

terase inhibitors, and weak inhibition could be detected at the origin (Test 1). Treatment with an alkaline solution of 4-nitrobenzenediazonium fluoroborate (Test 2), however, indicated six "phenolic" compounds to be present. One of these had the same chromatographic and color characteristics as 1-naphthol, and others may well be polyhydroxylated naphthalenes. Strongly oxidizing conditions (potassium permanganate solution, Test 5) revealed the same six substances.

Trinitrofluorenone (TNF) (Test 3) has been found effective in locating certain types of substituted aromatic compounds on paper chromatograms (3). In this case, only a single spot, corresponding to Sevin in color and  $R_f$ , could be detected.

Several fluorescent spots and much streaking could be detected under ultraviolet light (Test 4).

Chromatography on silica plates with acetone-hexane solvent (Figure 5B) provided somewhat different results upon application of the color reagents. Although the cholinesterase inhibition test could not be successfully applied, both Sevin and 1-naphthol were shown to be present. Another substance also was present in significant amounts, and its isolation from the plate as the TNF complex will be described in another communication.

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## CARBAMATE INSECTICIDES

### Synthesis of Dithiolane Oxime Carbamate Insecticides

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The methylcarbamate of 2-oximino-1,3-dithiolane (I) is a novel, broad-spectrum insecticide. Its preparation involved a study of the reaction of ethanedithiol with cyanogen chloride to give 2-imino-1,3-dithiolane hydrochloride. Conversion of the imino hydrochloride to the oxime was accomplished in good yield using one equivalent of hydroxylamine. The oxime could also be prepared from a 2-alkylimino-1,3-dithiolane and one equivalent of hydroxylamine hydrochloride. Methyl isocyanate converted the oxime to the desired methylcarbamate. Analogous compounds in which a ring sulfur atom is replaced by an oxygen atom or in which the ring is expanded by another methylene group were also prepared.

THE insecticidally active carbamates reported until very recently were derived from either phenols (1-naphthyl methylcarbamate) or enols (1-isopropyl-3-methyl-5-pyrazolyl dimethylcarbamate). They all contain ring systems—the phenol derivatives by definition, the enolic ones possibly because the ring systems used lend stability to the *O*-carbamylated form.

Some *N*-alkylcarbamates of dicyclopentyl ketoneoxime were reported in 1959 to be toxic to animals (4). Aryl carbamates of some simple ketoximes—e.g., acetone—have been described as herbicides (9), and alkyl and aryl carbamates of a series of hydroxamic acid chlorides have been reported to be fungicides (3). These compounds were not claimed to be insecticidal.

Recently, workers at Union Carbide reported a series of methylcarbamates of oximes derived from cycloaliphatic and bicyclic ketones (7). The limited data given show these to be active against a number of insect species.

#### Dithiolane Oxime Carbamates

Work with heterocyclic oximes in these laboratories has led to a new group of carbamate insecticides. An example is 2-methylcarbamoyloxyimino-1,3-dithiolane (I) (Figure 1). Carbamate (I) and analogs in which a ring-sulfur atom is replaced by an oxygen atom—e.g., compound V (Figure 1)—have been shown in the laboratory to be broad-spectrum insecticides (7, 14). Toxicity to mice and rats has also proved to be high, however. Examples of other active compounds (7)—i.e., II, III, and IV—are also shown in Figure 1.

#### Discussion

The method of preparation of carbamate (I) and its analogs is outlined in Equations 1 to 3 (Figure 2). Details of the reaction shown to obtain 2-imino-1,3-dithiolane hydrochloride (VI) have been described (2). Although oxime (VII) was known prior to this work (12),

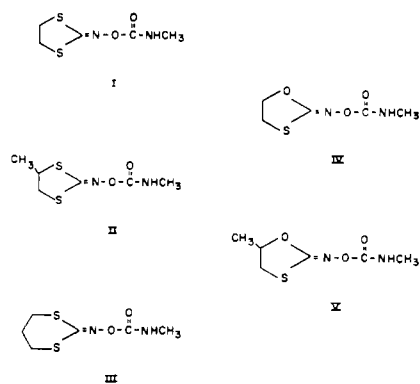


Figure 1. Oxime carbamates

the oxathiolane and dithiane analogs had not been reported. Conversion of VI to VII goes in high yield if one equivalent of hydroxylamine hydrochloride and one equivalent of a base such as sodium acetate are used. Under these conditions, the free imine ( $pK_B = 8.2$ ) (2) of VI should remain at least partially

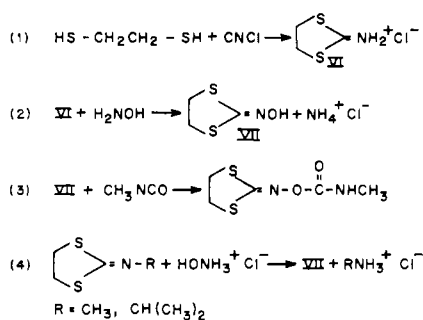


Figure 2. Syntheses

in its most reactive protonated form and a good leaving group, ammonium ion, is provided. The situation is presumed to be similar to that discussed for attack by nucleophilic reagents on ternary iminium compounds (10).

The reaction shown in Figure 2 by Equation 4 also yields oxime (VII). No additional base is required; indeed, it can have a detrimental effect on yield. In this case, acid-base equilibration effects protonation of the imine and facilitates attack by hydroxylamine. The unreported 2-alkylimino-1,3-dithiolanes used in Reaction 4 were prepared from ethylene bromide and the appropriate alkylammonium alkylthiocarbamate. Their structures were supported by elemental analyses, by the infrared spectra (strong C=N absorption at 1600  $\text{cm}^{-1}$ ), and, indeed, by conversion to oxime (VII). Reactions of a similar nature have been reported to prepare 2-dialkylimino-1,3-dithiolane salts (5, 6).

The author's few attempts to convert either ethylene trithiocarbonate or ethylene dithiocarbonate (2-keto-1,3-dithiolane) to the oxime (VII) failed, although Miolati reported success, without reporting yields, using the trithiocarbonate (12).

Conversion of the oxime (VII) to the carbamate (I) proceeds rapidly with methyl isocyanate in the presence of a little triethylamine. As with phenols, the oxime (VII) can be converted to a sodium salt and then to a carbamate by reaction first with phosgene and then with an amine.

Part of the success in converting the iminohydrochloride (VI) to the oxime (VII) could be attributed to a much faster reaction with hydroxylamine than with water. Even when boiled in water for 2 hours, VI was converted to its corresponding keto compound in only about 54% yield. The remaining material, besides ammonium chloride, was mostly unreacted VI. VI was also stable toward rearrangement. Both of these properties became less favorable with 2-imino-1,3-oxathiolane hydrochloride and with its 5-methyl analog. With

Table I. Acidity of Oximes

	Half-Neutralization Values Relative to Benzoic Acid Using Tetrabutylammonium Hydroxide in Pyridine, <sup>a</sup> Mv.	Calculated pK <sub>a</sub> in Water
Cyclohexanone oxime	Not titratable	>12
2-Oximino-5-methyl-1,3-oxathiolane	584	11.4
2-Oximino-1,3-dithiolane (VII)	486	10.7
Benzaldoxime	506	10.9
Phenol	348	9.8

<sup>a</sup> By C. A. Streuli, Central Research Laboratories, American Cyanamid Laboratories, Stamford, Conn. Streuli has applied this technique to benzoic acids and phenols (13).

aqueous hydroxylamine, both ring opening reactions and hydrolysis to the corresponding 2-keto-1,3-oxathiolanes competed with oxime formation. The result was generally lower yields of oximes with the oxathiolane series.

In addition to elemental analyses, the structures of the oximes mentioned here and of their methylcarbamoyl derivatives were supported by the infrared spectra. The C=N stretching frequency for the dithiolane oxime (VII) is at 1590  $\text{cm}^{-1}$ , for 2-oximino-1,3-oxathiolane at 1650  $\text{cm}^{-1}$ , and for their respective methylcarbamoyl derivatives (I and IV) at 1540 and 1620  $\text{cm}^{-1}$ .

The acidities of several oximes involved in this work were measured. The figures in Table I show the dithiolane and oxathiolane oximes to be more acidic than aliphatic oximes, as exemplified by cyclohexanone oxime. They approach phenol in acidity. In the case of phenyl carbamates, it has been suggested that cholinesterase inhibition and, in certain cases, insecticidal activity may bear an inverse relationship to hydrolytic stability and thus to acidity of the leaving phenol (8, 17). As expected, however, with oximecarbamates as a group, oxime acidity is but one factor which may affect insecticidal activity. For example, benzaldoxime, with a pK<sub>a</sub> equivalent to that of 2-oximino-1,3-dithiolane, gave a methylcarbamate found in these laboratories to be insecticidally inactive.

## Syntheses

**2-Isopropylimino-1,3-dithiolane.** To a mixture of 10.0 grams (0.053 mole) of ethylene bromide and 8.8 grams of finely divided potassium carbonate in 75 ml. of absolute ethanol at 35° to 40° was added 10.4 grams (0.054 mole) of isopropylammonium isopropylthiocarbamate in increments over a 1-hour

period. After heating to reflux for ca. 10 minutes, the mixture was cooled, the solids were collected, and the filtrate was diluted with ca. three volumes of water. The resulting oil recovered by ether extraction gave, on distillation, 6.5 grams (76%) of colorless 2-isopropylimino-1,3-dithiolane [b.p., 81–83°/0.3 mm.;  $n_D^{25} = 1.5671$ ;  $\lambda_{\text{max}}$  1600 (C=N)  $\text{cm}^{-1}$ ;  $\lambda_{\text{max}}^{\text{MeOH}}$  227  $\mu$  (log  $\epsilon$  3.98)].

**ANALYSES.** Calculated for C<sub>6</sub>H<sub>11</sub>NS<sub>2</sub>: C, 44.7; H, 6.9; S, 39.8; neutralization equivalent 161. Found: C, 44.4, 44.8; H, 7.3, 7.0; S, 40.4, 39.9; neutralization equivalent 164.

A 0.20-gram sample gave 0.45 gram (74%) of a picrate (m.p. 125–27°) after recrystallization from ethanol.

**2-Methylimino-1,3-dithiolane.** This material was obtained in 55% yield from methylammonium methylthiocarbamate and ethylene bromide by a procedure similar to that used for the isopropyl analog but in the absence of potassium carbonate [b.p., 61°/0.15 mm.;  $n_D^{25} = 1.6051$ ;  $\lambda_{\text{max}}$  1600 (C=N)  $\text{cm}^{-1}$ ;  $\lambda_{\text{max}}^{\text{MeOH}}$  226  $\mu$  (log  $\epsilon$  3.95)].

**ANALYSES.** Calculated for C<sub>4</sub>H<sub>7</sub>NS<sub>2</sub>: C, 36.1; H, 5.3; S, 48.1; neutralization equivalent 133. Found: C, 35.9; H, 5.2; S, 48.3; neutralization equivalent 137.

**2-Methylimino-4-methyl-1,3-dithiolane.** By adding 68.5 grams (0.50 mole) of methylammonium methylthiocarbamate to 99.7 grams (0.50 mole) of 1,2-dibromopropane in 300 ml. of ethanol at 40° over a 1-hour period and heating an additional hour at 50°, 15.9 grams (22%) of 2-methylimino-4-methyl-1,3-dithiolane was isolated on workup [b.p., 54°/0.04 mm.;  $n_D^{25} = 1.5781$ ;  $\lambda_{\text{max}}$  1590 (C=N)  $\text{cm}^{-1}$ ;  $\lambda_{\text{max}}^{\text{MeOH}}$  227  $\mu$  (log  $\epsilon$  3.95)].

**ANALYSES.** Calculated for C<sub>5</sub>H<sub>9</sub>NS<sub>2</sub>: C, 40.8; H, 6.2; S, 43.6. Found: C, 40.9; H, 6.2; S, 43.5.

Also recovered by distillation was 51% of the 1,2-dibromopropane used.

**2-Oximino-1,3-dithiolane (VII).** A mixture of 55.0 grams (0.35 mole) of 2-imino-1,3-dithiolane hydrochloride, 27.1 grams (0.39 mole) of hydroxylamine hydrochloride, and 34.8 grams (0.42 mole) of sodium acetate in 450 ml. of water was stirred at 70° to 80° for one hour. Crystallization of the oxime set in and, after the mixture had been cooled in an ice bath, the oxime was collected and water-washed. The dry oxime amounted to 41.9 grams (88%) [m.p. 126.8–28.2°; lit. (72), 126°;  $\lambda_{\text{max}}^{\text{Nujol}}$  3110 (O—H); 1590 (C=N); 950 (N—O)  $\text{cm}^{-1}$ ;  $\lambda_{\text{max}}^{\text{MeOH}}$  235  $\mu$  (log  $\epsilon$  3.88)].

A mixture of 0.207 gram (1.3 mmoles) of 2-isopropylimino-1,3-dithiolane and 0.101 gram (1.5 mmoles) of hydroxylamine hydrochloride in ca. 4 ml. of 3:1 water-ethanol was heated on a steam bath about 2 hours with partial solvent loss. Cooling the mixture afforded crystals which, after separation from solvent by decantation, water-washing, and vacuum drying amounted to 0.138 gram (80%) (m.p. 124–27°). In a comparable reaction including the addition of one equivalent of sodium acetate, the yield of oxime was 29%.

**2-Oximino-1,3-dithiane.** By the first

**Table II. Yield and Analytical Data on Oximecarbamates**

Carbamate	Recrystallized from	Yield, %	M.P., °C.	Analyses							
				Calculated				Found			
				C	H	N	S	C	H	N	S
I	Benzene-hexane or acetone-hexane	94-97	82.2-83.4	31.2	4.2		33.4	31.3	4.2		33.3
III	Benzene-hexane	68	92.8-93.8	34.9	4.9		31.1	35.4	5.1		31.2
IV	2-Propanol-hexane	58	89.6-90.8	34.1	4.6	15.9	18.2	34.4	4.9	16.1	18.4
V	Benzene-hexane	92-95	96.6-97.6	38.1	4.8	14.9	17.0	38.0	5.3	14.8	16.9

<sup>a</sup> Analytical sample.

procedure used to make 2-oximino-1,3-dithiolane, 18.0 grams of 2-imino-1,3-dithiane hydrochloride was converted to 11.6 grams of crude 2-oximino-1,3-dithiane isolated by benzene-ether extraction. Recrystallization from benzene-hexane (4:1) gave 6.9 grams of oxime (m.p., 92.4-94.8°). Another 2.0 grams were recovered by chromatographing the residue from the mother liquor on deactivated alumina and eluting with benzene-ether mixtures—total 8.9 grams (56%). A second recrystallization gave leaflets [m.p. 94.0-95.0°;  $\lambda_{\max}^{\text{Nujol}}$  1570 (C=N)  $\text{cm}^{-1}$ ;  $\lambda_{\max}^{\text{MeOH}}$  245  $\mu\text{m}$  ( $\log \epsilon$  3.50)].

ANALYSES. Calculated for  $\text{C}_4\text{H}_7\text{NO}_2\text{S}_2$ : C, 32.2; H, 4.7; N, 9.4; S, 43.0. Found: C, 32.1; H, 4.9; N, 9.3; S, 42.8.

**2-Oximino-1,3-oxathiolane.** To 19.0 grams (0.14 mole) of 2-imino-1,3-oxathiolane hydrochloride and 10.4 grams (0.15 mole) of hydroxylamine hydrochloride in 75 ml. of water were added 12.3 grams (0.15 mole) of sodium acetate in several portions over 2 hours. After 24 hours, 12.5 grams of sodium bicarbonate were added slowly. The mixture was filtered, diluted with an equal volume of saturated salt solution, and continuously ether-extracted. The semi-solid resulting from evaporation of the ether was extracted several times with hot benzene. Dilution of the benzene mixture with hexane gave several crystalline fractions which were combined. Recrystallization again from benzene plus a little hexane afforded 5.2 grams (32%) of 2-oximino-1,3-oxathiane (m.p., 111-116°). Material recrystallized further from benzene-hexane gave m.p. 116.4-17.2°;  $\lambda_{\max}^{\text{Nujol}}$  3250 (O-H), 1650 (C=N)  $\text{cm}^{-1}$ ;  $\lambda_{\max}^{\text{MeOH}}$  214  $\mu\text{m}$  ( $\log \epsilon$  3.82).

ANALYSES. Calculated for  $\text{C}_3\text{H}_5\text{NO}_2\text{S}_2$ : C, 30.2; H, 4.2; N, 11.8; S, 26.9. Found: C, 30.3; H, 4.1; N, 11.9; S, 27.0.

**2-Oximino-5-methyl-1,3-oxathiolane.** The procedure, starting with

2-imino-5-methyl-1,3-oxathiolane hydrochloride, was similar to that used for preparing 2-oximino-1,3-oxathiolane. Recrystallization of crude material, obtained in 25 to 40% yields, from 1:1 benzene-ether followed by vacuum sublimation gave oxime (m.p., 94.0-95.2°).

ANALYSES. Calculated for  $\text{C}_4\text{H}_7\text{NO}_2\text{S}_2$ : C, 36.1; H, 5.3; N, 10.5; S, 24.1. Found: C, 36.3; H, 5.5; N, 10.4; S, 24.2.

The use of methanol in place of water as solvent in this preparation did not improve yield.

**Methylcarbamoyl Derivatives of Oximes.** GENERAL PROCEDURE. To a 10 to 20% solution of the oxime in acetone containing about 0.1% triethylamine was added dropwise one equivalent of methyl isocyanate over a period of minutes to hours, depending upon run size. The mixture was generally stirred overnight at room temperature. The solid product remaining after evaporation of acetone was recrystallized from a suitable solvent. Pertinent data are included in Table II.

**2-Methylcarbamoyloxyimino-4-methyl-1,3-dithiolane (II).** By the second procedure used to make 2-oximino-1,3-dithiolane, 10.0 grams of 2-methylimino-4-methyl-1,3-dithiolane were converted to 9.1 grams (90%) of 2-oximino-4-methyl-1,3-dithiolane isolated by ether extraction as a yellow oil. Chromatography on silicic acid showed the material to be homogeneous and 9.1 grams were converted directly to the methylcarbamoyl derivative with methyl isocyanate. Molecular distillation at 100-10°/1-5 microns afforded 8.6 grams (68% of the oxime) of product ( $n_D^{25}$  1.5826 to 1.5853), with some decomposition near the end of distillation. A middle fraction ( $n_D^{25}$  = 1.5843) was analyzed.

ANALYSES. Calculated for  $\text{C}_6\text{H}_{10}\text{N}_2\text{O}_2\text{S}_2$ : C, 34.9; H, 4.9; N, 13.6; S, 31.1. Found: C, 34.9; H, 5.2; N, 13.8; S, 31.0.

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