(oxysulfinyl)methylcarbamate derivatives (**21** and **29**) were unexpectedly inactive and the remaining compounds showed poor to moderate toxicity to houseflies. The analogous derivatives of tsumacide (**33–39**) and propoxur (**40–41**) were all nontoxic to houseflies, showing LD_{50} values greater than 500 μg/g. A number of similar derivatives of carbaryl (not listed) were also prepared and evaluated, but none of these compounds showed any toxicity to houseflies at 500 μg/g. The poor housefly toxicity of the tsumacide and carbaryl derivatives was not surprising because of the low intrinsic activity of the parent methylcarbamates.

Screening data for a number of oxysulfinyl methylcarbamates against some agriculturally important insects are presented in Table III. Several of the derivatives showed good insecticidal activity. for example, compound **16**, a protected (glyceryloxy)sulfinyl derivative of methomyl, was almost equal to methomyl in its activity against the green peach aphid (systemic) and tobacco cutworm. Compound **20**, a bis(methomyl) derivative of an allyl ether of glycerol, was equal to methomyl against the green peach aphid as a systemic insecticide. In general, the various oxysulfinyl derivatives of tsumacide were highly effective against the brown plant hopper and were moderately active against the green rice leafhopper even though none of these compounds showed any activity against houseflies.

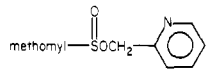
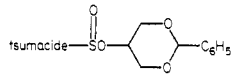
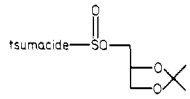
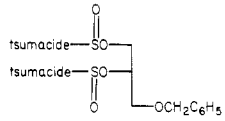
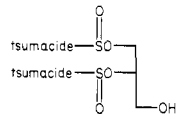
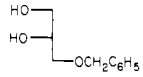
As in the case of the (pyridylalkoxy)sulfinyl derivatives, reduced mouse toxicity was observed in all cases with the glycerol and sugar derivatives and in some cases reduction was substantial. Reduction in mouse toxicity varied from 8- to 100-fold for the methomyl and propoxur derivatives but only 3- to 12-fold for the oxamyl, tsumacide, and MIP derivatives. Of all the different derivatives of the various methylcarbamates, attainment of high mammalian safety was the poorest with the oxamyl derivatives. These results are similar to those observed previously for the *N,N'*-thiodicarbamate derivatives where very little improvement in mouse toxicity was found for the oxamyl derivatives (Fahmy et al., 1978).

Anticholinesterase Activity. Bimolecular rate constants (k_i) for the inhibition of bovine erythrocyte

Table IV. Bimolecular Rate Constants (k_i) for the Inhibition of Bovine Erythrocyte (BAChE) and Housefly-Head Acetylcholinesterase (HFAChE) by Some Oxysulfinyl Methylcarbamates at 30 °C and pH 7.6

compound	$k_i \times 10^{-3}$, M^{-1} min^{-1} BAChE	HFAChE
Methomyl Derivatives		
1	37.1	21.4
2	41.3	50.9
4	29.5	27.1
5	30.8	24.4
17	3.1	7.8
19	1.1	31.5
21	6.1	44.5
22	2.9	5.1
methomyl	78.6	87.2
Tsumacide Derivatives		
34	1.6	
36	0.54	
38	0.49	
tsumacide	2.1	
MIP Derivatives		
12	250	24.7
13	48.8	31.7
MIP	461	87.9

Table V. Nature and Amounts of Degradation Products from Oxysulfinyl Methylcarbamates in Acidic Dioxane-Water at 24 °C

no.	compound	products	%
1		2-pyridylmethanol	90
		methomyl	trace
		1	10
33		benzaldehyde	57
34		tsumacide	100
36		tsumacide	27
			29[a]
			trace

[a] Structure is based on its NMR spectrum.

(BAChE) and housefly-head acetylcholinesterase (HFAChE) by a limited number of oxysulfinyl derivatives are presented in Table IV. In all cases, the oxysulfinyl derivatives were poorer inhibitors of BAChE and HFAChE than the respective parent methylcarbamates although the differences in anti-AChE activities were not as large as expected. Little if any relationship was apparent between anticholinesterase activity and toxicity to mice and houseflies.

Hydrolysis and Methanolysis. During the synthesis of the different (oxysulfinyl)methylcarbamate derivatives it became apparent that these compounds were somewhat labile when contaminated with an acid. Therefore, a limited number of compounds were examined to determine degradation products in an acidic environment. Table V provides information on the nature and amounts of products formed when compounds **1**, **33**, **34**, and **36** were allowed to stand in 1:1 dioxane–water containing 2 drops of 6 M hydrochloric acid for 3 h at room temperature (24 °C). The results supported earlier observations that these derivatives are unstable in an acidic environment. Identification of the methylcarbamate ester and alkanol as products revealed that the major pathway for degradation was by cleavage of one of the bonds attached to the sulfinyl sulfur atom. In the case of compound **1**, only a trace of methomyl was recovered after 3 h. This was attributed to further degradation of the initially formed carbamate. However, it is clear that other bonds were also being broken since benzaldehyde was the major product from compound **33** and the bis(tsumacide) derivative of glycerol was a major product from **36**.

Table VI. Nature and Amounts of Degradation Products from Oxysulfinyl Methylcarbamates in Methanol

no.	condition temp, °C	time, h	products	%
1	reflux	10	2-pyridylmethanol	9
			methomyl	15
			2-pyridylmethyl methyl sulfinate	13
			1	30
1	24	48	no reaction	
34	reflux	3	tsumacide	100
			2,2-dimethyl-1,3-dioxolane-4-methanol	64
36	reflux	7	no reaction	

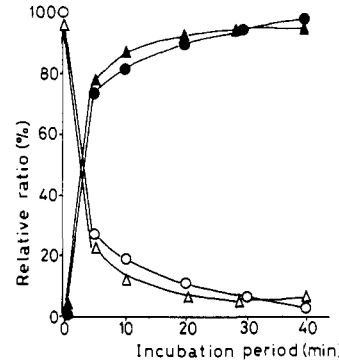


Figure 1. Plots showing the disappearance of the oxysulfinyl methylcarbamates **17** and **34** and formation of the respective parent methylcarbamates in acidic solution: (△) **17**; (○) **34**; (▲) methomyl; (●) tsumacide.

Results for the degradation of **1**, **34**, and **36** in refluxing methanol are presented in Table VI. The identification of methyl 2-pyridylmethyl sulfinate in the reaction of **1** with methanol indicates a nucleophilic attack of methanol on the sulfinyl sulfur atom as one of the possible degradation pathways. Compound **34** was degraded completely to tsumacide after 3 h in refluxing methanol while **36**, a related tsumacide derivative, was unaffected after 7 h in refluxing methanol. These results point out the existence of large differences in susceptibility to solvolysis of derivatives of similar structures.

Plots showing the disappearance of the two derivatized carbamates **17** and **34** and the formation of parent carbamate in acidic solution are presented in Figure 1. The breakdown profiles of both derivatives are nearly the same. Both compounds released about 80% parent carbamate in the first 10 min of incubation period and showed sigmoid relationships.

Plots showing the disappearance of **17** and **34** and the formation of parent carbamate in methanol are presented in Figure 2. In methanol, the breakdown profiles of both derivatives showed linear relationships. The tsumacide

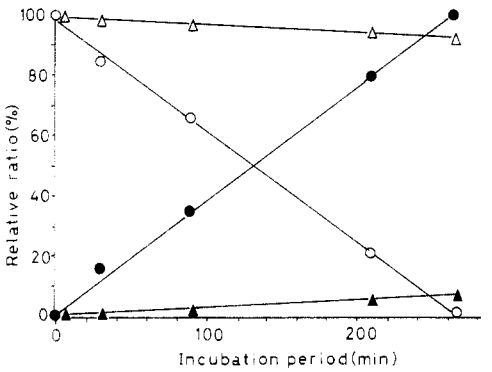


Figure 2. Plots showing the disappearance of the oxysulfinyl methylcarbamates **17** and **34** and formation of the respective parent methylcarbamates in methanol: (△) **17**; (○) **34**; (▲) methomyl; (●) tsumacide.

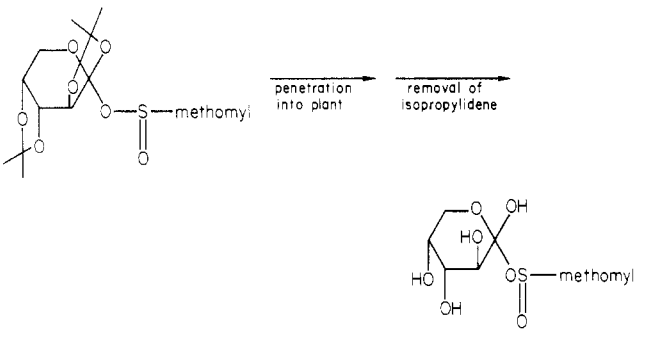
derivative **34** decomposed very rapidly, releasing a quantitative amount of tsumacide after 270 min, while the methomyl derivative **17** was very stable, releasing only 8% of the parent carbamate in the same period of incubation.

DISCUSSION

It is well-known that the physical properties of a compound may strongly influence its biological activity. This is evident in the numerous examples where excellent correlation has been attained between biological activity and a single physical parameter such as the octanol–water partition coefficient of the compound (Hansch, 1969). Therefore, this study was conducted to determine the feasibility of utilizing the (chlorosulfinyl)methylcarbamates as intermediates for the synthesis of methylcarbamate derivatives of widely different physical properties. For example, placement of a pyridine nucleus in the molecule (**1**–**14**) was expected to provide a basic moiety which conceivably could be protonated, thereby changing the physical properties and possible insecticidal activity of the original methylcarbamate. An example of the effect of the introduction of a pyridine moiety is seen in the observed, albeit small, systemic activity of the tsumacide derivatives **7** and **8**. Tsumacide itself is devoid of systemic activity.

Synthesis of the glycerol derivatives showed the feasibility of introducing more than one methylcarbamate ester into a molecule, e.g., compounds **18**–**21**, **27**–**29**, **35**–**37**, and **40**. Since several of these compounds showed good insecticidal activity (e.g., see Table III, compounds **18**, **19**, **20**, **27**), it would be of interest to determine whether the multiple methylcarbamate ester may be introduced in a polyhydroxy low molecular weight polymer. Compounds of this type possible may act as slow insecticide release materials.

Synthesis of the protected glycerol and sugar derivatives resulted in compounds which possibly may have unusual systemic activity. The rational for the synthesis of these derivatives was based on the well-known fact that sugars molecules are phloem mobile and may move downward as well as upward in plants (Meyer and Anderson, 1952). Attachment of a sugar molecule to a methylcarbamate insecticide therefore should enhance downward movement of the compound. Protection of the sugar molecule was necessary for two reasons: (1) protection with the labile isopropylidene moiety allowed the sulfinylation reaction to take place owing to the improved solubility of the protected sugar in organic solvents and (2) protection was considered necessary for the derivatized molecule to penetrate the waxy cuticle of the plant leaf. Therefore, the protected glycerol- or sugar–sulfinylmethylcarbamate derivatives such as compounds **17** and **22** and others would be expected to penetrate into the plant, and once in the plant, removal of the labile protecting group would provide a molecule which may have downward movement. The scheme for the overall process is shown with compound **22** as an example.



(may move downward)

Unfortunately, owing to the absence of an appropriate bioassay we have not been able to test our rationale. However, the approach, at least synthetically, is reasonable. Further work along these lines is proceeding. Needless to say, the design of a downward moving systemic pesticide would have far-reaching consequences.

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Registry No. **1**, 84384-86-1; **2**, 84384-88-3; **3**, 84603-44-1; **4**, 84384-89-4; **5**, 84384-90-7; **6**, 16752-77-5; **7**, 84384-91-8; **8**, 84384-92-9; **9**, 84384-87-2; **10**, 84603-45-2; **11**, 1129-41-5; **12**, 84384-94-1; **13**, 84384-95-2; **14**, 84384-96-3; **15**, 64-00-6; **16**, 84603-46-3; **17**, 81861-91-8; **18**, 81877-64-7; **19**, 81877-65-8; **20**, 81861-96-3; **21**, 81862-05-7; **23**, 81861-99-6; **24**, 84642-17-1; **25**, 84603-47-4; **26**, 81862-01-3; **27**, 81862-02-4; **28**, 81862-15-9; **29**, 84603-48-5; **31**, 81877-63-6; **32**, 23135-22-0; **33**, 84603-49-6; **34**, 81862-08-0; **35**, 81862-07-9; **36**, 81862-10-4; **37**, 81861-92-9; **39**, 81862-13-7; **40**, 81862-23-9; **42**, 114-26-1; AChE, 9000-81-1; methomyl, 16752-77-5; *S*-methyl *N*-(methylcarbamoyl)thioacetimidate, 84623-33-6; *S*-methyl *N*-(chlorosulfinyl)-*N*-[(methylcarbamoyl)oxy]thioacetimidate, 81862-24-0; 1,2,5,6-di-*O*-isopropylidene-α-glucose, 582-52-5; 2-pyridinemethanol, 58-69-8.

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