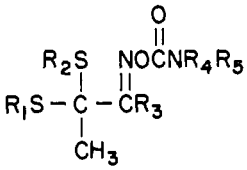
Synthesis and Biological Activity of α-Mercaptol *O*-(Carbamoyl)oximes

Tomas L. Fridinger,* Edward L. Mutsch, Jerold W. Bushong, and John W. Matteson

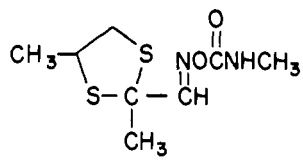
The selective condensation of α-dicarbonyl compounds with one equivalent of a dithiol followed by oxime formation and subsequent carbamoylation has afforded a series of novel α-mercaptol *O*-(carbamoyl)oximes, some of which possess good to excellent insecticidal, acaricidal, and nematicidal activity. The compound 2,4-dimethyl-1,3-dithiolane-2-carboxaldehyde *O*-(methylcarbamoyl)oxime has exhibited especially outstanding greenhouse and field control of nematodes with no phytotoxicity. Structure *vs.* activity relationships appear to be consistent with previously studied cholinesterase-inhibiting carbamates. Toxicological aspects are discussed.

The continuing search for improved carbamate insecticides has led, in the last decade, to a class of potent acetylcholinesterase inhibitors derived from a variety of oxime precursors. For example, significant pesticidal activity has been reported for *O*-(carbamoyl)oximes of cycloaliphatic and bicyclic ketones (Kilsheimer and Manning, 1963; Weiden, 1968), 2-keto-1,3-dithiolanes (Addor, 1965), 5-keto-1,3-dithianes (Addor, 1968), alkoxy and alkylthio esters (Felton, 1968), and trisubstituted acetaldehydes (Payne *et al.*, 1966; Weiden, 1968). Detailed structure *vs.* activity studies of the latter class of compounds, exemplified by 2-methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl)-oxime (aldicarb, Temik, UC 21149), have defined certain important criteria for high or optimum acetylcholinesterase inhibition. These include a conformational similarity to acetylcholine, the presence of an α-alkylthio (or electronegative) substituent, and monomethylation of the carbamate nitrogen. The special role of sulfide sulfur is also apparent in other *O*-(methylcarbamoyl)oximes; for example, *S*-methyl *N*-[(methylcarbamoyl)oxy]thioacetimidate (methomyl, Lannate, DuPont 1179), in substituted thiophenyl carbamates (Mahfouz *et al.*, 1969), and in the case of certain (methylcarbamoyloxy)benzaldehyde mercaptals (Durden and Weiden, 1969; Nikles, 1969).

The present work describes a new series of insecticidal–nematicidal α-mercaptol *O*-(carbamoyl)oximes of general structure I. The compound 2,4-dimethyl-1,3-dithiolane-2-carboxaldehyde *O*-(methylcarbamoyl)oxime (MBR 6168, Tirpate) has demonstrated especially outstanding greenhouse and field nematode control with no phytotoxicity, and is currently under development by 3M Company.



I



TIRPATE

Agrichemical Laboratory, 3M Company, 3M Center, St. Paul, Minn. 55101

CHEMISTRY

Figure 1 presents an overall schematic summary of the various synthetic routes employed in the course of this work.

Starting Materials. Pyruvaldehyde (40% aqueous solution), 2,3-butanedione, 1,2-cyclohexanedione, 1,2-ethanedithiol, 1,2-propanedithiol, 1,2-butanedithiol, 1,3-propanedithiol, and 3,4-dimercaptotoluene are commercially available. The method of converting an epoxide (commercially available) to a trithiocarbonate followed by lithium aluminum hydride reduction to the corresponding 1,2-dithiol (Iqbal and Owen, 1960; Hauptmann and Bobbio, 1960) was employed to obtain 2-phenyl-1,2-ethanedithiol, 2-methyl-1,2-propanedithiol, 3-methoxy-1,2-propanedithiol, 1,2-cyclohexanedithiol, and 3,4-sulfolanedithiol. The conversion of α,γ-dibromoalkanes to the corresponding α,γ-dithiols by way of diisothiuronium salts (Overberger *et al.*, 1961) was used to prepare 1,3-butanedithiol and 2,4-pentanedithiol.

α-Mercaptol Aldehydes and Ketones. The acid-catalyzed condensation of a 1,2- or 1,3-dithiol with one equivalent of pyruvaldehyde or an α-diketone afforded the desired carbonyl-substituted 1,3-dithiolane or 1,3-dithiane, respectively. The general novelty of the reaction plus the surprising specificity of dithiols toward pyruvaldehyde to afford exclusively the mercaptol aldehydes rather than the anticipated mercaptal ketones will be the subjects of a forthcoming publication (Fridinger and Henery-Logan, 1971). The open-chain compound 2,2-bis(methylthio)propionaldehyde was prepared by the acid-catalyzed condensation of acetaldehyde with methanethiol to afford acetaldehyde dimethyl mercaptal (Gibson, 1931), which was converted to its anion with butyllithium and then formylated with dimethylformamide (Corey and Seebach, 1965). In general, the intermediate α-mercaptol aldehydes and ketones were found to possess satisfactory infrared and/or nmr spectra, and then without further purification or analysis they were directly converted into their oxime derivatives. In several cases, for example 2,4-dimethyl-1,3-dithiolane-2-carboxaldehyde and 2,4,5-trimethyl-1,3-dithiolane-2-carboxaldehyde, attempts are in progress to separate or prepare separately the possible geometric isomers.

α-Mercaptol Oximes. The oxime intermediates (Table I) were readily prepared by heating an ethanol or ethanol–water solution of carbonyl compound, hydroxylamine hydrochloride, and potassium acetate at reflux for several hours. The products generally separated as solids from the cooled

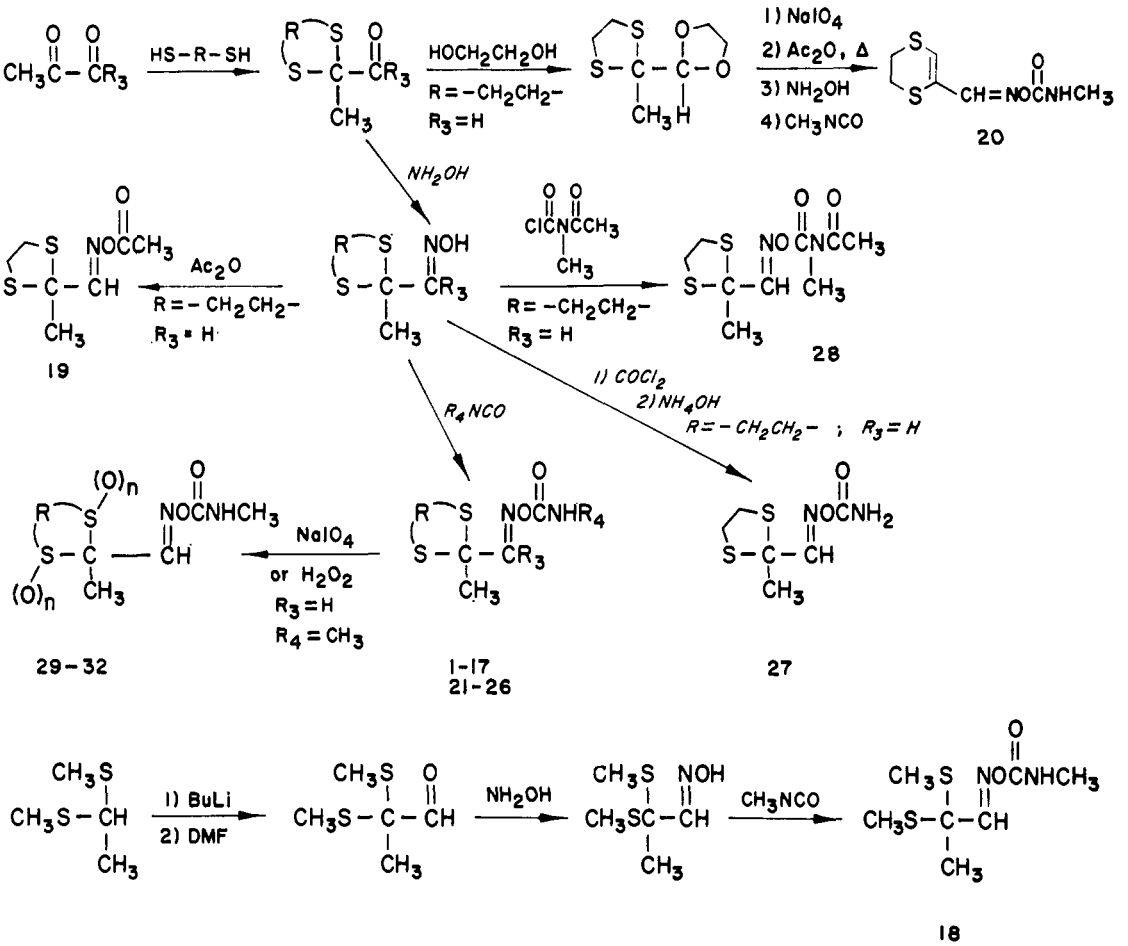
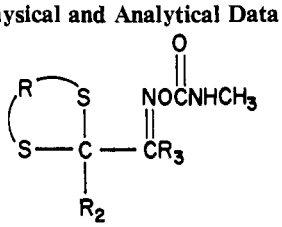
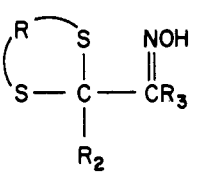


Figure 1. Synthetic pathways toward α-mercaptol *O*-(carbamoyl)oximes and related compounds

Table I. Physical and Analytical Data of *O*-(Methylcarbamoyl)oximes and Oximes

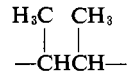
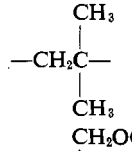
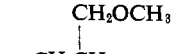
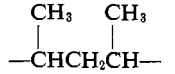
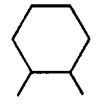
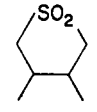
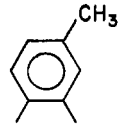
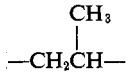




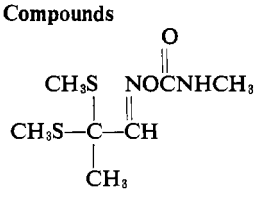
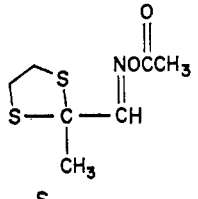
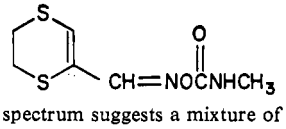
					Analysis			Analysis	
No.	R	R_2	R_3	mp, °C	Calcd, %	Found, %	mp, °C	Calcd, %	Found, %
1	$-CH_2CH_2-$	CH_3	H	121–2	C, 38.2 H, 5.5 N, 12.7 O, 14.5	C, 37.8 H, 5.4 N, 12.5 O, 14.6	106–7	C, 36.8 H, 5.6 N, 8.6	C, 37.0 H, 5.5 N, 8.3
2[a]	$-CH_2CH(CH_3)-$	CH_3	H	80–2	C, 41.0 H, 6.0 N, 12.0	C, 40.9 H, 5.9 N, 12.0	63–5	C, 40.7 H, 6.3 N, 7.9	C, 40.5 H, 6.3 N, 7.9
3	$-CH_2CH(CH_2CH_3)-$	CH_3	H	oil	C, 43.5 H, 6.5 N, 11.3	C, 44.2 H, 6.7 N, 10.9	*b*		
4	$-CH_2CH((CH_2)_3CH_3)-$	CH_3	H	94–6	C, 47.8 N, 10.1	C, 48.1 N, 10.2	63–7	C, 49.3 H, 7.8 N, 6.4	C, 49.4 H, 7.9 N, 6.3
5	$-CH_2CH(C_6H_5)-$	CH_3	H	129–32 (dec)	C, 52.7 H, 5.4 N, 9.4	C, 52.6 H, 5.4 N, 9.3	99–101	C, 55.2 H, 5.5 N, 5.8	C, 55.6 H, 5.5 N, 5.7

(*Continued on next page*)

Table I. (Continued)

No.	R	R_2	R_3	mp, °C	Analysis Calcd, %	Analysis Found, %	mp, °C	Analysis Calcd, %	Analysis Found, %
6[a]		CH_3	H	78–91	C, 43.5 H, 6.5 N, 11.3	C, 43.6 H, 6.5 N, 11.4	73–109	C, 44.0 H, 6.9 N, 7.3	C, 44.3 H, 6.9 N, 7.3
7		CH_3	H	70–3	C, 43.5 H, 6.5 N, 11.3	C, 43.6 H, 6.7 N, 11.6	113–5	C, 44.0 H, 6.9	C, 43.7 H, 6.7
8		CH_3	H	74–8	C, 40.9 H, 6.1 N, 10.6	C, 41.0 H, 6.3 N, 10.8	113–8 (bp °C) (0.05 mm)	C, 40.6 H, 6.3 N, 6.8	C, 41.0 H, 6.3 N, 6.7
9	$-CH_2CH_2CH_2-$	CH_3	H	96–7	C, 41.0 H, 6.0 N, 12.0	C, 41.0 H, 6.2 N, 12.4	145–7	C, 40.7 H, 6.3 N, 7.9	C, 40.6 H, 6.2 N, 7.9
10		CH_3	H	106–7	C, 43.5 H, 6.5 N, 11.3	C, 43.8 H, 6.6 N, 11.5	*b*		
11		CH_3	H	45–50	C, 45.8 H, 6.9 N, 10.7	C, 45.8 H, 7.0 N, 10.8	74–9	C, 46.8 H, 7.4 N, 6.8	C, 46.8 H, 7.5 N, 6.8
12		CH_3	H	132–4	C, 48.2 H, 6.6	C, 47.9 H, 6.3	126–8	C, 49.8 H, 7.0	C, 49.9 H, 6.8
13		CH_3	H	155–7 (dec)	C, 34.8 H, 4.5 N, 9.0	C, 35.5 H, 4.9 N, 9.5	*b*		
14		CH_3	H	125–7 (dec)	C, 51.1 H, 5.0 N, 9.9	C, 50.6 H, 5.1 N, 9.8	101–3	C, 53.3 H, 4.9 N, 6.2	C, 54.2 H, 5.1 N, 6.3
15	$-CH_2CH_2-$	CH_3	CH_3	108–9	C, 41.0 H, 6.0 N, 12.0	C, 40.9 H, 5.9 N, 11.9	94–6	C, 40.7 H, 6.3 N, 7.9	C, 40.7 H, 6.0 N, 8.0
16		CH_3	CH_3	89–92	C, 43.5 H, 6.5 N, 11.3	C, 43.6 H, 6.6 N, 11.4	71–3	C, 44.0 H, 6.8 N, 7.3	C, 44.1 H, 6.9 N, 7.3
17	$-CH_2CH_2-$	$-CH_2CH_2CH_2CH_2-$		106–110	C, 46.1 H, 6.2 N, 10.8	C, 46.2 H, 6.2 N, 10.8	98–118[b]		

Related Compounds

No.		mp, °C	Analysis Calcd, %	Analysis Found, %	mp, °C	Analysis Calcd, %	Analysis Found, %
18		62–5	C, 37.8 H, 6.3 N, 12.6	C, 38.1 H, 6.1 N, 12.4	*b*		
19		35–7	C, 41.0 H, 5.4 N, 6.8	C, 40.9 H, 5.5 N, 6.8	see opposite No. 1		
20		139–42 (dec)	C, 38.5 H, 4.6 N, 12.8	C, 38.6 H, 4.7 N, 12.8	*b*		

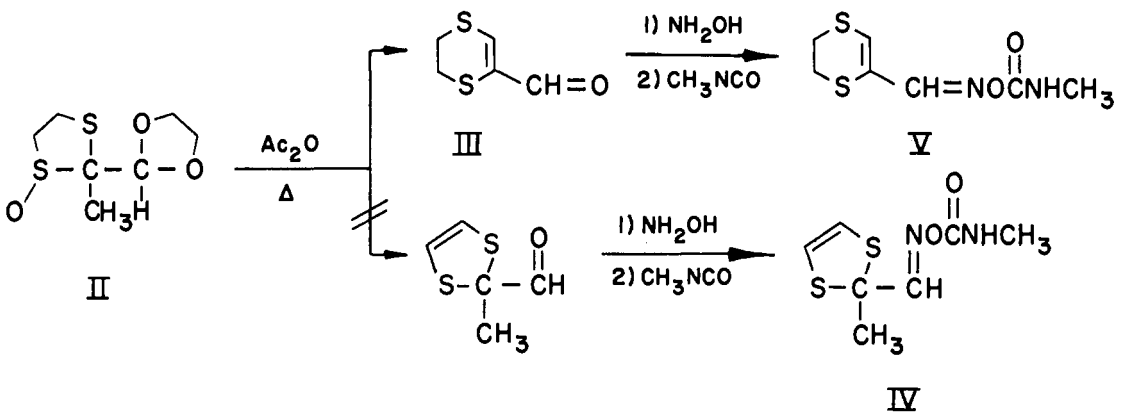
[a] Nmr spectrum suggests a mixture of ring isomers. [b] Crude oxime not analyzed.

solution and could be used directly for the carbamoylation step. In most cases a portion of the crude material was recrystallized to give an analytical sample. The nmr spectra of the aldoximes scanned suggest the presence of a single (syn or anti) isomer, which is assumed to be syn (aldehyde hydrogen to oximino oxygen) on the basis of steric considerations and analogy with related trisubstituted acetaldehyde oxime derivatives (Payne, 1966).

α-Mercaptol *O*-(Carbamoyl)oximes. Treatment of the α-mercaptol oximes with methyl isocyanate in the presence of a catalytic amount of triethylamine afforded the *O*-(methylcarbamoyl)oximes listed in Table I. Similarly, 2-methyl-1,3-dithiolane-2-carboxaldehyde oxime gave a variety of alkyl- and arylcarbamates (Table II) when combined with the appropriate isocyanate. Table II also includes the unsubstituted carbamate derivative **27** obtained from the above oxime and phosgene, followed by ammonium hydroxide addition, and the *N*-acetyl analog **28** from treatment of the oxime sodium salt with *N*-acetyl-*N*-methylcarbamoyl chloride (Robertson *et al.*, 1962). Efforts to acetylate directly the *O*-(methylcarbamoyl)oxime **1** were not successful.

Oxidations. The *O*-(methylcarbamoyl)oxime of 2-methyl-1,3-dithiolane-2-carboxaldehyde was converted to its monosulfoxide and disulfoxide (Table III) with one or two equivalents of sodium metaperiodate, as described by the general procedure of Leonard and Johnson (1962). The two products were not stable under ordinary laboratory storage conditions, with the monosulfoxide being the more labile. The stereochemistry of the sulfoxides, which may exist in several isomeric forms (Durden and Weiden, 1969), has not as yet been resolved. The disulfones (Table III) were prepared by heating the substituted 1,3-dithiolane *O*-(methylcarbamoyl)-oximes with excess 30% hydrogen peroxide in acetic acid at reflux for approximately 5 min.

Miscellaneous Reactions. An attempt was made to prepare 2-methyl-1,3-dithiole-2-carboxaldehyde *O*-(methylcarbamoyl)-oxime (IV) by subjecting the sulfoxide intermediate II to the conditions of the Pummerer reaction (Parham and Bhavsar, 1963). However, heating II at reflux in acetic anhydride followed by oxime formation and subsequent carbamoylation afforded not the expected dithiole derivative, but rather the isomeric dithiin V (Compound **20,** Table I), presumably through ring expansion to the noncharacterized intermediate aldehyde III.



The *O*-(acetyl)oxime **19** (Table I) was prepared by treating 2-methyl-1,3-dithiolane-2-carboxaldehyde oxime with acetic anhydride in aqueous sodium hydroxide.

BIOLOGICAL ASPECTS

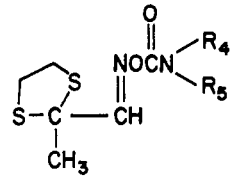
Pesticidal Activity. The results of greenhouse evaluations of the new *O*-(carbamoyl)oximes on eight insects, one mite species, and one nematode species are recorded in Table IV.

Structure *vs.* intrinsic activity correlations is most meaningfully made with an acetylcholinesterase inhibition assay and/or synergized insect toxicity measurements. However, in absence of these data several trends are noted which are based solely on the tabulated pesticidal efficacy. Thus, highest pest control was usually observed with *O*-(methylcarbamoyl)-oximes of 2-methyl-1,3-dithiolane-2-carboxaldehyde and the analogous 1,3-dithiane which possess no substitution or only simple alkyl substitution on the heterocyclic ring. The tendency toward lower activity for compounds with bulky substituents on the ring, for example compounds **4, 5, 12,** and **14,** is consistent with the suggestion that cholinesterase inhibition increases with increasing conformational similarity to acetylcholine in the so-called anionic site of the molecule (Metcalf and Fukuto, 1965; Payne *et al.*, 1966). It is interesting to note that monomethylation of the dithiolane ring (compare compounds **1** and **2**) nearly eliminates all systemic insecticidal activity while significantly improving mite (foliar) and nematode control. The open-chain mercaptol **18** possesses considerably poorer mite, aphid, and nematode activity than its cyclic congener **1.** The *O*-(methylcarbamoyl)-oximes of α-mercaptol ketones (compounds **15, 16,** and **17**) showed limited pest activity as did the sulfoxide **29,** disulfoxide **30,** and disulfone derivatives **31** and **32.** As frequently observed in a carbamate series of pesticides, departure from monomethylation of the carbamate nitrogen led generally to compounds (**21** through **28**) of decreased activity. The miscellaneous dithiin *O*-(methylcarbamoyl)oxime **20** and the *O*-acetyl derivative **19** were not significantly active.

Further Evaluations. Additional laboratory and field trials of 2-methyl-1,3-dithiolane-2-carboxaldehyde *O*-(methylcarbamoyl)oxime (compound **1**) and Tirpate (compound **2**) have repeatedly demonstrated outstanding control of plant parasitic nematodes with no phytotoxicity and moderate broad-spectrum miticidal and insecticidal activity. Of the two compounds, Tirpate has proven to be the superior nematicide and in field evaluations has given excellent control of many nematode genera. Following treatment, significant growth responses and/or yield increases have been observed in a wide variety of crops.

Toxicology and Cholinesterase Inhibition. Preliminary mammalian toxicity data for several of the pesticidally most active α-mercaptol *O*-(methylcarbamoyl)oximes are presented in Table V. The high acute oral toxicity is in marked contrast with results obtained from dermal administration. This suggests that the compounds do not readily penetrate intact skin. The molar I_{50} for rat red blood cell cholinesterase at pH 7.0 and 37° C with 10^{-2} *M* acetylcholine as substrate was determined for Tirpate to be approximately 1×10^{-7}. A 20-min room temperature preincubation with inhibitor was used.

Table II. N-Substituted Carbamates of 2-Methyl-1,3-dithiolane-2-carboxaldehyde Oxime



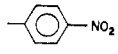
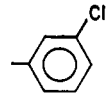
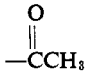
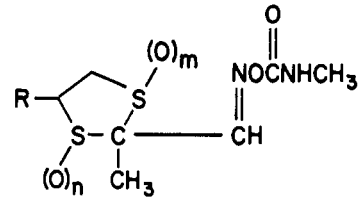
No.	R_4	R_5	mp, °C	Analysis	
				Calcd, %	Found, %
21	H	CH_2CH_3	122–5	C, 41.0 H, 6.0 N, 12.0	C, 41.0 H, 6.4 N, 11.8
22	H	$(CH_2)_3CH_3$	67–70	C, 45.8 H, 6.9 N, 10.7	C, 45.4 H, 6.7 N, 10.6
23	H	$C(CH_3)_3$	84–6	C, 45.8 H, 6.9 N, 10.7	C, 46.1 H, 7.1 N, 10.6
24	H	$CH_2CH{=}CH_2$	53–4	C, 43.9 H, 5.7 N, 11.4	C, 43.6 H, 5.7 N, 11.3
25	H		136–8	C, 44.1 H, 4.0 N, 12.8	C, 44.6 H, 4.1 N, 13.7
26	H		109–12	C, 45.5 H, 4.1 N, 8.8	C, 45.1 H, 4.1 N, 8.6
27	H	H	99–100	C, 35.0 H, 4.9 N, 13.6	C, 35.0 H, 4.9 N, 13.6
28	CH_3		117–9 (dec)	C, 41.2 H, 5.4 N, 10.7	C, 41.2 H, 5.6 N, 10.6

Table III. *O*-(Methylcarbamoyl)oxime Sulfoxides and Sulfones



No.	R	n	m	mp, °C	Analysis	
					Calcd, %	Found, %
29	H	0	1	96–7 (dec)	C, 35.6 H, 5.1 N, 11.9	C, 35.9 H, 5.3 N, 11.8
30	H	1	1	126 (dec)	C, 33.3 H, 4.8 N, 11.1	C, 33.0 H, 4.8 N, 11.0
31	H	2	2	151[a] (dec)	C, 29.6 H, 4.3 N, 9.9	C, 29.8 H, 4.2 N, 9.8
32	CH_3	2	2	136 (dec)	C, 32.2 H, 4.7 N, 9.4	C, 32.3 H, 4.9 N, 9.2

[a] Analytical sample obtained from column chromatography purification (silica gel; 1:1 benzene-ethyl acetate).

EXPERIMENTAL

Chemical Synthesis. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The infrared absorption spectra of the compounds were recorded on a Perkin-Elmer Model 137 spectrophotometer. Nmr spectra were obtained on a Varian A-60 instrument. Chemical shifts were measured with tetramethylsilane as internal reference.

The following examples illustrate the synthetic procedures used in this work. Other derivatives may be prepared in an analogous manner.

2,4,4-Trimethyl-1,3-dithiolane-2-carboxaldehyde. A stirred mixture of 18.0 g (0.1 mole) of 40% aqueous pyruvaldehyde, 12.2 g (0.1 mole) of 2-methyl-1,2-propanedithiol, 0.1 g of *p*-toluenesulfonic acid hydrate, and 200 ml benzene was heated at reflux for 1.5 hr, during which time 8.9 ml of water was separated with a Dean-Stark apparatus. The cooled reaction mixture was washed successively with 5% sodium bicarbonate solution and water, and then dried over magnesium sulfate. Filtration, evaporation of solvent under reduced pressure, and distillation at approximately 20 mm afforded a clear yellow liquid (11.4 g, bp 120–132° C) whose infrared and nmr spectra were in agreement with the desired product. Ir (neat) 5.8 μ (C=O); nmr ($CDCl_3$) τ 8.27, 8.30, 8.40 (three 3H singlets, three CH_3), 6.82 (2H quartet, CCH_2S), and 0.80 (1H singlet, CH=O).

2,2,4-Trimethyl-1,3-dithiolane-2-carboxaldehyde Oxime. A stirred mixture of 7.5 g (0.043 mole) of 2,4,4-trimethyl-1,3-dithiolane-2-carboxaldehyde, 4.9 g (0.050 mole) of potassium acetate, 3.5 g (0.050 mole) of hydroxylamine hydrochloride, 35 ml of 95% ethanol, and 50 ml of water was heated at reflux 10 hr. The hot solution was filtered, cooled, and the precipitated solid collected, washed with water, and dried briefly in air. The solid product was then dissolved in 100 ml of methylene chloride and the solution dried over magnesium sulfate. Filtration and removal of solvent under reduced pressure afforded the analytically pure oxime (7.2 g, mp 113–5° C).

2,4,4-Trimethyl-1,3-dithiolane-2-carboxaldehyde *O*-(Methylcarbamoyl)oxime (7). A stirred solution of 4.2 g (0.022 mole) of 2,4,4-trimethyl-1,3-dithiolane-2-carboxaldehyde oxime, 5.0 g (0.088 mole) of methyl isocyanate, 50 ml of acetone, and three drops of triethylamine was heated at reflux 1.5 hr. Evaporation of solvent from the cooled solution gave an oil which slowly crystallized on standing. Recrystallization from chloroform-hexane afforded 4.2 g of **7** as light yellow crystals. The compound gave satisfactory infrared and nmr spectra. Ir (Nujol) 2.85, 2.90 (split NH), 5.73, 5.79 μ (split C=O); nmr ($CDCl_3$) τ 8.05, 8.35, 8.40 (three 3H singlets, three CH_3), 7.11 (3H doublet, NCH_3), 6.80 (2H quartet, CCH_2S), 3.85 (1H quartet, NH), and 2.16 (1H singlet, CH=N).

2,2-Bis(methylthio)propionaldehyde *O*-(Methylcarbamoyl)oxime (18). To a stirred cold (−20° C) solution of 71.5 ml (0.1 mole) of 1.4 *N n*-butyllithium in hexane was added 11.6 g (0.1 mole) of *N,N,N′,N′*-tetramethylethylenediamine followed by the dropwise addition of 12.2 g (0.1 mole) of acetaldehyde dimethyl mercaptal. After 2 hr 8.05 g (0.11 mole) of dimethylformamide was added dropwise, the mixture allowed to warm to room temperature, and stirred overnight. The mixture was poured into 200 ml of water, acidified, extracted with hexane, and the combined extracts washed successively with 2% potassium hydroxide solution and water and dried over magnesium sulfate. Filtration and evaporation of solvent under reduced pressure afforded 9.95 g of a liquid residue whose infrared spectrum was consistent for 2,2-bis(methylthio)propionaldehyde. Ir (neat) 5.86 μ (C=O).

A stirred mixture of 9.95 g (0.066 mole) of 2,2-bis(methylthio)propionaldehyde, 6.47 g (0.066 mole) of potassium acetate, 4.58 g (0.066 mole) of hydroxylamine hydrochloride, and 80 ml of ethanol was heated at reflux 3 hr. The mixture was cooled, potassium chloride removed by filtration, and the filtrate evaporated under reduced pressure to near dryness. The addition of ice precipitated a cream-colored solid (3.8 g) whose infrared spectrum was consistent with 2,2-bis(methylthio)propionaldehyde oxime.

To a stirred solution of 3.8 g (0.023 mole) of 2,2-bis(methylthio)propionaldehyde oxime, 30 ml of chloroform, and four drops of triethylamine was added dropwise 5.24 g (0.092 mole) of methyl isocyanate. The solution was heated at reflux for 2 hr, cooled, and the solvent evaporated under reduced pressure to give an oil. Trituration with hexane-benzene afforded an off-white solid which was recrystallized from benzene-hexane to give pure 18 (3.0 g). The infrared and nmr spectra of **18** were consistent for the proposed structure. Ir (Nujol) 2.97 (NH), 5.75 μ (C=O); nmr ($CDCl_3$) τ 8.26 (3H singlet, CH_3C), 7.91 (6H singlet, two SCH_3), 7.08 (3H doublet, NCH_3), 3.86 (1H broad singlet, NH), and 2.38 (1H singlet, CH=N).

2-Methyl-1,3-dithiolane-2-carboxaldehyde *O*-Acetyloxime (19). To a stirred turbid solution of 8.2 g (0.05 mole) of 2-methyl-1,3-dithiolane-2-carboxaldehyde oxime, 3.0 g (0.075 mole) of sodium hydroxide and 50 ml of water was added 100 g of crushed ice followed by 6.6 g (0.065 mole) of acetic anhydride. An oil separated which slowly solidified on standing. Collection of the solid by filtration and crystallization from ethanol–water afforded 8.5 g of pure **19**.

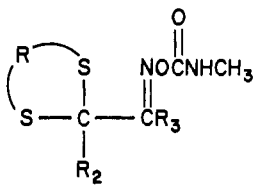
5,6-Dihydro-1,4-dithiin-2-carboxaldehyde *O*-(Methylcarbamoyl)oxime (20). A stirred mixture of 14.8 g (0.1 mole) of 2-methyl-1,3-dithiolane-2-carboxaldehyde, 6.2 g (0.1 mole) of ethylene glycol, 0.1 g of *p*-toluenesulfonic acid hydrate, and 200 ml of benzene was heated at reflux for 5 hr, during which time the water formed was separated in a Dean-Stark trap. The cooled reaction mixture was washed successively with 5% sodium bicarbonate and water, and dried over magnesium sulfate. Filtration, evaporation of solvent under reduced pressure, and distillation at 0.08 mm afforded a colorless liquid (14.2 g, bp 94–101° C), whose infrared spectrum was consistent with 2-methyl-1,3-dithiolane-2-carboxaldehyde ethylene acetal. A sample (bp 100–101° C) was analyzed. Calculated for $C_7H_{12}O_2S_2$: C, 43.8; H, 6.3. Found: C, 43.7; H, 6.2.

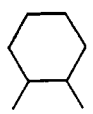
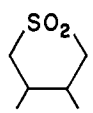
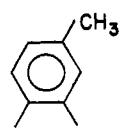
To a stirred cold (ice bath) solution of 11.4 g (0.052 mole) of 2-methyl-1,3-dithiolane-2-carboxaldehyde ethylene acetal and 300 ml of methanol was added dropwise 11.4 g (0.053 mole) of sodium metaperiodate in 100 ml of water. The mixture was stirred 1 hr cold, the precipitated sodium iodate removed by filtration, and the filtrate allowed to stand overnight. The filtrate was evaporated under reduced pressure to near dryness, chloroform was added, a small aqueous layer separated and the organic layer dried over magnesium sulfate. Filtration and evaporation of solvent under reduced pressure gave a yellow liquid (15 g) whose infrared spectrum was consistent with the presence of a sulfoxide. Ir (neat) 9.65 μ (S=O), no carbonyl absorption.

To the above crude sulfoxide was added 30 ml of acetic anhydride and the solution heated at reflux 4.5 hr. The darkened solution was cooled, stirred overnight at room temperature, and distilled at 20 mm to afford a yellow-orange distillate (approximately 7 g, bp 78–165° C), whose in-

Table IV. Biological Activity[a]

O-(Methylcarbamoyl)oximes

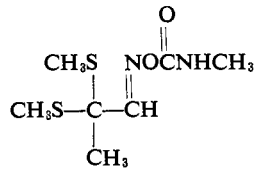
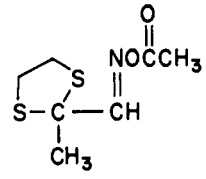
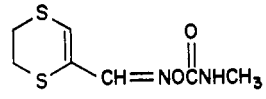


No.	R	R_2	R_3	MOS (1.0)[b]	HF (500)[b]	BWE (500)[b]	(BWE) (100)[b]	MITE (500)[b]	(MITE) (100)[b]	(CLA) (100)[b]	CR (500)[b]	NEM (3.0)[b]
1	$-CH_2CH_2-$	CH_3	H	+++	+++	++	+	+	+++	+++	++	++
2 Tirpate	$-CH_2CH(CH_3)-$	CH_3	H	+++	+++	+	+	+++	0	0	++	+++
3	$-CH_2CH(CH_2CH_3)-$	CH_3	H	+	++	++	0	0	0	0	+	++
4	$-CH_2CH((CH_2)_3CH_3)-$	CH_3	H	0	0	+++	0	0	0	0	0	0
5		CH_3	H	+	0	++	0	+++	0	0	0	0
6	$-CH(CH_3)CH(CH_3)-$	CH_3	H	+++	++	0	0	0	0	0	++	++
7	$-CH_2C(CH_3)_2-$	CH_3	H	0	+++	0	0	0	0	0	0	0
8	$-CH_2CH(CH_2OCH_3)-$	CH_3	H	0	+++	0	0	++	0	0	0	+
9	$-CH_2CH_2CH_2-$	CH_3	H	+	++	+	P	+	+++	0	0	++
10	$-CH_2CH_2CH(CH_3)-$	CH_3	H	0	+++	+	0	0	0	0	0	+++
11	$-CH(CH_3)CH_2CH(CH_3)-$	CH_3	H	+	+++	+	0	0	0	+++	+	0
12		CH_3	H	0	++	0	0	0	+	0	0	+
13		CH_3	H	0	0	0	0	0	0	0	0	0
14		CH_3	H	++	0	0	0	0	0	0	0	0
15	$-CH_2CH_2-$	CH_3	CH_3	0	+	0	0	0	+++	0	0	+
16	$-CH_2CH(CH_3)-$	CH_3	CH_3	0	0	+	0	0	0	0	0	0
17	$-CH_2CH_2-$	$-CH_2CH_2CH_2CH_2-$		0	0	+	0	0	0	0	0	0

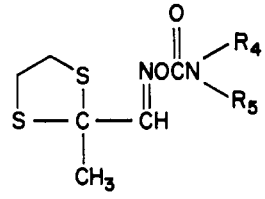
(*Continued on next page*)

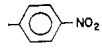
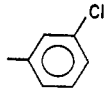
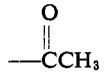
Table I. (Continued)

O-(Methylcarbamoyl)oximes

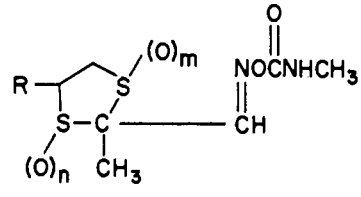
No.	R	R_2	R_3	MOS (1.0)[b]	HF (500)[b]	BWE (500)[b]	(BWE) (100)[b]	MITE (500)[b]	(MITE) (100)[b]	(CLA) (100)[b]	CR (500)[b]	NEM (3.0)[b]
18				+++	+++	0	0	0	0	0	...	0
19				0	0	++	0	0	0	0	0	+
20				0	0	+	0	0	0	0	0	0

N-Substituted Carbamates of 2-Methyl-1,3-dithiolane-2-carboxaldehyde Oxime



No.	R_4	R_5	MOS (1.0)[b]	HF (500)[b]	BWE (500)[b]	(BWE) (100)[b]	MITE (500)[b]	(MITE) (100)[b]	(CLA) (100)[b]	CR (500)[b]	NEM (3.0)[b]
21	H	CH_2CH_3	0	++	+	0	0	0	0	0	0
22	H	$(CH_2)_3CH_3$	0	+	0	0	0	0	0	0	0
23	H	$C(CH_3)_3$	0	0	0	0	0	0	0	0	0
24	H	$CH_2CH{=}CH_2$	+++	+++	0	0	0	+	0	0	0
25	H		0	0	0	++	0	0	0	0	0
26	H		0	0	0	0	0	0	0	0	0
27	H	H	0	0	0	0	0	0	0	0	0
28	CH_3		0	+	0	0	0	0	0	0	0

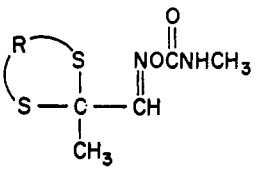
O-(Methylcarbamoyl)oxime Sulfoxides and Sulfones



No.	R	n	m	MOS (1.0)[b]	HF (500)[b]	BWE (500)[b]	(BWE) (100)[b]	MITE (500)[b]	(MITE) (100)[b]	(CLA) (100)[b]	CR (500)[b]	NEM (3.0)[b]
29	H	0	1	0	+	0	0	0	0	0	0	0
30	H	1	1	0	0	0	0	0	0	0	0	...
31	H	2	2	0	+	0	0	0	0	0	0	0
32	CH_3	2	2	0	0	0	0	0	0	0	0	...

[a] MOS, mosquito (*Aedes aegypti*); HF, housefly (*Musca domestica*); BWE, boll weevil (*Anthonomus grandis*); (BWE), boll weevil, systemic, cotton; MITE, two-spotted spider mite (*Tetranychus urticae*); (MITE), two-spotted spider mite, systemic, cotton; (CLA), corn leaf aphid (*Rhopalosiphum maidis*), systemic, wheat; CR, cockroach (*Blattella germanica*); NEM, root-knot nematode (*Meloidogyne incognita*). [b] Rate of application in ppm. Rating system: 0 = inactive; +, ++ = intermediate activities; +++ = 100% control of pest species; P = chemical too phytotoxic for meaningful evaluation; ... indicates not evaluated.

Table V. Mammalian Toxicity of Selected α-Mercaptol *O*-(Methylcarbamoyl)oximes



No.	R	Acute Toxicity (mg/kg ± S.E.) Oral LD_{50} Male Mice[a]	Oral LD_{50} Female Rats[a]	Dermal ALD_{50} Female Rabbits[b]
1	$-CH_2CH_2-$	4.6 ± 0.47	5.9 ± 1.3	...
2 (Tirpate)	$-CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}H-$	3.1 ± 0.7	1.13 ± 0.25	350–400
6	$-\underset{\displaystyle H_3C}{\underset{\vert}{C}}H-\underset{\displaystyle CH_3}{\underset{\vert}{C}}H-$	...	2.5 – 5.0	...
9	$-CH_2CH_2CH_2-$	0.1 – 0.5	...	...

[a] Ten animals used per dosage level. [b] Four rabbits used per dosage level.

frared spectrum showed the presence of a carbonyl group (5.77 μ).

A stirred mixture of the above crude carbonyl compound, 4.9 g (0.050 mole) potassium acetate, 3.5 g (0.050 mole) hydroxylamine hydrochloride, and 50 ml of 1:1 ethanol-water was heated at reflux overnight. The hot solution was filtered, cooled, and the precipitated solid collected by filtration and dried to afford yellow crystals (2.2 g, mp 165–170° C) whose infrared spectrum was not inconsistent for 5,6-dihydro-1,4-dithiin-2-carboxaldehyde oxime.

To a stirred solution of the above crude oxime, 50 ml of acetone and three drops of triethylamine, was added 2.8 g (0.050 mole) of methyl isocyanate. The solution was heated at reflux 2 hr, cooled, and the solvent removed under reduced pressure to give a brown oil. Addition of hexane afforded a solid which was recrystallized from chloroform-hexane to yield pure **20** as yellow-orange crystals (1.9 g). The infrared and nmr spectra of **20** were in agreement with the suggested structure. Ir (Nujol) 2.97 (NH), 5.87 μ (C=O); nmr (DMSO-d_6) τ 7.31 (3H doublet, NCH_3), 6.75 (4H multiplet, SCH_2CH_2S), 3.00 (1H quartet, NH), 2.86 (1H singlet, SCH=C), and 1.87 (1H singlet, CH=N).

2-Methyl-1,3-dithiolane-2-carboxaldehyde *O*-(Carbamoyl)-oxime (27). To a stirred (nitrogen atmosphere) cold (0–5° C) solution of 24 g (0.2 mole) of *N,N*-dimethylaniline and 200 ml of ether was added bubblewise 22 g (0.22 mole) of gaseous phosgene. To the cloudy solution was next added (0° C) 32.6 g (0.2 mole) of 2-methyl-1,3-dithiolane-2-carboxaldehyde oxime in 200 ml of ether over 2.5 hr. The thick mixture was stirred an additional hour at 0° C, the solid removed by filtration, and the filtrate evaporated under reduced pressure to a volume of 240 ml. To 80 ml of this solution cooled to 0–5° C was added dropwise over 45 min 80 ml (0.2 mole) of 4.7% ammonium hydroxide. The mixture was stirred an additional hour at 0° C, the precipitated solid removed by filtration, and recrystallized from chloroform-hexane to afford pure **27** as white crystals (3.4 g). The compound gave a satisfactory infrared spectrum. Ir (Nujol) 5.78 μ (C=O).

2-Methyl-1,3-dithiolane-2-carboxaldehyde *O*-(*N*-Acetyl-*N*-methylcarbamoyl)oxime (28). To a stirred mixture of 4.5 g (0.1 mole) of 50% sodium hydride in mineral oil and 100 ml of toluene was added in portions 12.2 g (0.075 mole) of 2-methyl-1,3-dithiolane-2-carboxaldehyde oxime and the mixture was stirred 1 hr. This slurry of oxime sodium salt was then added over 10 min to a cold toluene solution of *N*-acetyl-*N*-methylcarbamoyl chloride, prepared (Robertson *et al.*, 1962) from 21.9 g (0.3 mole) of *N*-methylacetamide, and the mixture stirred at room temperature 1.5 hr. Filtration and removal of solvent under reduced pressure gave a brown oil which slowly solidified on the addition of hexane-ether. Recrystallization from chloroform-hexane and then benzene-hexane afforded pure **28** as colorless crystals (1.9 g). The compound gave a satisfactory infrared spectrum. Ir (Nujol) 5.67 (carbamate C=O), 5.90 μ (amide C=O).

2-Methyl-1,3-dithiolane-2-carboxaldehyde *O*-(Methylcarbamoyl)oxime Sulfoxide (29). To a stirred cold (0–5° C) solution of 4.4 g (0.02 mole) of 2-methyl-1,3-dithiolane-2-carboxaldehyde *O*-(methylcarbamoyl)oxime (**1**) and 100 ml of methanol was added dropwise over 30 min 4.3 g (0.02 mole) of sodium metaperiodate in 50 ml of water. The mixture was stirred at 0–5° C for 4 hr, allowed to warm to room temperature, the solid sodium iodate removed by filtration, and the solvent evaporated under reduced pressure to give an oil which slowly solidified on standing. Recrystallization from benzene-ethyl acetate afforded pure **29** as tan crystals (1.5 g). The infrared spectrum of **29** was consistent with the proposed structure. Ir (Nujol) 3.00 (NH), 5.75 (C=O), 8.45 μ (S=O). No attempt was made to determine whether the product was a single isomer. After laboratory storage for several weeks, the sulfoxide darkened and began to liquify.

2-Methyl-1,3-dithiolane-2-carboxaldehyde *O*-(Methylcarbamoyl)oxime Disulfoxide (30). The above procedure was repeated with 9.0 g (0.042 mole) sodium metaperiodate to afford 1.0 g of 30 as a tan solid (chloroform-hexane). The infrared spectrum of 30 was consistent with the proposed structure but, as above, isomer possibilities were not investigated. Ir (Nujol) 2.91 (NH), 5.71 (C=O), 9.69 μ (S=O). After laboratory storage for several months, the disulfoxide showed signs of decomposition.

2,4-Dimethyl-1,3-dithiolane-2-carboxaldehyde *O*-(Methylcarbamoyl)oxime Disulfone (32). To a stirred cold (cold-water bath) solution of 9.4 g (0.040 mole) of 2,4-dimethyl-1,3-dithiolane-2-carboxaldehyde *O*-(methylcarbamoyl)oxime and 75 ml of acetic acid was added dropwise over 15 min 36.2 g (0.32 mole) of 30% aqueous hydrogen peroxide. The

stirred solution was heated slowly to reflux (CAUTION! Exothermic near reflux temperature), maintained at reflux 5–10 min, 100 ml of water added, and the solution cooled. An additional 100 ml of water was added, the solution frozen in dry ice, and then warmed slowly to room temperature. The precipitated white solid was analytically pure **32** (3.8 g) whose infrared spectrum was satisfactory for the proposed structure. Ir (Nujol) 2.91 (NH), 5.75 (C=O), 7.56 (SO_2), and 8.85 μ (SO_2).

Biology Test Methods. Ten to 15 mosquito (*Aedes aegypti*) larvae, 5 to 7 days old, were treated with an aqueous solution containing 1.0 ppm of the candidate compound. Mortality data (average of three replicates) were recorded at 48 hr.

One milliliter of a 500 ppm acetone solution of compound was placed in a pint jar. The jar was rolled and shaken so as to coat the inside surface with a deposit of chemical. After allowing sufficient time for acetone evaporation, about 2 g of a sugar and dry milk mixture were added to the jar. Ten to 15 housefly (*Musca domestica*) adults were placed in the jar and mortality readings (average of three replicates) made after 24 hr.

The preceding method was repeated except that four or five German cockroach (*Blattella germanica*) adults were used in place of *Musca domestica*, and no food or water was provided. Mortality readings (average of three replicates) were obtained at 48 hr.

A cotton plant was immersed for approximately 2 sec in a 500 ppm water solution of compound, plus three drops of Triton X-100 surfactant. After allowing sufficient time for drying, the plant was infested by caging five boll weevil (*Anthonomus grandis*) adults. Mortality data (average of three replicates) were taken after 48 hr.

The upper leaf surface of a cotton plant was infested with two-spotted spider mites (*Tetranychus urticae*) so that the leaf contained 25 to 50 female adults. After approximately 30 min the infested plant was treated in the same manner as described in the preceding method. Mortality data (average of three replicates) were recorded after 48 hr.

A 4-in. plastic pot containing standard soil mix and three cotton plants was watered with sufficient solution of the candidate compound to give a concentration of 100 ppm in the soil. Care was taken to avoid wetting the foliage. After a 5-day translocation period the plants were infested with *Anthonomus grandis* adults, as described in the foliar test methods. Mortality data (average of two replicates) were recorded after 48 hr.

The systemic method was repeated except cotton plants were infested with *Tetranychus urticae* as described in the foliar test.

The systemic method was repeated except 3–4-in. wheat plants were used instead of cotton and infested with corn leaf aphid (*Rhopalosiphum maidis*) nymphs.

A wettable powder formulation containing 25% active ingredient was added to soil in a quantity sufficient to give a concentration of 3.0 ppm. The treated soil was placed in pots and a sand culture of the tomato root-knot nematode (*Meloidogyne incognita acrita*) was added to the soil to give approximately 1000 larvae per pot. After 2 days tomato plants were transplanted into the treated inoculated soil. Root-knot galls developed in 3 to 4 weeks and data (average of three replicates) were recorded so that complete control (+++) represents no galling and 0 is equivalent to the untreated control.

The acute toxicity studies were conducted with nonfasted male Simonsen Swiss-Webster mice weighing 20–23 g, 18-hr fasted female Simonsen Sprague-Dawley rats weighing 80–100 g, and female New Zealand white rabbits weighing 1650–2100 g. All animals were housed in an air-conditioned and humidity controlled environment. They were observed for 14 days, during which time food and water were available *ad libitum*. Rodent oral LD_{50} values were obtained by the method of Miller and Tainter (1944). Dermal measurements were made by applying the compound under a rubber sleeve to moistened rabbit skin that had been clipped free of hair the day prior to dosing, and the rabbits were then immobilized for 24 hr in stocks.

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