Novel Insecticidal Oxathiolane and Oxathiane Oxime Carbamates

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A series of 4-[(methylcarbamoyl)oximino]-1,3-oxathiolane and related oxathiane insecticides has been synthesized. These compounds, monooxygen analogues of recently reported (carbamoyloximino)dithiolanes and -dithianes, show the same level of insecticidal activity as do the disulfur materials. Replacement of the sulfide link with oxygen, however, reduces both mite and mammalian toxicity relative to the disulfur compounds.

The previous paper in this series (D'Silva et al., 1985) presents the synthesis and biological properties of a new series of insecticidal oxime carbamate derivatives of 1,3-dithiolanes and 1,4-dithianes (**1a**) and gives an overview of earlier important work in insecticidal oxime carbamates. Contemporary with this work on the dithia series, a study was conducted of analogous oxathia compounds generalized by formula **1b**. This paper reviews the synthesis and outstanding insecticidal and acaricidal properties of compounds in the previously unreported oxathiolane and oxathiane oxime carbamate series (Chart I).

Comparisons between aldicarb and its methoxy analogue (Table I) suggested that the series **1b** might retain the excellent insecticidal activity of the analogous dithia series **1a**, while realizing reduction of the substantial toxicity to mammals (as measured by the rat) characteristic of the dithia series. Replacement of the sulfur of aldicarb with oxygen resulted in decreased insecticidal activity, 10-fold and 6-fold, respectively against the aphid and the mite but gave a more substantial (15-fold) reduction in toxicity to the rat (Table I). The study of the oxathiolane series **1b** was undertaken in an effort to exploit this trend toward diminished toxicity to rats while, hopefully, recovering the concurrent loss in aphid and mite activity shown in Table I.

Structures and biological data for the oxathiolane and oxathiane insecticide compounds reported herein are collected in Tables II and III. Although carbamoyl nitrogen substitution patterns other than *N*-monomethyl were studied (see Table III), broad spectrum activity was limited to the methylcarbamates presented in Table II.

CHEMISTRY

The oxathiolane and oxathiane carbamoyloximes **1b** were prepared from the precursor oximes **3** by reaction with an isocyanate or a carbamoyl halide or by reaction of an oxime chloroformate with ammonia or a disubstituted amine. Compounds **1b** (where one of R_1 and R_2 is acyl) were prepared by reaction of the parent *N*-monoalkylcarbamoyl oxime with a suitable acylating agent. Carbamate compounds **50–52** having an oxidized sulfur atom were prepared from the sulfide precursors via peracetic acid oxidation.

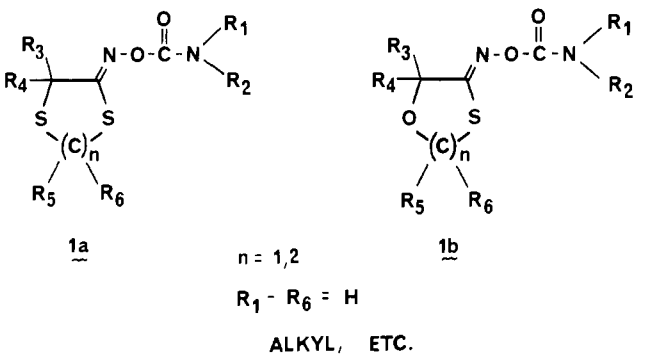
Each oxime, **3**, was synthesized by treatment of the precursor 2-[(acetylthio)alkoxy]nitroalkane **2** with sodium hydroxide (Scheme I). This reaction presumably involves deacylation to yield a reactive mercaptide salt that subsequently produces the heterocyclic thiohydroximate by addition to the nitroalkane moiety through a process analogous to that described by Copenhaver (1957) for the synthesis of aliphatic thiohydroximates. The reaction has also been used in the synthesis of oximinodithiolanes and -dithiolanes as reported earlier (D'Silva et al., 1985).

The synthetic routes to the oximes described herein differ from one another only in details of the methods chosen for synthesis of the (acetylthio)alkyl nitroalkyl ether intermediates **2a–2c**, as shown in Scheme II.

For unsubstituted, 5-substituted, and 2,5-disubstituted 4-oximino-1,3-oxathiolanes (**3**, $n = 1$) the precursor **2a** was achieved via a chloroalkylation followed by thioacetylation (Scheme IIA).

Since tertiary alcohols cannot be chloroalkylated (Summers, 1955), the precursors **2b** to *gem*-5,5-dialkyl-substituted 4-oximino-1,3-oxathiolanes were synthesized via the nitroalkene **6b** (Schwarz and Nelles, 1941) utilizing the method of Lambert et al. (1947) to generate the simple ether **7b**. Chlorination in the presence of light afforded **8b**, the chloroalkyl precursor to **2b**, which upon exposure to thioacetate afforded **2b** (Scheme IIB). The reaction of the monosodium salt of ethylene glycol with suitable nitro olefins **6b** according to the method of Kozlov et al. (1962) gave **9**, hydroxyethyl precursors to **2c**. Reaction of the

Chart I



Scheme I

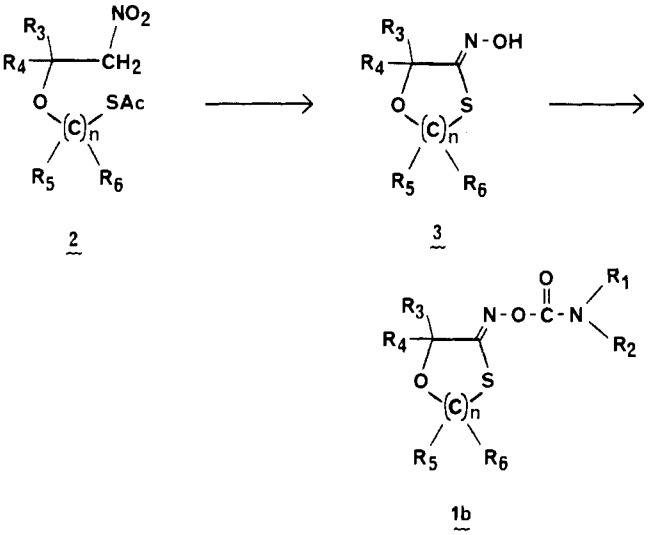


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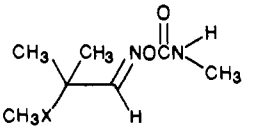
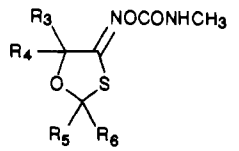
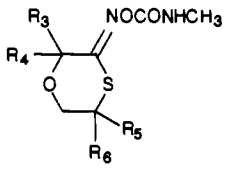
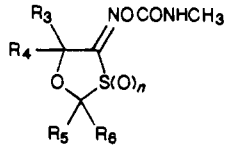
Table I. Comparative Toxicology for Aldicarb and Its Methoxy Analogue



X	LC_{50}, ppm: buckthorn aphid	two-spotted spider mite	southern armyworm	Mexican bean beetle	housefly	LD_{50} (AO rat), mg/kg
S	2	15	500	70	5	1.0
O	23	95	350	100	8	15.0

Table II. Structures and Toxicology for [(Methylcarbamoyl)oximino]oxathiolanes and -oxathianes

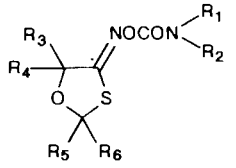
no.	R_3, R_4	R_5, R_6	notes[a]	LC_{50}, ppm: buckthorn aphid	two-spotted spider mite	southern armyworm	Mexican bean beetle	housefly	AChE[b] $I_{50} \times 10^6$, M	LD_{50} (AO rat),[c] mg/kg
										
11	H, H	H, H	syn	25	150	150	180	3	2.5	49
12	H, H	H, H	anti	60	>200	>200	>200	>12		
20	CH_3, H	H, H		6	340	14	14	5	0.8	12
29	H, H	CH_3, H	syn	33	200	500	70	3	1.0	12
30	H, H	CH_3, H	anti	~300	>500	>500	>500	7	7.0	49
31	H, H	CH_3CH_2, H		45	200	500	~500	18	0.4	60
32	CH_3CH_2, H	H, H		25	180	110	25	3		24
33	$CH_3(CH_2)_2$, H	H, H		>250	>250	>250	>250	4	0.5	83
35	$(CH_3)_2CH$, H	H, H		40	500	500	60	9	0.8	16
36	$CH_3O(CH_2)_2$, H	H, H		>500	~500	~500	170	5		
37	CH_3OCH_2, H	H, H		44	200	>500	~10	~50		
38	CH_3, H	CH_3, H	50/50 cis/trans	15	85	25	17	11	0.05	5
41	CH_3, H	CH_3CH_2, H	40% cis	10	10	140	70	60		8
42	CH_3CH_2, H	CH_3, H	40% cis	13	85	140	60	35		15
43	CH_3, H	$CH_3(CH_2)_2$, H	isomer A (trans)	58	500	500	180	60		
44	CH_3, H	$CH_3(CH_2)_2$, H	isomer B (cis)	70	~500	>500	140	~40		
45	CH_3, CH_3	H, H		4	40	11	14	16		2
										
46	H, H	H, H		500	500	100	38	2	1.5	37
47	CH_3, H	H, H		12	112	8	6	3	0.25	6
48	CH_3CH_2, H	H, H		20	100	>500	>500	11		19
49	CH_3, CH_3	H, H		8	18	17	3	18	0.06	0.6
										
50	CH_3, H	H, H	$n = 1$		>500	>500	~500	8	10.0	
51	CH_3, H	H, H	$n = 2$	>500	>500	>500	>500	180	3.5	
52	CH_3, H	$CH_3(CH_2)_2$, H	$n = 1$	>500	>500	>500	250	~400		

[a] Syn unless noted otherwise. [b] Fly head acetylcholinesterase I_{50} by Warburg technique (Moorefield and Tefft, 1958). [c] Acute oral rat LD_{50} (stomach intubation).

terminal hydroxy group with thionyl bromide and subsequent displacement of bromide with thioacetate gave precursors **2c** to the oxathiane oximes having one or two methyl groups α to the oximino function (Scheme IIC).

To avoid the necessity of preparing the unstable 2-nitroethylene **2c** ($R_3 = R_4 = H$), the precursor to the unsubstituted oxathiane oxime was prepared by converting bis(bromoethyl) ether to crude 2-(nitroethoxy)ethyl bromide via reaction with sodium nitrite in Me_2SO and conversion of the crude bromonitro derivative to 2-(nitroethoxy)ethyl thioacetate by reaction with sodium thioacetate.

Table III. Structures and Toxicology for Miscellaneous Carbamate Derivatives



					LC_{50}, ppm						
no.	R_1, R_2	R_3, R_4	R_5, R_6	notes[a]	buckthorn aphid	two-spotted spider mite	southern armyworm	Mexican bean beetle	housefly	AChE[b] $I_{50} \times 10^6$, M	LD_{50} (AO rat),[c] mg/kg
13	C_6H_5, H	H, H	H, H		>500	>500	>500	>500	>500		
14	CH_3, CH_3	H, H	H, H		90	>500	>500	>500	8	20.0	
15	H, H	H, H	H, H		>250	>500	>500	>500	5		
16	$Cl(CH_2)_2$, H	H, H	H, H	19% syn; 81% anti	>500	>500	>500	>500	60		
17	CH_3, $COCH_3$	H, H	H, H		>500	>500	>500	>500	500		
18	H, CH_2CH_3	H, H	H, H		35	>500	>500	32	10		
19	CH_3CH_2, $COCH_3$	CH_3, H	H, H		240	>500	>500	>500	>500		
21	C_6H_5, H	CH_3, H	H, H		>250	>500	>500	500	>500	7.5	
22	CH_3, CH_3	CH_3, H	H, H		60	~500	~500	~500	15		
23	H, H	CH_3, H	H, H	63% syn; 37% anti	<30	<500	130	180	8		
24	$Cl(CH_2)_2$, H	CH_3, H	H, H		180	>500	>500	>250	110		
25	CH_3CH_2, H	CH_3, H	H, H		>30	~400	150	~30	14	2.0	28
26	CH_2=$CHCH_2$, H	CH_3, H	H, H		6	~500	300	100	20		
27	CH_3OCH_2, H	CH_3, H	H, H		90	>500	>500	~500	30	3.0	
28	CH_3, $COCH_3$	CH_3, H	H, H		<500	~500	115	~180	>500	>700	453
34	H, H	$CH_3(CH_2)_2$, H	H, H		>500	>500	>250	120	50		
39	CH_3CH_2, H	CH_3, H	CH_3, H	50/50 cis/trans	20	23	~150	>500	~20		
40	CH_2=$CHCH_2$, H	CH_3, H	CH_3, H	50/50 cis/trans	17	190	>500	>500	<30		

[a] Syn unless noted otherwise. [b] Fly head acetylcholinesterase I_{50} by Warburg technique (Moorefield and Tefft, 1958). [c] Acute oral rat LD_{50} (stomach intubation).

Scheme II

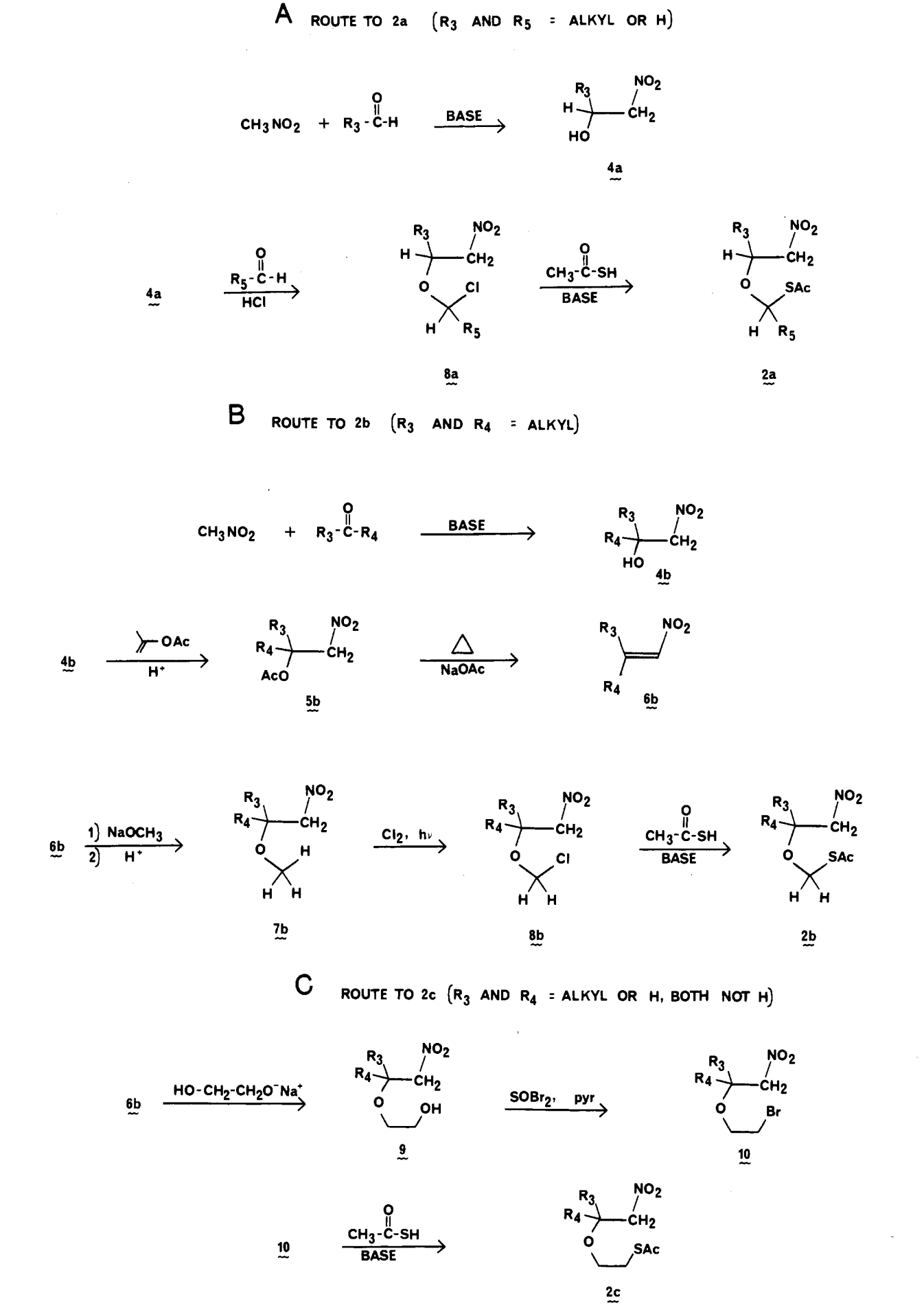
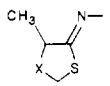
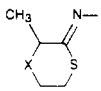
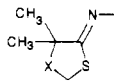
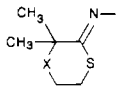

A ROUTE TO 2a (R3 AND R5 = ALKYL OR H)
CH3NO2 + R3-C(=O)-H
BASE
4a
4a
R5-C(=O)-H
HCl
8a
CH3-C(=O)-SH
BASE
2a
B ROUTE TO 2b (R3 AND R4 = ALKYL)
CH3NO2 + R3-C(=O)-R4
BASE
4b
4b
OAc
H+
5b
NaOAc
6b
6b
1) NaOCH3
2) H+
7b
Cl2, hν
8b
CH3-C(=O)-SH
BASE
2b
C ROUTE TO 2c (R3 AND R4 = ALKYL OR H, BOTH NOT H)
6b
HO-CH2-CH2O-Na+
9
SOBr2, pyr
10
10
CH3-C(=O)-SH
BASE
2c

Table IV.[a] Selected Oxathia/Dithia Cyclic Oxime Methylcarbamate Data Pairs

	X	LC_{50}, ppm: buckthorn aphid	two-spotted spider mite	southern armyworm	Mexican bean beetle	housefly	AChE $I_{50} \times 10^6$, M	LD_{50} (AO rat), mg/kg
(A) Unsubstituted Compounds								
	O	25	150	150	180	3.0	2.5	49.0
	S	6	55	100	28	1.0	3.0	13.0
	O	500	500	100	38	2.0	1.5	37.0
	S	5	6	40	52	0.8	1.0	15.4
(B) α-Methyl Substituted Compounds								
	O	6	340	14	14	5.0	0.8	12.0
	S	5	15	22	10	1.5	2.0	0.88
	O	12	112	8	6	3.0	0.25	6.0
	S	4	6	60	11	4.0	0.07	2.2
(C) α,α-Dimethyl Substituted Compounds								
	O	4	40	11	14	16.0	0.06	1.6
	S	6	2	16	23	4.0	0.25	0.67
	O	8.0	18	17	3	18.0	0.06	0.6
	S	0.8	4	140	80	12.0	0.1	0.27

[a] Data for Disulfur compounds are taken from D'Silva et al. (1985).

The physical properties and elemental analyses of all the target carbamate compounds are given in Table V (supplementary material). Structures were established in each case by IR and NMR spectroscopies and elemental analysis.

Syn/Anti and Cis/Trans Isomers. An interesting feature of the oxime and carbamate derivatives in this series is the possibility of syn (oximino oxygen cis to the thiohydroximate sulfur) or anti configuration about the imino moiety. Syn/anti pairs were commonly observed in both oximes and carbamates in instances where both R_3 and R_4 were H; if both R_3 and R_4 are alkyl, the syn isomer overwhelmingly predominates. Syn/anti isomers were easily detected and identified by NMR where mixtures occurred: in all cases, the protons at the 5-position in the anti isomer (e.g., δ 4.74 in compound **12**) resonate ~0.1 ppm downfield relative to the same protons at the 5-position in the syn isomer (δ 4.65 in compound **11**). Where data were available for both isomers (see Table IV), the syn isomer was always the lower melting.

It is interesting to note that when an oxime capable of facile syn/anti interconversion (e.g., **3**, $n = 1$, $R_3 = R_4 = R_5 = H$, $R_6 = H$ or CH_3) was carbamoylated with methyl isocyanate, use of ether as solvent and dibutyltin diacetate catalyst afforded a mixture in which the anti isomer predominates (e.g., **12**, **16**, **30**) while use of triethylamine in acetonitrile afforded mixtures in which the syn isomer predominates (e.g., **11**, **29**). This result is apparently general for carbamoylation of oxathiolane oximes free of alkyl groups in the 5-position.

A second interesting feature of these compounds is the possibility of encountering cis/trans isomer pairs in compounds where $R_3 \neq R_4$ and $R_5 \neq R_6$, i.e., compounds having dominant alkyl groups on the same (cis) or opposite (trans) sides of the ring. Such cis/trans pairs were encountered in compounds **38–40** ($R_3 = R_5 = CH_3$, $R_4 = R_6 = H$), **41** ($R_3 = CH_3$, $R_4 = R_5 = H$, $R_6 = CH_3CH_2$), **42** ($R_3 = CH_3CH_2$, $R_4 = R_5 = H$, $R_6 = CH_3$), and **43** and **44** ($R_3 = CH_3$, $R_4 = R_5 = H$, $R_6 = CH_3CH_2CH_2$) and the appropriate precursor oximes. Where cis/trans isomerism is possible, cyclization reactions yielded oximes having ~50/50 cis/trans composition, which was carried through to product carbamates. In one instance (compounds **43**/**44**), the cis/trans isomers had physical properties differing sufficiently to make isomer separation practical as described in the Experimental Section.

Cis/trans isomer composition was readily monitored in these studies via the definitive chemical shift separation for methine protons cis or trans to an alkyl group across the ring in the NMR spectra as outlined in detail in the Experimental Section.

BIOLOGY

Data on the insecticidal and acaricidal activities of the oxathiolane and oxathiane oxime carbamates are presented in Tables II and III. The highly active monomethylcarbamates are summarized in Table II. Other less active carbamates having nitrogen substituent patterns other than monomethyl are contained in Table III. The toxicity data (LC_{50}, ppm) are for foliage spray tests against buckthorn aphid adults, two-spotted spider mite (all stages), southern armyworm larvae, and Mexican bean beetle larvae and from a bait test involving the adult housefly. Protocols for all these tests have been described earlier (Payne et al., 1966). The aphid and mite tests have a contact toxicity component as well as a feeding toxicity component since the foliage in these two tests was infested prior to spraying. Toxicity in the southern armyworm and Mexican bean beetle tests is predominantly feeding toxicity since foliage is introduced to the larvae after the spray treatment. Where available, fly head acetylcholinesterase inhibition I_{50} data (Moorefield and Tefft, 1958) and acute mammalian toxicity data (acute oral rat, stomach intubation in corn oil) are also presented. All data are from single series of dose–response experiments. In general, the 95% confidence interval for individual LC_{50}'s in these tests is $LC_{50}/2$ to $LC_{50} \times 2$ (e.g., the CI for an LC_{50} of 50 is 25–100).

Seemingly subtle changes in the structure of compounds in this oxathia series cause substantial changes in biological activity in a pattern analogous to that observed for the previously reported dithia series (D'Silva et al., 1985). Comparative data for analogous oxathia/dithia pairs given in Table IV indicate that the expectations suggested by the aldicarb and methoxy analogue comparison in Table I were generally realized. A quantitative treatment of the structure–activity relationships that control activity in the oxathia series is reported and contrasted with the dithia series in a companion paper (Kurtz and Durden, 1987). A few summarizing statements are appropriate, however.

1. There are no obvious structure–activity contrasts in the oxathia/dithia comparisons for the southern armyworm, the Mexican bean beetle, or the housefly. However, against the aphid and the mite the dithia series is invariably more active, moreso in the case of the mite than the aphid. Relative to their dithia counterparts, the mammalian toxicity of the more insecticidal compounds in the oxathia series is generally decreased, in one case as much as 14-fold. These results, particularly with the rat and the mite, are consistent with the premise that the easily oxidizable sulfur atom (β to the oximino function) may be a promoter of activity on a species-selective basis in these series. Further information on this trend is developed in the companion paper.

2. Insecticidal and cholinesterase inhibiting potency in both the oxathia and dithia series is controlled by the presence, location, and nature of ring alkyl groups. However, an examination of the data in Table II reveals no clear relationship between activity against the fly head enzyme and activity against the whole insects in the foliage spray or bait tests. This lack of correlation may be attributed in a large part to the role of sulfoxidation of the β-sulfur in determining toxicity in the whole organism; sulfoxidation is not operative in the in vitro systems used to assay acetylcholinesterase inhibition. This point also is expanded in the companion paper.

In the *N*-monomethylcarbamate series (Table II), data for compounds **11** vs. **12** and **29** vs. **30** suggest that the oximino syn isomers are more active than the anti isomers. This agrees with results reported for the syn and anti isomers of 1-(methylthio)acetaldoxime *N*-methylcarbamate (the syn isomer is methomyl) and the methoxy analogues (Felton, 1968).

Data for the one pair in which isomers were isolated (**43** vs. **44**) suggest that there is no remarkable difference in potency between cis and trans configurations for ring alkyl groups.

Finally, the oxathiane analogues are very similar in biological activity levels to oxathiolane analogues having related ring substituents.

Data for carbamate compounds in this series where the carbamate nitrogen is substituted with other than a single methyl group (Table III) follow structure–activity relationships common to most oxime carbamate insecticides: derivatives other than the monomethylcarbamate are substantially inferior in biological activity.

EXPERIMENTAL SECTION

All intermediates and carbamates were characterized by NMR and IR spectral and elemental analyses as outlined in Table V (supplementary material). The melting points are corrected. NMR spectra were obtained on a Varian A-60 spectrometer with Me_4Si as an internal standard. IR spectra were recorded on a Perkin-Elmer 197 spectrometer. Elemental analyses were obtained from the Union Carbide Analytical Chemistry Group at the South Charleston, WV, Technical Center. Supplementary material containing other experimental details and physical properties is available (see paragraph at end of paper).

2-(Chloromethoxy)-1-nitroethane (8a, $R_3 = R_5 = H$). Dry hydrogen chloride was bubbled through a stirred slurry of 50 g of 2-nitroethanol [prepared according to the method of Noland (1961)], 16.5 g of paraformaldehyde, and 15.2 g of calcium chloride, which was cooled to maintain a temperature of 0–10 °C on an ice bath. When excess HCl (over 1 equiv) had been absorbed, the cold mixture was filtered. Distillation in vacuo afforded 42.8 g (56%) of 2-(chloromethoxy)-1-nitroethane [**8a**, $R_3 = R_5 = H$; bp 72 °C (0.1 mmHg)] of purity appropriate for use in the next synthetic step. Anal. Calcd for $C_3H_6ClNO_3$: C, 25.82; H, 4.30; Cl, 25.39; N, 10.04. Found: C, 26.26; H, 4.60; C, 24.42; N, 9.80.

2-[(Acetylthio)methoxy]-1-nitroethane (2a, $R_3 = R_5 = H$). Thioacetic acid (22.8 g) and 41.7 g of 2-(chloromethoxy)-1-nitroethane (**8a**, $R_3 = R_5 = H$) were mixed into 100 mL of tetrahydrofuran at room temperature, and the clear solution was heated at reflux for 2 h. The solution was cooled, and 25 g of pyridine was added. After an additional period of 2 h at reflux, the mixture was filtered and the solvent was removed from the filtrate by flash evaporation. The residue was taken up in ether, washed with 5% aqueous hydrochloric acid and water, and dried over magnesium sulfate and the solvent again evaporated. Distillation in vacuo afforded 24.7 g (46%) of 2-[(acetylthio)methoxy]-1-nitroethane (**2a**, $R_3 = R_5 = H$), bp 106–109 °C (0.2–0.5 mmHg); structure was confirmed by spectral analysis.

4-Oximino-1,3-oxathiolane (3, $n = 1$, $R_3 = R_4 = R_5 = R_6 = H$). A 171-mL portion of 1.68 N ethanolic sodium hydroxide and an equal volume of toluene were stirred vigorously at room temperature, and a solution of 25.8 g of the thioacetate **2a** ($R_3 = R_5 = H$) dissolved in 25 mL of toluene was added dropwise over 1 h (slightly exothermic). After it was stirred at room temperature for 3 h, the mixture was diluted with water and ether and the aqueous phase was adjusted to pH 4 with 50% aqueous HCl. The organic phase was separated and the aqueous phase extracted with a second portion of ether. Both organic solutions were washed with brine containing 5% aqueous sodium bicarbonate, dried over magnesium sulfate, and evaporated to give 16.5 g of crude 4-oximino-1,3-oxathiolane. Recrystallization from toluene afforded pure oxime **3** ($n = 1$, $R_3 = R_4 = R_5 = R_6 = H$): 10.1 g (59%); mp 91.0–92.5 °C. Anal. Calcd for $C_3H_5NO_2S$: C, 30.25; H, 4.20; N, 11.76; S, 26.9. Found: C, 30.22; H, 4.50; N, 11.59; S, 27.1.

4-[(Methylcarbamoyl)oximino]-1,3-oxathiolane (Syn, 11; Anti, 12). A 5.78-g sample of the oxime **3** ($R_3 = R_4 = R_5 = R_6 = H$) was charged to a pressure bottle with 7.5 mL of methyl isocyanate, 4 drops of dibutyltin diacetate, and 150 mL of ethyl ether. After the mixture was allowed to stand for 60 h, crystals had deposited in the bottom of the reactor. The solution was washed with water and brine and dried over magnesium sulfate and the solvent evaporated. Recrystallization from 5/1 isopropyl ether/ethyl acetate afforded pure 4-[(methylcarbamoyl)oximino]-1,3-oxathiolane (syn isomer, **11**): mp 100.0–101.5 °C; structure confirmed by IR and NMR. The use of proton chemical shifts in assaying the syn vs. anti isomer is discussed in the main text. Anal. Calcd for $C_5H_8N_2O_3S$: C, 34.08; H, 4.57; N, 15.89; S, 18.19. Found: C, 34.03; H, 4.94; N, 15.82; S, 18.1.

While TLC/NMR data on an aliquot of the original reaction mixture had indicated predominance of the anti isomer, it could not be isolated free of contamination from

syn isomer by fractional crystallization. Pure anti isomer 12 was isolated by dry-column chromatography (silica gel G, 30% ethyl acetate/70% benzene) of mother liquors from the recrystallization: mp 138–140 °C; NMR and IR confirmed structure and freedom from contamination with syn isomer; high-resolution mass measurement (theory) 176.02555, (obsd) 176.0255514.

Later experiments showed that alternative conditions lead to a predominance of syn isomer in carbamoylation of oxathiolane oximes *not* having alkyl groups at the 5-position. See examples for compounds **29** and **30**.

4-[(*N*-Methyl-*N*-acetylcarbamoyl)oximino]-5-methyl-1,3-oxathiolane (28). A quantity of 2.0 g of 4-[(methylcarbamoyl)oximino]-5-methyl-1,3-oxathiolane was dissolved in 20 mL of ethyl acetate in a stirred reaction vessel at room temperature. After the addition of 3 mL of acetic anhydride, a solution containing 1 drop of concentrated sulfuric acid in 5 mL of ethyl acetate was added. After the clear solution was stirred for 2 h, approximately 1 g of powdered sodium bicarbonate was added and the heterogeneous mixture was stirred for 5 min. The solids were removed by filtration, 30 mL of hexane was added to the filtrate, and the resulting solution was cooled at −10 °C for several hours. Filtration afforded 0.95 g (27%) of crude 4-[(*N*-acetyl-*N*-methylcarbamoyl)oximino]-5-methyl-1,3-oxathiolane, which on recrystallization from 2/1 isopropyl ether/ethyl acetate melted at 109–110 °C. Anal. Calcd for $C_8H_{12}N_2O_4S$: C, 41.37; H, 5.21; N, 12.06. Found: C, 41.1; H, 5.35; N, 11.9.

4-[(Methylcarbamoyl)oximino]-2-methyl-1,3-oxathiolane (Syn, 29; Anti, 30). These preparations exemplify change in production of carbamate syn/anti isomer ratios with change in carbamoylation reaction conditions.

A quantity of 8.0 g of the crude oxime **3** ($R_3 = R_4 = R_5 = H$, $R_6 = CH_3$; 90% contained syn or anti oximes in a ratio of ~3/1 by NMR and TLC analyses) was treated with 8.0 mL of methyl isocyanate in the presence of dibutyltin diacetate in ethyl ether and allowed to react for 16 h at room temperature. After the ether solution was rinsed with water and saturated brine and dried over magnesium sulfate, evaporation of solvent gave 8.3 g of crude 4-[(methylcarbamoyl)oximino]-2-methyl-1,3-oxathiolane. NMR indicated this crude product to contain predominantly anti isomer. Repeated recrystallization from isopropyl ether/ethyl acetate mixtures afforded pure anti isomer **30**, mp 131–140 °C dec. Isomeric purity of greater than 95% was confirmed by NMR and TLC analyses. Anal. Calcd for $C_4H_7NO_2S$: C, 37.87; H, 5.30; N, 14.7; S, 16.9. Found: C, 37.61; H, 5.08; N, 14.6; S, 17.2.

The syn isomer could not be readily recovered from the mother liquors without anti isomer contamination. Carbamoylation of 5.0 g of crude oxime with methyl isocyanate in acetonitrile in the presence of triethylamine, however, afforded crude 4-[(methylcarbamoyl)oximino]-2-methyl-1,3-oxathiolane having a syn/anti ratio of about 3/2. Repeated recrystallization from isopropyl ether/ethyl acetate mixtures afforded pure syn isomer **29**, mp 80–81 °C. Anal. Calcd for $C_6H_{10}N_2O_3S$: C, 37.87; H, 5.30; N, 14.7; S, 16.9. Found: C, 37.7; H, 5.08; N, 14.7; S, 17.3.

4-Oximino-5-methyl-2-propyl-1,3-oxathiolane (Cis/Trans Isomers; 3, $n = 1$, $R_3 = CH_3$, $R_4 = R_5 = H$, $R_6 = CH_3CH_2CH_2$). 2-[1-(Acetylthio)butoxy]-1-nitropropane (**2a**, $R_3 = CH_3$, $R_5 = CH_3CH_2CH_2$) was prepared by chloroalkylation of 1-nitro-2-propanol with *n*-butyraldehyde and hydrogen chloride followed by treatment of the intermediate chlorobutyl ether with thioacetic acid and then pyridine. A 40-g quantity of the acetylthio product of this reaction was dissolved in toluene and cyclized with ethanolic sodium hydroxide as described earlier. Crude 4-oximino-5-methyl-2-propyl-1,3-oxathiolane comprised of a mixture of isomer A [NMR (suggests trans isomer, see below; $CDCl_3$) δ 4.74 (5-methine), 5.53 (2-methine)] and isomer B [NMR (suggests cis isomer, see below; $CDCl_3$) δ 5.02 (5-methine), 5.74 (2-methine)] was obtained. Trituration of 26 g of the crude oxime mixture with 150 mL of hexane and filtration afforded 3.0 g of pure isomer A, mp 86–88 °C. Anal. Calcd for $C_7H_{13}NO_2S$: C, 47.98; H, 7.48; N, 7.99. Found: C, 47.55; H, 7.61; N, 7.93.

A second crop (4.0 g; mp 80.5–84 °C) analyzed (NMR) for 90% A/10% B.

Evaporation of the mother liquors gave an oil: 17.5 g; 20% A/80% B by NMR. Since this sample (in which isomer B predominated) could not be further purified by direct recrystallization, it was derivatized for further purification from non-oxime impurities. A quantity of 17 g of the crude oxime sample containing predominantly isomer B was reacted with 30 mL of trimethylchlorosilane by stirring in 100 mL of pyridine at 10 °C for 30 min and then approximately 18 h at room temperature. Filtration of pyridinium chloride, evaporation, dissolution in anhydrous ether, drying over magnesium sulfate, filtration, a second solvent evaporation, and distillation in vacuo afforded 9 g of 4-[(trimethylsilyl)oximino]-5-methyl-2-propyl-1,3-oxathiolane: bp 61–63 °C (0.1 mmHg); 15% isomer A/85% isomer B by NMR analysis. Anal. Calcd for $C_{10}H_{21}NO_2SSi$: C, 48.54; H, 8.55; N, 5.66. Found: C, 48.6; H, 8.31; N, 5.33.

The trimethylsilyl ether was quantitatively cleaved by mixing with small increments of 6 mL of water in 50 mL of 3/1 ethanol/tetrahydrofuran for 18 h at room temperature. Evaporation of the solvents, dissolution in ether, rinsing with brine, drying over magnesium sulfate, filtration, and evaporation afforded 5.7 g of an oil, nearly pure oxime (isomer mixture), isomer ratio unchanged from that of the trimethylsilyl ether. This sample, containing a predominance of isomer B was now free of non-oxime contaminants. Since it could not be made to crystallize, elimination of the remaining (~15%) contamination with isomer A was accomplished after conversion to the methylcarbamate.

4-[(Methylcarbamoyl)oximino]-5-methyl-2-propyl-1,3-oxathiolane (43, Isomer A, Trans; 44, Isomer B, Cis). Both the isomer A oxime and (separately) the predominantly isomer B oxime samples described above were converted to the corresponding methylcarbamates by reaction with methyl isocyanate in ether in the presence of dibutyltin diacetate as described earlier. Recrystallization of both products from isopropyl ether afforded, in one instance, pure isomer A (NMR suggests A is trans), mp 88.5–89.0 °C, and in the other instance, pure isomer B (NMR suggests cis), mp 59–60 °C.

The NMR assignment of trans to isomer A and cis to isomer B rests on the similarity of chemical shifts in each case with the chemical shifts of protons having analogous magnetic environments in simpler analogues where the assignment is unequivocal. The following exemplifies the line of reasoning used in the assignments. In compound **11**, both 2-methylene protons, cis to 5-hydrogens, resonate at 5.42 ppm. In compound **45**, both 2-methylene protons, cis to 5-methyl groups, resonate at 5.33 ppm (upfield). The data for the 2-methylene protons in compound **20** serve to substantiate the premise that the upfield protons in these compounds at the 2- or (5-) positions are cis to alkyl groups. In **20**, one proton at the 2-position resonates at 5.43 ppm, almost identical with the chemical shift for the protons cis to H in **11**. This is assigned cis to the 5-hy-

drogen. The other proton at the 2-position in **20**, assigned cis to the methyl group, resonates at 5.21 ppm, upfield from the other by 0.2 ppm. The proton at the 2-position in isomer A of the pair **43/44** resonates at 5.53 ppm. This is assigned cis to an alkyl group in the trans isomer. In isomer B, the 2-methine resonates at 5.74 ppm. This is assigned cis to a hydrogen in the cis isomer. $\Delta = 0.21$ ppm, equivalent to the Δ observed internally in compound **20** and in the direction associated with the **11**, **45**, **20** data set. A similar analysis of NMR chemical shifts for the 5-methine proton in **43/44** supports the assignment of isomer A (**43**) as trans and isomer B (**44**) as cis. Anal. Calcd for $C_9H_{16}N_2O_3S$: C, 46.53; H, 6.94; N, 12.06; S, 13.80. Found for A: C, 46.7; H, 6.93; N, 12.0; S, 14.52. Found for B: C, 46.3; H, 6.87; N, 11.9; S, 13.87.

2-Methyl-1-nitropropene (6b, $R_3 = R_4 = CH_3$). 2-Methyl-1-nitropropan-2-ol (**4b**, $R_3 = R_4 = CH_3$) was synthesized by condensation of acetone and nitromethane in the presence of sodium methoxide as described in the literature (Lambert and Lowe, 1947). The alcohol (120 g) was converted to the corresponding nitroalkyl acetate (**5b**, $R_3 = R_4 = CH_3$) by condensation with 165 mL of isopropenyl acetate at 25–65 °C (exothermic) in the presence of 20 drops of sulfuric acid (nitro alcohol added over about 1 h allowing exotherm to 65 °C followed by equilibration at 50 °C for 72 h). After evaporation of volatile components, distillation afforded 161 g of 2-acetoxy-2-methyl-1-nitropropane [bp 51–52 °C (0.8 mmHg)] in essentially quantitative yield. The acetoxy compound was converted to the title olefin by the following modification of the procedure detailed by Schwarz and Nelles (1941). A slurry of 2.0 g of anhydrous sodium acetate in 300 g of 2-acetoxy-2-methyl-1-nitropropane was agitated with a nitrogen purge while heating at 115 °C for 2 h. After cooling to 70 °C and application of vacuum, 166 g of acetic acid was distilled off until a kettle temperature of 78 °C (35 mmHg) was reached. The pressure was then lowered to 10 mmHg, and 118 g of 90% pure 2-methyl-1-nitropropene (contaminated with ~5 mol % acetic acid and ~5 mol % starting material by NMR analysis) was collected by fractional distillation: bp 50–57 °C (10 mmHg); yield of 2-methyl-1-nitropropene contained in this fraction, 57%.

2-[(Acetylthio)methoxy]-1-nitro-2-methylpropane (2b, $R_3 = R_4 = CH_3$, $R_5 = H$). Sodium methoxide was added to the nitroalkene by the following modification of the procedure of Lambert et al. (1947).

A solution of sodium methoxide in anhydrous methanol was prepared under nitrogen in the conventional manner by dissolving 64.0 g of sodium in 2 L of methanol. A 118-g portion of 2-methyl-1-nitropropene dissolved in 200 mL of anhydrous methanol was added over 30 min to the alkoxide solution at ambient temperatures under nitrogen, and the resulting soltuion was stirred overnight. The basic solution was cooled to 5 °C and neutralized with 232 mL of concentrated hyrochloric acid. After sodium chloride was filtered off, the solution was charged to a still equipped with a 12-in. Vigreux column and was fractionated at reduced pressures. After most of the methanol was removed to bp 40 °C (45 mmHg), five fractions (A-1–A-5) having bp 42–63 °C (45 mmHg) were obtained. Four of these fractions, A-1–A-4, each consisted of two phases (an aqueous phase and a nitro-organic phase). A-1–A-4 were each diluted with water and ether and the nitro-organic phases separated. The water layers were individually extracted with ether and combined with the appropriate "parent" ether solutions. After drying over $MgSO_4$, the ether was removed from each fraction and NMR analysis was used to identify those fractions containing predominance of 2-methoxy-2-methyl-1-nitropropane over 2-methyl-1-nitropropene. Those fractions containing predominantly the desired product were combined and concentrated and added to fraction A-5, a 15-g distillation fraction that was pure 2-methyl-2-methoxy-1-nitropropane, bp 63 °C (45–50 mmHg). The final mixture totalled 27.5 g (14% yield contained methoxy product) and analyzed for 80 mol % 2-methoxy-2-methyl-1-nitropropane (**7b**, $R_3 = R_4 = CH_3$)/20 mol % mixed nitroalkenes by NMR.

A solution of 27.5 g of 2-methoxy-2-methyl-1-nitropropane (80% pure) in 250 mL of hydrocarbon-stabilized chloroform containing 50 mg of benzoyl peroxide was exposed to a conventional sunlamp for 24 h during which chlorine gas was bubbled through the stirring solution. At 24 h, NMR examination of an aliquot indicated essentially all (OCH_3) compound had been consumed, with the chloromethoxy derivative predominating. The chlorination solution was evaporated, yielding 41 g of a nearly colorless oil that analyzed for ~75% 2-(chloromethoxy)-2-methyl-1-nitropropane (**8b**, $R_3 = R_4 = CH_3$) by NMR; 87% contained product yield.

The preceding intermediate was dissolved in 250 mL of anhydrous ether and was treated sequentially with 40 g of thioacetic acid and then 25 mL of pyridine. After the initial exothermic reaction had subsided, the reaction mixture was heated at reflux for 2 h and then allowed to stir at ambient temperatures overnight. Filtration of salts, washing the ether solution with dilute acid and water, drying over $MgSO_4$, and evaporation afforded 37.5 g of an oil that NMR indicated to contain 60 mol % of the desired product: 2-[(acetylthio)methoxy]-2-methyl-1-nitropropane (**2b**, $R_3 = R_4 = CH_3$), 52% yield from the starting methyl ether. Conversion of this material to **3** ($n = 1$, $R_3 = R_4 = CH_3$, $R_5 = R_6 = H$) and carbamoylation to yield **45** are described in the supplementary material.

2-[2-(Acetylthio)ethoxy]-1-nitropropane (2c, $R_3 = CH_3$, $R_4 = H$). 2-Acetoxy-1-nitropropane (**5b**, $R_3 = CH_3$, $R_4 = H$) was synthesized from 1-nitropropan-2-ol with isopropenyl acetate in a manner similar to that described above under the heading of 2-methyl-1-nitropropene. The acetate was converted to 1-nitropropene (**6b**, $R_3 = CH_3$, $R_4 = H$) by a route similar to that described above for 2-methyl-1-nitropropene. The product olefin had bp 33–36 °C (8 mmHg) and NMR/IR consistent with the desired structure.

Reaction of 139 g of 1-nitropropene with a solution of the sodium salt of ethylene glycol (from 36 g of sodium and 800 mL of ethylene glycol) and workup and distillation in a manner similar to that described in the literature (Kozlov et al., 1964) afforded 115 g (44%) of 2-(hydroxyethoxy)-1-nitropropane (**9**, $R_3 = CH_3$, $R_4 = H$), bp 99–103 °C (0.5 mmHg), having correct NMR and IR spectra.

A solution of 65.0 mL of thionyl bromide in 500 mL of anhydrous ethyl ether was stirred at room tempeature with occasional external cooling, while a solution of 108 g of 2-(hydroxyethoxy)-1-nitropropane in 500 mL of ethyl ether and a solution of 68 g of pyridine in 300 mL of ethyl ether were added simultaneously over a period of 1 h in such a manner that the volume of the alcohol solution dispensed was at all times about 20 mL more than that of the pyridine solution. The reaction mixture was then stirred for 3 h and allowed to stand overnight. The clear yellow ether solution was decanted from the dark sticky mass at the bottom of the flask, and the latter was extracted with 100 mL of ethyl ether. The mixed-ether solutions were treated with carbon black and magnesium sulfate, filtered, and washed with two 400-mL portions of water. The resulting solution was dried over magnesium sulfate, filtered, and

concentrated by vacuum rotary evaporation. Trituration with 400 mL of acetone caused precipitation of a small amount of solid that was removed by filtration. Concentration afforded 90.5 g (56% contained yield) of crude 2-(bromoethoxy)-1-nitropropane (**10**, $R_3 = CH_3$, $R_4 = H$): 95% desired product by NMR analysis; IR (neat, μm) 3.40, 6.48, 6.91, 7.05, 7.28, 7.50, 7.85, 8.2–8.4, 8.71, 8.9–9.3, 9.8–10.0, 11.0, 13.7; NMR ($CDCl_3$) δ 1.27 (d, CH_3), 3.3–4.1 (m, OCH_2 and $BrCH_2$), 4.43 (m, CH_2NO_2 and methine).

A solution of potassium thioacetate in aqueous ethanol was prepared by adding 34.8 g of thioacetic acid to a slurry of 61 g of potassium carbonate in 100 mL of water and diluting after stirring for 15 min with 260 mL of ethanol. While this solution was being stirred, 90 g of the bromoethyl intermediate was added over 45 min and the resulting slurry was stirred at room temperature overnight under a nitrogen atmosphere. The salts were removed by filtration, and the product solution was diluted with 800 mL of ether. After separation of a small aqueous phase and washing with one portion of 0.1 N aqueous hydrochloric acid, the ether solution was dried over magnesium sulfate and concentrated, yielding 70 g (50% contained yield) of crude 2-[(acetylthio)ethoxy]-1-nitropropane (**2c**, $R_3 = CH_3$, $R_4 = H$): IR (neat, μm) 3.35, 3.42, 5.91, 6.45, 6.90, 7.05, 7.27, 7.41, 8.0–8.5, 8.5–9.6, 10.5, 11.1, 11.4; NMR ($CDCl_3$) δ 1.27 [d, $CH_3(CH)$], 2.33 [s, $(CO)CH_3$], 3.01 (t, SCH_2), 3.63 (m, OCH_2), 4.42 (m, CH_2NO_2 and methine). The product was about 60% pure by the NMR assay and was used without further refinement to prepare the corresponding oxime. Conversion of this material to **3** ($n = 2$, $R_3 = CH_3$, $R_4 = R_5 = R_6 = H$) and carbamoylation to yield **47** are described in the supplementary material.

4-[(Methylcarbamoyl)oximino]-5-methyl-1,3-oxathiolane 3-Oxide (50). A quantity of 13.7 g of a solution of peracetic acid (22.8%) in ethyl acetate was added over 1.5 h to a stirring solution of 7.65 g of 4-[(methylcarbamoyl)oximino]-5-methyl-1,3-oxathiolane dissolved in 200 mL of ethyl acetate maintained at 0–5 °C. The resulting clear solution was allowed to warm gradually to room temperature and to stand overnight. The solution was then washed with 50 mL of saturated aqueous sodium bicarbonate and 25 mL of saturated brine, dried over magnesium sulfate, filtered, and evaporated. The thick oil resulting (5 g of a mixture of starting material and product sulfoxide) was induced to crystallize by redissolving in 50 mL of ethyl acetate at room temperature and addition of hexane until just turbid. Recrystallization of the first crop, 1.9 g, from 2/1 isopropyl ether afforded 1.1 g of 4-[(methylcarbamoyl)oximino]-5-methyl-1,3-oxathiolane 3-oxide, mp 115–120 °C. The sulfoxide was free of contamination by either sulfide or sulfone by NMR and TLC assays. The broad melting point range and NMR spectrum confirmed the presence of two isomers (ring methyl cis to S=O; ring methyl trans to S=O. Anal. Calcd for $C_6H_{10}N_2O_4S$: C, 34.94; H, 4.88; N, 13.58; S, 15.55. Found: C, 34.8; H, 4.93; N, 13.4; S, 15.71.

4-[(Methylcarbamoyl)oximino]-5-methyl-1,3-oxathiolane 3,3-Dioxide (51). A quantity of 3 g of 4-[(methylcarbamoyl)oximino]-5-methyl-1,3-oxathiolane was treated with peracetic acid in a manner similar to that described above for the monooxide but using increments of peracetic acid (22.8% in ethyl acetate) solution at varying temperatures and for varying time periods as follows: 12 g (room temperature for 1 h; 40 °C for 18 h, room temperature for 30 h); 8 g (40 °C for 14 h); 8 g (40 °C for 24 h). Workup as described earlier for the monooxide afforded 2.5 g of a thick oil. Thin-layer chromatography, IR, NMR, and elemental analyses confirmed the structure assignment and attested to freedom from contamination with starting material or sulfoxide. The product could not be induced to crystallize and, even after exposure to 0.01 mmHg vacuum for 24 h at 35 °C, showed 10.6 mol % contamination with ethyl acetate (NMR). Anal. Calcd for $C_6H_{10}N_2O_5S$ plus 10.6 mol % EtOAc: C, 34.77; H, 5.02; N, 11.27. Found: C, 34.6; H, 4.98; N, 11.6.

BIOLOGICAL TEST METHODS

The biological evaluations were carried out as described by Payne et al. (1966) with the exception that the leaves to which the southern armyworm and the Mexican bean beetle larvae were exposed were treated by spraying plants on a turntable instead of by dipping excised leaves.

Acute oral rat tests were run by intubation of corn oil suspensions using four animals per dose according to standard range-finding procedures established at Union Carbide's Bushy Run Research Center.

Fly head acetylcholinesterase inhibition I_{50} data were determined according to the Warburg method described by Moorefield and Tefft (1958).

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Supplementary Material Available: Experimental details for carbamate compounds **14**, **15**, **20**, **24**, **26**, **27**, **37**, **45–47**, and **49**, many of the key synthesis precursors thereto, and Table V listing the physical properties and elemental analysis results for compounds **11–52** (14 pages). Ordering information is given on any current masthead page.

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