# Pesticidal Activity of $\alpha,\alpha$-Bis(alkylthio)oxime Carbamates

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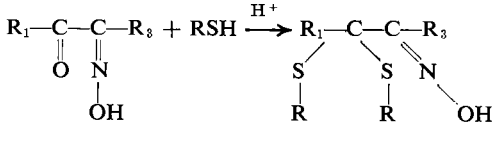
The insecticidal, miticidal, nematicidal, and anticholinesterase activities of a series of $\alpha,\alpha$-bis(alkylthio)oxime carbamates were investigated. Structure–activity relationships between the various biological groups were often nonparallel. Although several compounds displayed high biological activity in one or more of the screens, 2-methyl-1,3-dithiolane-2-carboxaldehyde *O*-(methylcarbamoyl)oxime demonstrated the best broad spectrum activity.

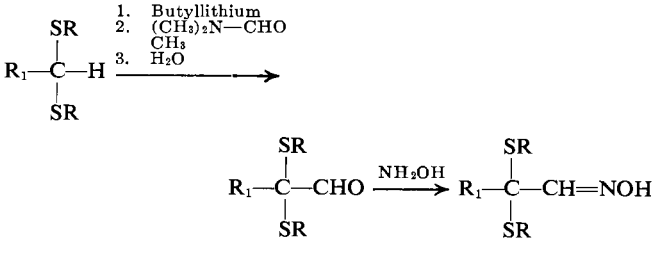
We have been involved in the synthesis and pesticidal testing of a series of $\alpha,\alpha$-bis(alkylthio)oxime carbamates in this laboratory. Fridinger *et al.* (1970, 1971) have also reported on the synthesis and pesticidal activity of a series of $\alpha$-mercaptal carbamoyloximes. Although we are reporting on some of the same compounds disclosed by them, the main thrust of their work concentrated on the cyclic compounds. Other workers (Fukuto *et al.*, 1969; Payne *et al.*, 1966; Weiden *et al.*, 1965) have reported on the pesticidal activity of substituted oxime carbamates and have attempted to correlate structure with biological activity. These workers also concluded that, like phenyl carbamates, oxime carbamates exert their pesticidal action by inhibition of acetylcholinesterase. Our work attempts to correlate chemical structure with degree of cholinesterase inhibition and with insecticidal, miticidal, and nematicidal effectiveness.

## SYNTHESIS OF COMPOUNDS

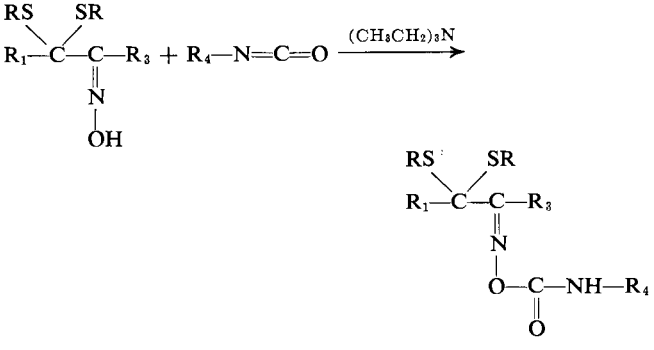
**Oximes.** METHOD 1. Treatment of an $\alpha$-keto oxime with one equivalent of the dithiol or two equivalents of alkyl thiol in the presence of an acid catalyst (Posner, 1899).



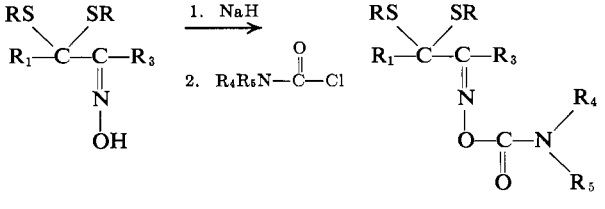
METHOD 2. Treatment of an aldehyde thioketal with butyllithium, followed by treatment with dimethylformamide, water, and then hydroxylamine (Corey and Seebach, 1965).



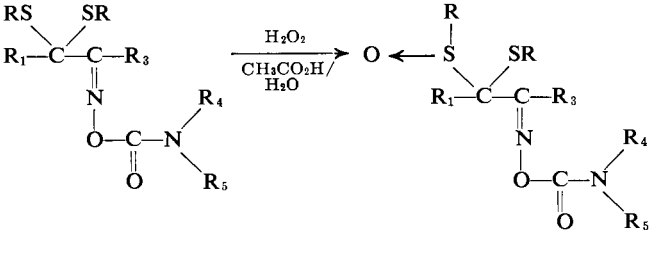
**Carbamates.** METHOD A. Treatment of an $\alpha,\alpha$-bis(alkylthio)oxime with alkyl isocyanate in the presence of triethylamine.



METHOD B. Treatment of an $\alpha,\alpha$-bis(alkylthio)oxime with sodium hydride followed by treatment with a dialkyl carbamoyl chloride.



**Sulfoxides.** Treatment of the $\alpha,\alpha$-bis(alkylthio)oxime carbamate in aqueous acetic acid solution with hydrogen peroxide.



The compounds synthesized are shown in Table I.

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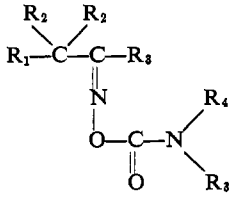
**Table I.** α,α-Bis(alkylthio)oxime Carbamates



| Compd no. | $R_1$ | $R_2$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Methods | mp, °C |
|---|---|---|---|---|---|---|---|---|
| I | $CH_3$ | $SCH_3$ | $SCH_3$ | $CH_3$ | $CH_3$ | H | 1,A | Oil |
| II | $CH_3$ | $SCH_3$ | $SCH_3$ | $C_6H_5$ | $CH_3$ | H | 1,A | 145–146 |
| III | $CH_3$ | $SCH_3$ | $SCH_3$ | H | $CH_3$ | H | 1,A | 64–66 |
| IV | $CH_3$ | $SCH_2$–$CH_2S$ | | $CH_3$ | $CH_3$ | H | 1,A | 107.5–108.5 |
| V | $CH_3$ | $SCH_2$–$CH_2S$ | | H | $CH_3$ | H | 1,A | 117–119 |
| VI | $C_2H_5$ | $SCH_3$ | $SCH_3$ | H | $CH_3$ | H | 2,A | 74–76 |
| VII | $n$-$C_3H_7$ | $SCH_3$ | $SCH_3$ | H | $CH_3$ | H | 2,A | Oil |
| VIII | $CH_3$ | $SCH_2$–$CH_2$–$CH_2S$ | | H | $CH_3$ | H | 2,A | 99–102 |
| IX | $C_2H_5$ | $SCH_2$–$CH_2$–$CH_2S$ | | H | $CH_3$ | H | 2,A | 58–68 |
| X | $n$-$C_3H_7$ | $SCH_2$–$CH_2$–$CH_2S$ | | H | $CH_3$ | H | 2,A | 48–50 |
| XI | $CH_3$ | $SC_2H_5$ | $SC_2H_5$ | H | $CH_3$ | H | 2,A | 65–67 |
| XII | $CH_3$ | S-$n$-$C_3H_7$ | S-$n$-$C_3H_7$ | H | $CH_3$ | H | 2,A | 71–72.5 |
| XIII | $CH_3$ | $SCH_3$ | $SCH_3$ | H | $C_2H_5$ | H | 1,A | 73–75 |
| XIV | $CH_3$ | $SCH_3$ | $SCH_3$ | H | $n$-$C_3H_7$ | H | 1,A | 52–54 |
| XV | $CH_3$ | $SCH_3$ | $SCH_3$ | H | $CH_3$ | $CH_3$ | 1,B | Oil |
| XVI | $CH_3$ | $SCH_3$ | $SCH_3$ | H | $C_2H_5$ | $C_2H_5$ | 1,B | Oil |
| XVII | $CH_3$ | $SCH(CH_3)$–$CH_2S$ | | H | $CH_3$ | H | 1,A | 80–82 |
| XVIII | $CH_3$ | $SCH_2$—$CH_2$–$CH_2S$ ↓ O | | H | $CH_3$ | H | 2,A + [0] | 114–115 |
| XIX | $CH_3$ | $SC_2H_5$ | $SC_2H_5$ | $CH_3$ | $CH_3$ | H | 1,A | Oil |

**Table II. Synopsis of Pesticidal Assays**

| Pest | Stage[a] | Principal mode of contact | Method of application | Rate |
|---|---|---|---|---|
| Boll weevil | A | Feeding | Treated 10% sugar solution | 50 ppm |
| House cricket | N | Residual contact | Glass residue | 750 μg/ft² |
| Housefly | A | Feeding | Treated 10% sugar solution | 25 ppm |
| Mexican bean beetle | L | Residual contact-feeding | Leaf[b] dip | 50 ppm |
| Southern armyworm | L | Residual contact-feeding | Leaf[b] spray | 1000 ppm |
| Yellow fever mosquito | L | Contact | Treated larval water | 1 ppm |
| Two-spotted spider mite | N,A | Contact | Spray[b,c] | 100 ppm |
| Two-spotted spider mite | N,A | Feeding | Systemic[b,d] | 50 ppm |
| Southern root-knot nematode | L,A | Contact | Soil incorporation | 16#/acre |

[a] Stage: A = adult, N = nymph, L = larva. [b] Lima bean, *Phaseolus limensis* var. Henderson bush. [c] Plant infested 24 hr prior to treatment. [d] Plant infested 24 hr posttreatment.

## BIOLOGICAL TESTS

**Cholinesterase Assays.** The molar concentration for 50% inhibition of bovine erythrocyte acetylcholinesterase (Nutritional Biochemicals Corp.) was determined by a procedure similar to that described by Robbins *et al.* (1958). The $I_{50}$ values were obtained from duplicate assays by interpolation from an eye-fitted line of the semilog plot of the inhibitor concentration *vs.* percentage inhibition.

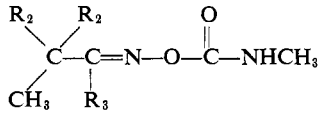
**Insecticide, Miticide, and Nematicide Assays.** Compounds were dissolved in acetone and diluted with "wet water" [0.0132% v/v water solution of Tween 20 (Atlas Chemical Industries, Inc.)] for use in all tests except the residual contact house cricket test. In this latter test acetone solutions of the chemical were placed on glass surfaces and the acetone was allowed to evaporate. The 1000-ppm "wet water" suspensions were used to prepare the desired concentrations for bioassay against the various pests.

A synopsis of the test procedures is outlined in Table II. The test organisms, randomly selected from a large population of mixed sexes, were encaged in proximity to the treated environments for the entire holding period (see Results). No additional food was offered to the test species, with the exception of the mosquitoes, which received the addition of dried yeast to the larval water 24 hr posttreatment. The percentage of dead (including moribund) individuals was recorded after specified time intervals with the exception of the root-knot nematodes. In the case of the nematicide test, tomato transplants set into the treated nematode-infested soil were excised and the roots examined for the degree of galling. Where applicable, results of replicated experiments are presented as averages of all replicates, corrected by use of Abbott's formula (Finney, 1964).

## RESULTS AND DISCUSSION

Changing $R_3$ from hydrogen to methyl decreases pesticidal activity as seen when the activities of Compounds III *vs.* I, V *vs.* IV, and XI *vs.* XIX are compared (Table III). Payne *et al.* (1966) and Fridinger *et al.* (1970) have made similar observations when comparing the activities of aldoximes *vs.* ketoximes. Even though compound II failed to demonstrate activity against the test organisms at rates higher than indicated, it is a comparatively good inhibitor of AChE. Al-

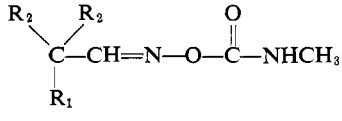
**Table III. Bioactivity of Ketoxime and Aldoxime Carbamates**



| Compd no. | $R_2$ | $R_2$ | $R_3$ | Percent mortality 2 days posttreatment BW | HC | HF | MBB | SAW | YFM | Mi-C | Mi-S[a,b] | R-K index[c] RKN | Molar $I_{50} \times 10^{-6}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | $SCH_3$ | $SCH_3$ | $CH_3$ | <80 | 0 | 0 | | 0 | 0 | 0 | <10 | 4 | |
| III | $SCH_3$ | $SCH_3$ | H | 100 | 95 | 100 | 87 | 0 | 100 | 100 | 98 | 2 | 32 |
| II | $SCH_3$ | $SCH_3$ | $C_6H_5$ | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 5 | 2.8 |
| IV | $SCH_2$–$CH_2S$ | | $CH_3$ | <10 | 0 | 60 | | 0 | 0 | 0 | <65 | 5 | 17 |
| V | $SCH_2$–$CH_2S$ | | H | 100 | 100 | 100 | 100 | 20 | 100 | 50 | 95 | 2 | 1.0 |
| XIX | $SC_2H_5$ | $SC_2H_5$ | $CH_3$ | 0 | 0 | 0 | | 0 | 0 | 0 | <37 | 5 | 43 |
| XI | $SC_2H_5$ | $SC_2H_5$ | H | 98 | <70 | 54 | 0 | 0 | 0 | 24 | ~50 | 2 | 35 |

[a] Scientific names: BW = boll weevil, *Anthonomus grandis;* HF = housefly, *Musca domestica;* HC = house cricket, *Acheta domesticus;* MBB = Mexican bean beetle, *Epilachna varivestis;* SAW = Southern armyworm, *Prodenia eridania;* YFM = yellow-fever mosquito, *Aedes aegyptii;* Mi-C = two-spotted spider mite, *Tetranychus urticae,* contact test; Mi-S = mite systemic test; RKN = Southern root-knot nematode, *Meloidogyne incognita.* [b] 5-Day mortality. [c] 1 = no galling; 5 = severe galling.

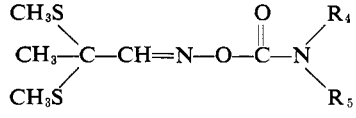
**Table IV. Bioactivity of 2 Position Alkyl Substituents of 2,2-Bis(methylthio)- and *m*-Dithiane *O*-(Methylcarbamoyl)oximes**



| Compd no. | $R_2$ | $R_2$ | $R_2$ | Percent mortality 2 days posttreatment BW | HC | HF | MBB | SAW | YFM | Mi-C | Mi-S[a] | R-K index RKN | Molar $I_{50} \times 10^{-6}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| III | $CH_3$ | $SCH_3$ | $SCH_3$ | 100 | 95 | 100 | 87 | 0 | 100 | 100 | 98 | 2 | 35 |
| VI | $C_2H_5$ | $SCH_3$ | $SCH_3$ | 80 | 58 | 5 | 90 | 0 | 0 | 22 | 80 | 4 | 2.6 |
| VII | *n*-$C_3H_7$ | $SCH_3$ | $SCH_3$ | 0 | 0 | 0 | | 0 | 0 | 0 | <50 | 4 | |
| VIII | $CH_3$ | $SCH_2$–$CH_2$–$CH_2S$ | | 70 | 0 | 0 | 0 | 0 | 100 | 70 | 100 | 1.5 | 3.1 |
| IX | $C_2H_5$ | $SCH_2$–$CH_2$–$CH_2S$ | | 0 | 0 | 0 | | 0 | | 60 | ~90 | 2 | 21 |
| X | *n*-$C_3H_7$ | $SCH_2$–$CH_2$–$CH_2S$ | | <30 | 0 | <40 | | 0 | 0 | 0 | 0 | 4 | 26 |

[a] See Table III for explanation of abbreviations and footnotes.

**Table V. Bioactivity of 2,2-Bis(methylthio)propionaldehyde *O*-(Alkyl- and Dialkylcarbamoyl)oximes**



| Compd no. | $R_5$ | $R_4$ | Percent mortality 2 days posttreatment BW | HC | HF | MBB | SAW | YFM | Mi-C | Mi-S[a] | R-K Index RKN | Molar $I_{50} \times 10^{-6}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| III | H | $CH_3$ | 100 | 95 | 100 | 87 | 0 | 100 | 100 | 98 | 2 | 35 |
| XIII | H | $C_2H_5$ | <60 | 40 | 60 | | 0 | <50 | 0 | | 2 | 280 |
| XIV | H | *n*-$C_3H_7$ | 0 | 0 | 0 | | 0 | 80 | 0 | 0 | 2 | 20 |
| XV | $CH_3$ | $CH_3$ | <50 | 0 | 0 | | 0 | 0 | 0 | 0 | 2 | |
| XVI | $C_2H_5$ | $C_2H_5$ | 0 | <40 | 0 | | 0 | 0 | 0 | 0 | 2 | |

[a] See Table III for explanation of abbreviations and footnotes.

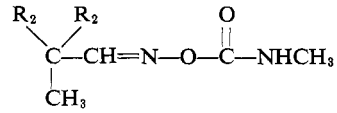
though low pesticidal activity was shown for compounds I, IV, and XIX at the rates indicated, they were more active at higher treatment levels.

Lengthening the alkyl chain $R_1$ (Table IV) reduces overall pesticidal activity. With the cyclic compounds, the anti-AChE activity is also reduced. Interestingly, however, there is a significant negative correlation between anti-AChE activity and pesticidal activity when compounds III and VI are compared.

Despite the obvious chemical similarities between the cyclic and acyclic compounds listed in Table IV, the pesticidal activities are not parallel, *i.e.*, the acyclic compounds have considerably higher insecticidal activity, while the cyclic compounds have the higher nematicidal activity. The miticidal activity is nearly the same for both.

Both insecticidal and miticidal effectiveness are markedly reduced when the *N*-methylcarbamate is converted to its *N,N*-dimethyl or *N,N*-diethyl analog, or to its *N*-ethyl or *N*-*n*-propyl homolog (Table V). This is in agreement with previous reports regarding the insecticidal and miticidal effectiveness of both phenyl and oxime carbamates (Metcalf and Fukuto, 1965; Payne *et al.*, 1966). Perhaps the greatest

**Table VI. Bioactivity of Various 2,2-Bis(alkylthio) *O*-(Methylcarbamoyl)oximes**



| Compd no. | $R_2$ | $R_2$ | Percent mortality 2 days posttreatment | | | | | | | | R-K index[b] RKN | Molar $I_{50} \times 10^{-6}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | BW | HC | HF | MBB | SAW | YFM | Mi-C | Mi-S[a] | | |
| III | $SCH_3$ | $SCH_3$ | 100 | 95 | 100 | 87 | 0 | 100 | 100 | 98 | 2 | 35 |
| XI | $SC_2H_5$ | $SC_2H_5$ | 98 | <70 | 54 | 0 | 0 | 0 | 24 | ~50 | 2.2 | 8.9 |
| XII | S-*n*-$C_3H_7$ | S-*n*-$C_3H_7$ | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 4 | 12 |
| XVIII | O ← $SCH_2$–$CH_2$–$CH_2S$ | | 90 | 0 | 0 | | 0 | 100 | 60 | 100 | 2 | 1.6 |
| VIII | $SCH_2$–$CH_2$–$CH_2S$ | | 70 | 0 | 0 | <10 | 0 | 100 | 70 | 100 | 1.5 | 3.1 |
| XVII | $SCH(CH_3)$–$CH_2S$ | | 100 | 30 | 10 | | 0 | 100 | 70 | 70 | 1.0 | 0.95 |
| V | $SCH_2$–$CH_2S$ | | 100 | 100 | 100 | 100 | 20 | 100 | 50 | 95 | 2 | 1.0 |

[a] See Table III for explanation of abbreviations and footnotes.

significance of these findings is the fact that the nematicidal activity of these compounds was not markedly impaired by these alterations.

Increasing the length of the *S*-alkyl substituent $R_2$ from methyl to ethyl or *n*-propyl was ineffective in increasing pesticidal efficacy even though AChE inhibition was increased (Table VI). 2,2-Bis(methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime (compound III) has good insecticidal and miticidal activity. Substitution at the 2 position with the cyclic 1,3-dithiane function gives compound VIII, which has excellent nematicidal and miticidal activity. However, substitution at the 2 position with the cyclic dithiolane function results in the highly active insecticidal, miticidal, and nematicidal compound V.

Bull and coworkers (1967) reported that although *in vitro* conversion of aldicarb to its sulfoxide markedly enhanced anti-AChE activity (22×), insecticidal activity was not greatly altered. However, sulfoxidation of Compound VIII (Compound XVIII, Table VI) increased anti-AChE activity only moderately (2×) and did not affect pesticidal activity. This activity more closely parallels the results of Payne *et al.* (1966) concerning their work with aldicarb and aldicarb sulfoxide.

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