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N-Sulfinylated Derivatives of Methylcarbamate Esters

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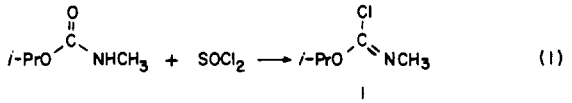
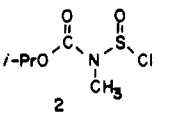
Alkyl, aryl, and oxime carbamates react with thionyl chloride to give the corresponding *N*-chlorosulfinyl derivatives. This new reaction provided a useful intermediate for the synthesis of a large variety of new N-derivatized carbamates. *N*-(Chlorosulfinyl)carbamates reacted with alcohols and phenols to give *N*-[(alkyloxy)- and -(aryloxy)sulfinyl]carbamates, with alkane- and arenethiols to give *N*-[(alkanethio)- and -(arenethio)sulfinyl]carbamates, with carbamates to give either symmetrical or asymmetrical *N*,*N'*-sulfinylbiscarbamates, with monosubstituted alkyl- or arylsulfonamides to give *N*-[[(alkyl- or -(arylsulfonyl)amino]sulfinyl]carbamates, and with trisubstituted sulfondiamides to give *N*-[[(aminosulfonyl)amino]sulfinyl]carbamates. Application of these reactions to insecticidal methylcarbamates resulted in novel derivatives of high insecticidal activity but of a much lower mammalian toxicity as compared to the parent methylcarbamate insecticide.

During the course of a study concerned with the reaction between trimethyl phosphite and isopropyl *N*-(chlorosulfenyl)-*N*-methylcarbamate, it became necessary to prepare a sample of isopropoxy-*N*-methyliminoyl chloride (1). Since *N*-alkylamides are known to react with thionyl chloride to form the corresponding imidoyl chloride (Vaughan and Carlson, 1962), isopropyl methylcarbamate was reacted with thionyl chloride with the expectation that the carbamate would be converted to 1 according to



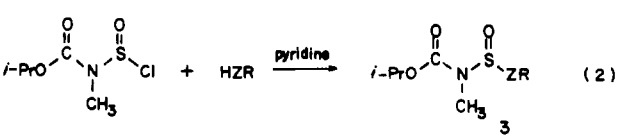
(1)

However, the reaction did not proceed according to the above equation and instead gave isopropyl *N*-(chlorosulfinyl)-*N*-methylcarbamate (2) in excellent yield.



2

In the presence of pyridine, 2 reacted with a variety of nucleophiles, e.g., alcohols, mercaptans, etc., resulting in the displacement of the chloride ion and formation of the corresponding sulfinate derivative (3) according to



(2)

3

where Z = O, S, and N and R is a variety of different substituents. This paper is concerned with the synthesis of chlorosulfinyl intermediates of methylcarbamate esters, including methylcarbamate insecticides, and the reactions between the chlorosulfinyl intermediates and different kinds of nucleophilic agents. Preliminary data on the

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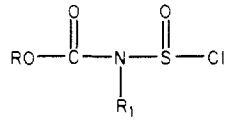
Table I. *N*-Chlorosulfinyl Derivatives of Alkyl and Substituted Alkyl Carbamates



R	R_1	bp, °C/mmHg	n^{25}_D	method of preparation
CH_3	CH_3	66-68/3.0	1.4980	A
C_2H_5	CH_3	58-60/1.2	1.4870	A
C_2H_5	C_3H_7	70/0.8	1.4800	B
C_2H_5	$CH(CH_3)_2$	65/0.45	1.4790	B
C_3H_7	CH_3	85-86/2.8	1.4815	A
C_3H_7	C_2H_5	75-78/1.3	1.4785	A
$CH(CH_3)_2$	CH_3	70/2.8		A
C_7H_{15}	CH_3	98-100/0.05	1.4765	A
$CH_3O(CH_2)_2$	C_2H_5	74-75/0.12	1.4837	B
$HC{\equiv}CCH_2$	C_2H_5	74-75/0.3	1.5054	B
benzyl	C_2H_5	127-128/0.15	1.5437	B
$CH(CH_3)_2$	phenyl	110-112/0.15	1.5430	B

toxicological properties of the final derivatized products are also presented.

MATERIALS AND METHODS

Thionyl chloride was distilled before use. Pyridine and triethylamine were distilled over sodium hydroxide pellets and kept dry by storing over the same reagent. All solvents were dried and distilled before use. Aliphatic carbamates were prepared in the conventional manner by reacting the appropriate alcohol and alkyl- or phenylisocyanates or alkyl chloroformate with alkylamine. Insecticidal methylcarbamates, i.e., carbofuran, propoxur, carbaryl, aldicarb, methomyl, and oxamyl, were obtained from their respective manufacturers as technical materials and were purified by recrystallization from appropriate solvents.

Alkyl (Chlorosulfinyl)alkylcarbamates. All compounds in Table I were identified by their ^1H NMR spectra and/or elemental analysis. ^1H NMR spectra were obtained with a Varian 390 spectrometer. These compounds were prepared by two general procedures.

Method A: Heating Thionyl Chloride with the Carbamate. The synthesis of isopropyl (chlorosulfinyl)methylcarbamate is given as an example of this procedure. A mixture of 40 g of isopropyl methylcarbamate (0.34 mol) and 60 g of thionyl chloride (0.5 mol) was stirred at room temperature for 1 h. The temperature was then raised to 60–75 °C and heating was continued until HCl evolution ceased. Excess thionyl chloride was removed under vacuum and the residue was distilled. The product distilled at 70 °C/2.8 mmHg (Table I). The yield was 57 g (84% yield). Anal. Calcd for $C_5H_{10}NO_3SCl$: C, 30.08; H, 5.01. Found: C, 30.51; H, 5.02.

Method B: Use of Pyridine as a Hydrogen Chloride Acceptor. This procedure is particularly useful when the nitrogen atom of the carbamate moiety is substituted by a bulky group such as isopropyl and/or the carbamate is substituted by substituents that are susceptible to acids, e.g., C≡C or C≡N groups. The synthesis of ethyl (chlorosulfinyl)isopropylcarbamate is given as an example of this procedure. To a mixture of ethyl isopropylcarbamate (6.5 g, 0.05 mol) and 40 mL of dry dichloromethane was added in one portion 8.0 g of thionyl chloride (0.067 mol). The mixture was chilled in an ice–water bath and 6.0 g of pyridine (0.075 mol) was added dropwise with stirring. After the addition of the pyridine, the mixture was stirred at room temperature overnight. Pyridine hydrochloride was removed by filtration and the filtrate was concentrated under vacuum. Hexane (150 mL) was added to the residue and the mixture was filtered again to remove residual pyridine hydrochloride and the hexane was removed under vacuum. The oily residue was distilled to give 8.5 g of product, bp 65 °C/0.45 mmHg (Table I), in 79.7% yield. Anal. Calcd for $C_6H_{12}NO_3SCl$: C, 33.71; H, 5.66. Found: C, 33.94; H, 5.77.

Aryl (Chlorosulfinyl)methylcarbamates. *Method A: Heating with Thionyl Chloride.* The synthesis of 3-isopropylphenyl (chlorosulfinyl)methylcarbamate is given as an example of this procedure. A mixture of 4 g of 3-isopropylphenyl methylcarbamate (0.021 mol) and 12.0 g of thionyl chloride (0.1 mol) was heated under reflux until HCl evolution ceased. The excess thionyl chloride was removed by distillation and the residue was subjected to high vacuum (0.1 mm) for 1 h. ^1H NMR of the residue in chloroform-*d* and Me_4Si gave the following absorptions: δ 7.5–6.9 (m, 4 H, aromatic protons), 3.25 (s, 3 H, NCH_3), 3.2–2.7 (m, 1 H, CH), and 1.3–1.2 [d, 6 H, $C(CH_3)_2$]. The conversion to the *N*-chlorosulfinyl derivative was evident from the singlet and downfield shift of the *N*-methyl protons as compared to the doublet and upfield absorption (δ 2.8) of the *N*-methyl protons of the parent carbamate.

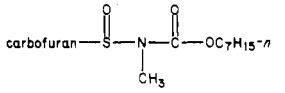
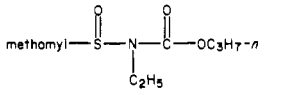
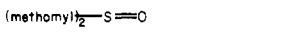
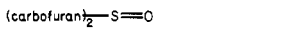
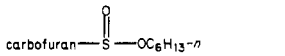
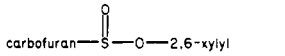
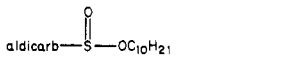
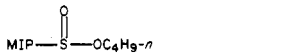
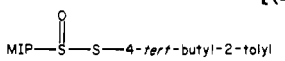
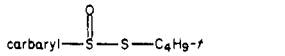
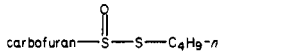
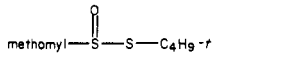
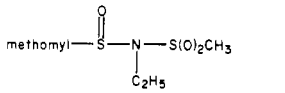
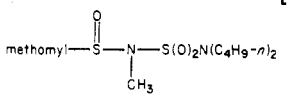
Method B: Use of Pyridine as a Hydrogen Chloride Acceptor. This procedure was more convenient than method A. It reduced the amount of thionyl chloride and the reaction proceeded much faster than by method A. Further, as discussed later, reactions with the *N*-chlorosulfinyl derivative can be carried out without the isolation of this intermediate. Also, method B is particularly useful when the aryl moiety of the carbamate is substituted by acid labile groups such as dialkylamino (as in aminocarb or mexacarbate) or acetal or ketal groups such as in dioxacarb and bendiocarb. Overall, it is the preferred procedure for N-chlorosulfinylation of aryl methylcarbamates. The synthesis of 2,3-dihydro-2,2-dimethyl-7-benzofuranyl (chlorosulfinyl)methylcarbamate is given as a typical example. Carbofuran (2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate, 5.5 g, 0.025 mol) and 2.5 g of pyridine (0.032 mol) were dissolved in 25 mL of dry tetrahydrofuran, followed by the addition of 3.5 g of thionyl chloride (0.03 mol) in one portion. The mixture was stirred at room temperature for 6 h and filtered to remove pyridine hydrochloride. The filtrate was concentrated under vacuum and the residue was subjected to high vacuum (0.05 mm) for 1 h. ^1H NMR spectrum of the oily residue showed the following absorptions: δ 7.3–6.7 (m, 3 H, aromatic protons), 3.3 (s, 3 H, NCH_3), 3.05 (s, 2 H, benzylic CH_2), and 1.45 [s, 6H, *gem*-$(CH_3)_2$].

Reaction of Thionyl Chloride with *O*-Methylcarbamoyl Oximes. N-Chlorosulfinylation of oxime carbamates was carried out by method B because of the sensitivity of oxime carbamates to acids. No attempt was made to isolate the *N*-chlorosulfinyl derivative of these carbamates, and, instead, further reactions with these intermediates were carried out, in situ, as described later.

Reaction of *N*-(Chlorosulfinyl)carbamates with Different Nucleophiles. Table II shows several different products obtained from the reaction of *N*-chlorosulfinyl derivatives of different aromatic and oxime methylcarbamates with alcohols, phenols, thiols, carbamates, sulfonamides, and sulfondiamides. Methods for the synthesis of these derivatives are described in the following six examples.

(1) Reaction of Aliphatic N-(Chlorosulfinyl)carbamates with Aromatic and Oxime Carbamates. The following procedure for the synthesis of 2,3-dihydro-2,2-dimethylbenzo-7-furanyl *N*-[[*N'*-(*n*-heptoxycarbonyl)-*N'*-methyl-

Table II. Physical and Toxicological Properties of N-Sulfinylated Derivatives of Methylcarbamate Insecticides

entry	structure[a]	mp, °C	analysis[a] calcd	analysis[a] found	housefly[b] LD_{50}, μg/g	mouse (oral)[c] LD_{50}, mg/kg
	N,N'-Sulfinylbiscarbamates					
1		oil	C: 57.25 H: 7.32	57.56 7.32	13.5 (6.7)	150 (10)
2		oil	C: 38.92 H: 6.23	38.38 5.78	7.0 (3.7)	115 (10)
3		142–143	C: 32.45 H: 4.90	32.86 5.02	40 (3.7)	210 (10)
4			C: 59.00 H: 5.78	59.60 5.54	20 (6.7)	165 (10)
	[(Alkyloxy)- and [(Aryloxy)sulfinyl]carbamates					
5		oil	C: 58.51 H: 7.37	59.24 8.08	13 (6.7)	280 (10)
6		oil	C: 61.68 H: 5.95	62.02 6.29	13.5 (6.7)	100 (10)
7		oil	C: 51.74 H: 8.69	51.99 8.55	11.5 (5.5)	60 (0.5)
8			C: 57.48 H: 7.40	57.80 7.21	50 (41)	
	[(Alkylthio)- and [(Arylthio)sulfinyl]carbamates					
9		oil	C: 62.97 H: 6.97	63.40 6.89	62.5 (41)	450 (16)
10		57–60	C: 56.95 H: 5.68	57.51 5.82	235 (>900)	>1000[d] (500)
11			C: 53.75 H: 6.48	53.97 6.48	16.5 (6.7)	450 (16)
12		51–53	C: 36.22 H: 6.08	36.80 6.29	5.5 (3.7)	135 (10)
	[[(Alkylsulfonyl)amino]sulfinyl]carbamate					
13		125–127	C: 29.00 H: 5.14	29.67 5.19	20 (3.7)	250 (10)
	[[(Aminosulfonyl)amino]sulfinyl]carbamate					
14		61–63	C: 39.07 H: 6.98	39.16 7.13	9 (3.7)	100 (10)

[a] The sulfinyl sulfur atom is attached to the nitrogen atom of the carbamyl moiety. Carbofuran is 2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate, methomyl is methyl *N*-[[(methylamino)carbonyl]oxy]ethanimidothioate, aldicarb is 2-methyl-2-(methylthio)propanal *O*-[(methylamino)carbonyl]oxime, MIP is 3-isopropylphenyl methylcarbamate, and carbaryl is 1-naphthyl methylcarbamate. [b] Elemental analyses were carried out by C. F. Geiger, Ontario, CA. [c] Parenthetical numbers are the LD_{50} values of the parent methylcarbamate. [d] No mortality at 1000 mg/kg.

amino]sulfinyl]-*N*-methylcarbamate (entry 1 of Table II) is a typical example for this reaction. A mixture of 1.1 g of 2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate (carbofuran, 0.005 mol), 0.5 g of pyridine (0.006 mol), and 1.3 g of *n*-heptyl (chlorosulfinyl)methylcarbamate (0.0054 mol) in 5 mL of dry dichloromethane was allowed to stand at room temperature overnight. Ether (25 mL) was added, and the mixture was washed with water (3 times), dried over anhydrous sodium sulfate, and concentrated. A sample of the oily residue was purified by preparative silica gel thin-layer chromatography using an ether–hexane (3:1) mixture as the developing solvent. Elemental analyses of all compounds are presented in Table II.

(2) *Preparation of N,N'-Sulfinylbiscarbamates.* These compounds can be obtained directly from the reaction of alkyl, aryl, or oxime methylcarbamates with thionyl chloride, using triethylamine as a hydrogen chloride acceptor. A typical example is given for the synthesis of *N,N'*-sulfinylbis[*S*-methyl *N''*-(*N*-methylcarbamoyloxy)-thioacetimidate] (entry 3 of Table II). To a solution of 3.3 g of *S*-methyl *N*-(*N*-methylcarbamoyloxy)thioacet-

imidate (methomyl, 0.02 mol) in 20 mL of dry tetrahydrofuran was added 1.2 g of thionyl chloride (0.01 mol). The mixture was cooled in an ice–water bath and 2.0 g of triethylamine (0.02 mol) was added dropwise with stirring. Stirring was continued at room temperature for 1 h and the reaction mixture was diluted with 100 mL of dichloromethane. After several washings with water, the dichloromethane layer was dried over anhydrous sodium sulfate and concentrated. The solid residue was crystallized from a chloroform–ether mixture to give 2.2 g of product, mp 142–143 °C.

(3) *Reaction of N-(Chlorosulfinyl)carbamates with Alcohols and Phenols.* A typical example for this reaction is given for the synthesis of 2,3-dihydro-2,2-dimethyl-7-benzofuranyl (hexoxysulfinyl)methylcarbamate (entry 5 of Table II). A mixture of 5.5 g of 2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate (0.025 mol), 2.5 g of pyridine (0.032 mol), 3.0 g of thionyl chloride (0.025 mol), and 25 mL of anhydrous tetrahydrofuran was stirred at room temperature for 6 h. To this mixture was added 2 g of pyridine (0.025 mol), followed by 3 g of hexyl alcohol (0.029 mol) added dropwise. After the mixture was stirred for an additional 1 h, 150 mL of ether was added and the reaction mixture was worked up in the same manner as the other products. The oily product (7.4 g virtually free of carbofuran) was purified further by preparative thin-layer chromatography using an ether–hexane (3:1) mixture as the developing solvent.

(4) *Reaction of N-(Chlorosulfinyl)carbamates with Alkane- and Arenethiols.* *N*-(Chlorosulfinyl)carbamates react with alkane- and arenethiols in the same manner as they do with alcohols and phenols, producing *N*-alkane- and *N*-(arenethiosulfinyl)carbamates (entries 9–12 of Table II). The temperature of the reaction mixture should be lowered to 0–5 °C during the thiol addition. In most cases, higher temperatures usually result in lower yield of the thiosulfinyl derivative.

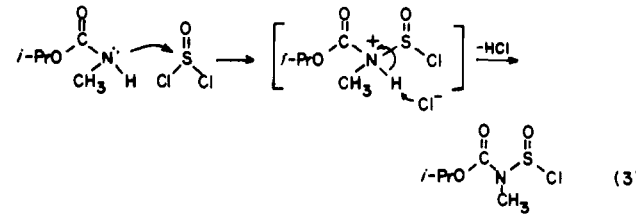
(5) *Reaction of N-(Chlorosulfinyl)carbamates with Sulfonamides and Sulfondiamides.* The *N*-chlorosulfinyl derivative of methomyl was prepared in the usual manner and 1 equiv of the sulfonamide or sulfondiamide was added and the reaction mixture was cooled in an ice–water bath. One equivalent of triethylamine was added dropwise, and the mixture was worked up in the usual manner after standing overnight. Purification of the products (entries 13 and 14 of Table II) was accomplished by recrystallization from dichloromethane–ether or ether–hexane mixtures.

Toxicity to House Flies and Mice. Insecticidal activities were determined against a susceptible (NAIDM) strain of house flies, *Musca domestica*, according to usual procedures (March and Metcalf, 1949). Mammalian toxicity was determined orally with Swiss white mice by using corn oil or propylene glycol as the carrier (Hollingworth et al., 1967).

RESULTS

Reaction between Isopropyl Methylcarbamate and Thionyl Chloride. When a mixture of isopropyl methylcarbamate and excess thionyl chloride was heated at 60–70 °C, a steady evolution of a gas occurred, indicating that a reaction was taking place. Distillation of the product after cessation of the gaseous evolution gave a colorless liquid (bp 70 °C at 2.8 mmHg) which weighed substantially more than the theoretical yield based on the formation of isopropoxy-*N*-methyliminoyl chloride (1). Further heating of the liquid at 120–150 °C had no effect on its composition and the product was returned unchanged. Its infrared spectrum showed a strong carbonyl absorption at 1750 cm^{-1} and a sulfinyl absorption at 1040 cm^{-1}. The ^1H NMR spectrum showed the presence of the isopropoxy and *N*-methyl moieties but did not reveal an NH group. The product decomposed in water, resulting in the return of isopropyl methylcarbamate. The above findings and a carbon and hydrogen analysis which was consistent with the empirical formula $C_5H_{10}ClNO_3S$ indicated the structure of the product to be isopropyl *N*-(chlorosulfinyl)-*N*-methylcarbamate (2). In contrast to amides which react with thionyl chloride to give first the imidoyl chloride and eventually the corresponding nitrile, carbamate esters react to form the *N*-chlorosulfinyl derivative, even upon prolonged heating.

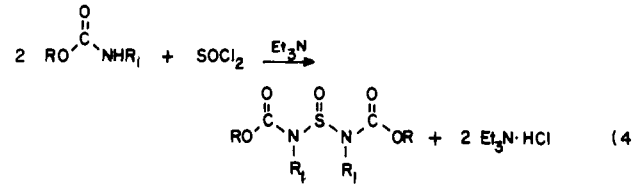
The reaction between the carbamate and thionyl chloride probably takes place by an attack of the carbamate nitrogen on the sulfur, displacing the chloride ion, which in turn abstracts a proton to give the chlorosulfinyl derivative:



(3)

The same product was also obtained when the reaction was carried out in the presence of a proton acceptor such as pyridine and an enert solvent (method B). In this case, the reaction required equimolar amounts of carbamate, thionyl chloride, and pyridine, although in actual practice a slight excess (10%) of pyridine and thionyl chloride was employed. The reaction was carried out in a variety of solvents, ranging from nonpolar hexane and benzene to the more polar dichloromethane and tetrahydrofuran, the velocity of the reaction increasing as the solvent polarity was increased. The reaction proceeded exothermically at room temperature and chilling was required.

When the carbamate was heated with thionyl chloride, the only product isolated was the *N*-(chlorosulfinyl)carbamate. The *N*-(chlorosulfinyl)carbamate also was the major product when equimolar amounts of carbamate, thionyl chloride, and pyridine were used. However, it was possible to displace both chlorine atoms by the carbamate moiety when 2 equiv of the carbamate and organic base was allowed to react with thionyl chloride, resulting in the formation of the *N,N'*-sulfinylbiscarbamate:



(4)

Formation of the sulfinylbiscarbamate occurred much more readily when a stronger base, e.g., triethylamine, was used and a substantially longer reaction time was required with pyridine.

Of the two methods for the preparation of the *N*-(chlorosulfinyl)carbamate derivatives, the second method, i.e., use of pyridine as a proton acceptor, was preferred, owing to its more gentle reaction condition. It was particularly useful in cases where the carbamate ester contained acid-sensitive functional groups.

Reaction of Thionyl Chloride with Insecticidal Methylcarbamate Esters. The above-described reaction was extended to several insecticidal methylcarbamate es-

ters, i.e., carbamate esters which were either aryl or oxime methylcarbamates. *N*-Chlorosulfinyl derivatives of aryl methylcarbamates were readily prepared by reaction with thionyl chloride in the presence or absence of pyridine. For example, esters such as phenyl, 2-isopropoxyphenyl (propoxur), 3-isopropylphenyl, and 2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate (carbofuran) all reacted with thionyl chloride after heating the methylcarbamate with excess thionyl chloride or upon treatment with an equivalent amount of thionyl chloride and pyridine in the cold to give the respective *N*-chlorosulfinyl derivative in high yield. However, the method using pyridine and thionyl chloride was required for the preparation of the *N*-chlorosulfinyl derivatives of oxime methylcarbamates, e.g., oxamyl or methyl 2-(dimethylamino)-*N*-[[(methylamino)carbonyl]oxy]-2-oxoethanimidothioate, owing to the sensitivity of oxime methylcarbamates to the hydrochloric acid which was evolved when thionyl chloride was used alone. The *N*-chlorosulfinyl intermediates prepared by either method were not isolated and used without purification for reaction with different nucleophiles as described under reaction of the *N*-Chlorosulfinyl Intermediate with different nucleophiles.

The conversion of the aryl or oxime methylcarbamate to its *N*-chlorosulfinyl derivative was followed by analysis of the ^{1}H NMR spectrum of the reaction mixture. The change in absorption from a doublet centered at about δ 2.8 for the *N*-methyl protons of the methylcarbamyl moiety to a downfield singlet (about δ 3.3) provided evidence for the replacement of the nitrogen proton by a chlorosulfinyl moiety. Excellent yield of the chlorosulfinyl intermediate generally was obtained by employing slightly more than an equivalent amount of thionyl chloride (5–10% excess) and pyridine (20–25% excess) compared to the amount of the methylcarbamate. The amount of solvent, e.g., benzene, dichloromethane, and tetrahydrofuran, was kept at a minimum (~100 mL/mol of methylcarbamate). After the mixture was initially chilled in ice during the addition of reactants, the reaction mixture was allowed to come to room temperature, and the reaction was usually completed wihin 3–5 h. In a few cases, a longer reaction time was required for complete conversion of the methylcarbamate to the *N*-chlorosulfinyl derivative.

Reaction of the *N*-Chlorosulfinyl Intermediate with Different Nucleophiles. The *N*-chlorosulfinyl derivatives of the methylcarbamate esters readily reacted with a number of different nucleophiles in the presence of pyridine, e.g., alcohols, phenols, alkane- and arenethiols, carbamates, and sulfonamides, to give a wide variety of sulfinyl derivatives of the original methylcarbamate. The different types of reactions and products obtained are indicated in Figure 1. In general, these reactions were carried out in situ following the preparation of the *N*-(chlorosulfinyl)carbamate. A number of specific examples which illustrate the variety of final products that can be prepared are given in Table II. Needless to say, the number of new derivatives which can be synthesized through the *N*-chlorosulfinyl intermediates is enormously large.

Toxicological Properties of the Sulfinyl Derivatives of Methylcarbamate Insecticides. The toxicity to house flies and mice of the different derivatives prepared from the *N*-chlorosulfinyl intermediates of insecticidal methylcarbamates is presented in Table II. Most of the derivatives in the table showed activities against the house fly which were comparable to that of the parent methylcarbamate insecticide, particularly when the molecular weight of the derivative was taken into consideration.

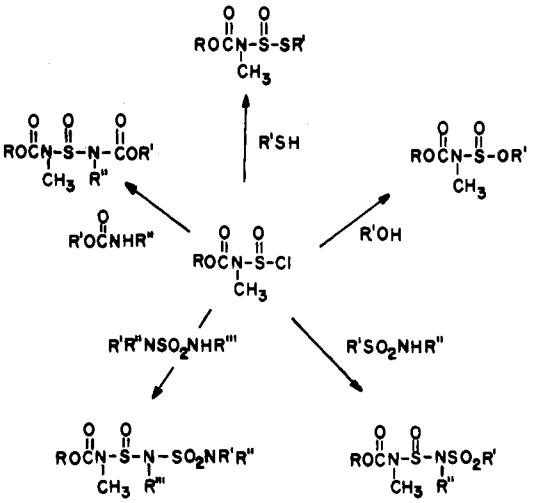
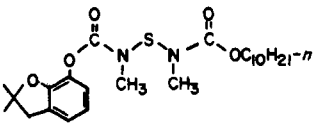


Figure 1. Equations showing the reaction between the *N*-chlorosulfinyl intermediate obtained from methylcarbamate esters and different types of nucleophilic agents.

In general, the various N-sulfinylated derivatives were substantially less toxic to the white mouse compared to the related methylcarbamate insecticide with reduction in mouse toxicity comparable to that found with previously derivatized methylcarbamates (Fahmy et al., 1970; Black et al., 1973; Fukuto et al., 1975; Fahmy et al., 1974, 1978).

Of interest is the low mouse toxicity of the *n*-hexoxysulfinyl derivative (entry 4 of Table II) of carbofuran compared to that of carbofuran, i.e., 280 mg/kg compared to 10 mg/kg, respectively. In a previous paper (Fahmy et al., 1978), a direct relationship was observed between the lipophilicity of *N,N'*-thiobiscarbamates, as estimated by the logarithm of the octanol/water partition coefficients, and mouse toxicity. Of the *N,N'*-thiobiscarbamate derivatives of carbofuran, the derivative containing the C_{10}



alcohol moiety with a mouse LD_{50} of 250 mg/kg was least toxic to the mouse. However, entry 4 of table II contains only a C_6 alcohol chain and is less toxic to the mouse. This comparison points out that while lipophilicity of the derivatized carbamate is an important contributing factor to the mouse toxicity of these compounds, other factors also must be involved. It is possible that the (alkoxysulfinyl)carbamate derivatives are more stable to acid-catalyzed hydrolysis compared to the *N,N'*-thiobiscarbamates. Of special significance is the relatively low mouse toxicity of the *n*-decoxysulfinyl derivative of aldicarb (entry 7 of Table II) compared to aldicarb. This is the first case in which we have achieved notable reduction in mouse toxicity with an aldicarb derivative, while still retaining good insecticidal activity.

DISCUSSION

Previous studies have shown that substitution of the hydrogen atom on the carbamyl nitrogen of insecticidal methylcarbamate esters by different functional groups such as acyl (Fraser et al., 1967), dialkoxyphosphinothioyl (Fahmy et al., 1970), alkyl- and arylsulfenyl (Black et al., 1973), aminosulfenyl (Fukuto et al., 1975), and symmetrical and asymmetrical *N,N'*-thiobiscarbamates (Fahmy et al., 1974, 1978) almost always results in compounds of lower mammalian toxicity compared to the parent methylcarbamate. The derivatized methylcarbamates often

showed good insecticidal activity, in some cases being superior to the parent material against certain insects. Derivatization of insecticidal methylcarbamates generally resulted in compounds of lower anticholinesterase activity and different physical properties. These two factors appear to provide an opportunity for alternate detoxification pathways to take place in mammals in which the derivatized material is degraded to nontoxic products (Fahmy et al., 1970; Krieger et al., 1976). In insects, however, the active methylcarbamate is generated in vivo, resulting in intoxication.

As in the case of the different derivatives mentioned above, the various N-sulfinylated products described in this paper also showed favorable properties of selectivity. The *N*-chlorosulfinyl intermediates which are easily synthesized by reaction of methylcarbamate esters with thionyl chloride may be converted into a wide variety of new derivatives with potential usefulness as insecticides and other pesticides. The reaction between different *N*-(chlorosulfinyl)methylcarbamates and other nucleophilic agents is currently being investigated.

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Synthesis and Insecticidal Activity of Some *gem*-Dicyanopyrethroid Analogues

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The synthesis and insecticidal activity of a series of 2,2-dicyanocyclopropanecarboxylic acid (3-phenoxyphenyl)methyl esters were investigated. The 2,2-dicyanocyclopropanecarboxylic acid esters were also substituted at position 3 of the cyclopropane ring with phenyl or substituted phenyl groups, an alkenyl group, a combination of one of the foregoing groups with a methyl group (3,3′ substitution), or a spiro cycloalkyl group. Synthesis of the compounds was accomplished by reaction of dimethylsulfonium 2-(3-phenoxyphenylmethoxy)-2-oxoethylide with alkylidenepropanedinitrile derivatives. Final products were purified by dry column chromatography employing silica gel. Insecticidal activity was determined at 500-ppm application with permethrin as the standard against houseflies, Mexican bean beetles, and southern army worms. Compared with the activity permethrin, the activity of these compounds was low; the spiro cycloalkyl compounds exhibited the greatest spectrum of insecticidal activity.

Synthetic pyrethroids have attracted considerable attention in recent years as potential replacements for current insecticides (Elliott and Janes, 1978). Several pyrethroids containing cyano groups in the acid moiety have appeared in the literature (Elliott et al., 1976a; Matsui and Yamada, 1964). To our knowledge, no substituted 2,2-dicyanocyclopropanecarboxylic acids esterified with pyrethroid alcohols have appeared in the literature. We decided to prepare a series of analogues of active pyrethroids in which the ring methyl groups have been replaced with cyano groups. Preparation of the compounds was effected in essentially one step by reaction of dimethylsulfonium 2-(3-phenoxyphenylmethoxy)-2-oxoethylide with an alkylidenedicyano compound. The dicyano alkylidene compounds were prepared by Knovenagel condensation of the appropriate ketone or aldehyde with malononitrile.

EXPERIMENTAL SECTION

General. ^{1}H NMR spectra were obtained on a 60-Hz Hitachi Perkin-Elmer R-24B spectrometer in $CDCl_3$ or CCl_4 with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Beckman IR-33 spectrometer. Melting points were taken in a Thomas-Hoover melting point apparatus and are uncorrected. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU 6E spectrometer at 70 eV. Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis, IN. Hardwicke Chemical Co. kindly supplied the (3-phenoxyphenyl)methanol and 3-phenoxybenzaldehyde employed in the synthesis of the final compounds. Preparative dry column chromatography was performed on silica gel that had been heated at 120 °C for 2 days (Loev and Snader, 1965). Elemental analyses were conducted on selected compounds (below and Table I). The analytical data were within ±0.4% of the theoretical values in all cases.

Insecticidal Testing Procedures. Compounds were tested for insecticidal activity as 50:50 mixtures of their cis/trans isomers by an independent laboratory. In the case of 2,2-dicyano-3-(2-methyl-1-propenyl)cyclopropanecarboxylic acid (3-phenoxyphenyl)methyl ester, the compound was tested as its separate cis and trans isomers. All testing was performed at 500 ppm with permethrin as the standard; data are expressed as percent mortality at the end of 24 h. For houseflies (*Musca domestica*), 1 mL of

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