

Insecticidal Thiophan-3-one *O*-(Methylcarbamoyl)oximes

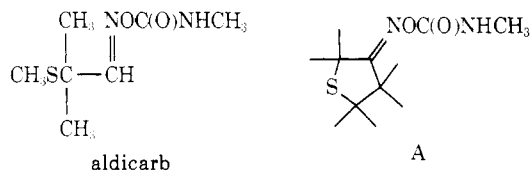
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Nine of the subject compounds have been synthesized and evaluated for their insecticidal properties. These materials are characterized by good activity to the housefly, a lower order of effectiveness against the bean aphid, and very little toxicity to the Mexican bean beetle and the southern armyworm. Only the cyclic aldicarb an-

alog, 2,2-dimethyl-3-thiophanone *O*-(methylcarbamoyl)oxime, elicits a miticidal response; this material is also toxic to the aphid and housefly and shows a high order of systemic activity. In general, these cyclic oxime carbamates fall between their open-chain aldoxime and ketoxime analogs with regard to insect toxicity.

The initial disclosure of the insecticidal properties of the oxime carbamates involved carbamoyloximes derived from a series of alicyclic ketones (Kilsheimer and Manning, 1962). This early work led ultimately to the discovery of aldicarb announced in 1965 (Weiden *et al.*) and detailed in 1966 (Payne *et al.*). Subsequently, carbamoyloximes derived from saturated sulfur-containing ketones have been described, *e.g.*, 1,3-dithiolan-2-ones and 1,3-dithian-2-ones (Addor, 1965a), 1,3-oxathiolan-2-ones (Addor, 1965a), and thiophan-2-ones (Addor, 1965b). Carbamoyl derivatives of hydroximates and thiolhydroximates have been widely investigated (Felton, 1968, and references therein). Carbamoyloximes derived from variously substituted benzaldehyde and alkyl aryl ketones have also been reported (Fukuto *et al.*, 1969; Jones *et al.*, 1972).

The appearance of a patent (Diamond Shamrock, 1971) describing a series of oxime carbamates derived from 3-thiophanones has prompted the publication of our results with this class of compounds. These materials, exemplified by A, may be considered as cyclic analogs of aldicarb.



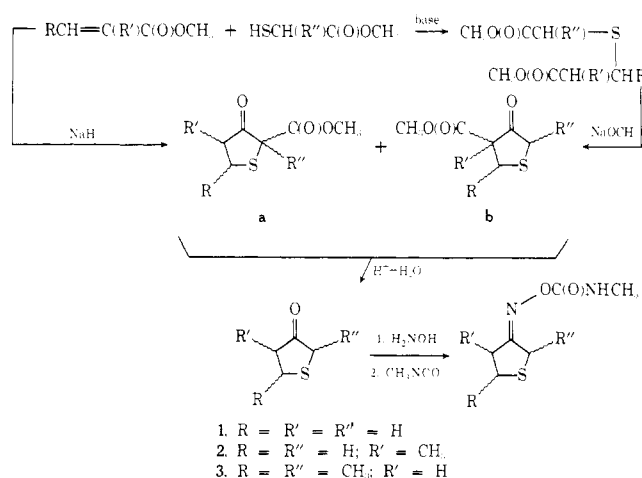
The compounds prepared in this study together with their physical and biological properties are presented in Table I; their analytical data are in Table II.

## CHEMISTRY

The relatively simple and direct syntheses employed for the compounds described in this report are illustrated by the following equations. For compounds bearing single substituents on ring carbons a Michael-type addition reaction with a simultaneous or subsequent Dieckmann cyclization was employed (Scheme I).

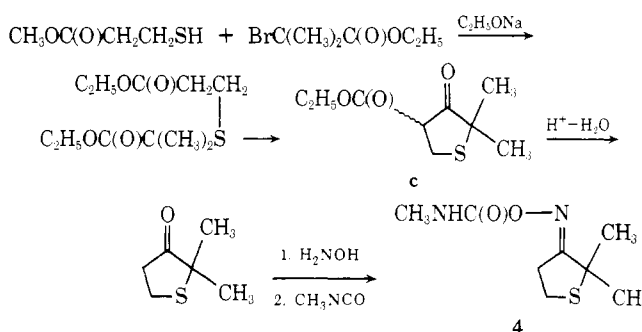
When the desired product possessed geminate-disubstituted ring carbons, as with 4 [4 was prepared in two portions, 4a and 4b, which were shown to be different syn-anti isomer mixtures (see Experimental Section)], a Williamson-type ether synthesis followed by cyclization was the most useful approach (Scheme II), while, with the furan derivative 5, an ester of 2,2-dimethylglycolic acid was caused to react with methyl acrylate using sodium hydride in tetrahydrofuran (Gianturca *et al.*, 1964). The resulting adduct cyclized simultaneously to the keto ester analogous to c in Scheme II. Sequential decarboxylation,

## Scheme I



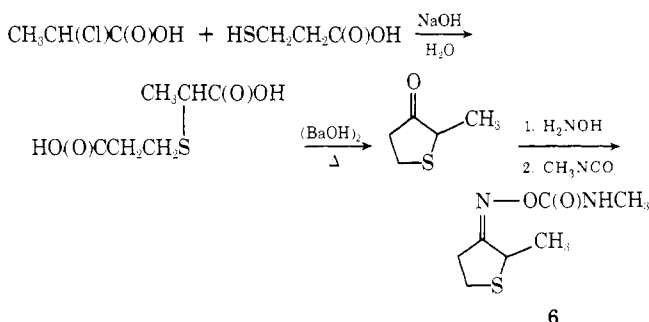
oximation, and methylcarbamoylation as shown in Scheme II gave 5.

## Scheme II



Scheme III outlines the route used to prepare the 2-methylthiophan-3-one required for 6.

## Scheme III



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**Table I. Biological and Physical Properties of Compounds 1-9 and Biological Properties of Certain Homologs and Analogs**

| Compd no. | R =                                 | X =             | Mp, °C    | Yield, % | Insect toxicity (LD <sub>50</sub> , ppm) <sup>a</sup> |                |                    |                     |          | AChE I <sub>50</sub> × 10 <sup>6</sup> |
|-----------|-------------------------------------|-----------------|-----------|----------|-------------------------------------------------------|----------------|--------------------|---------------------|----------|----------------------------------------|
|           |                                     |                 |           |          | Bean aphid                                            | 2-Spotted mite | Southern army-worm | Mexican bean beetle | Housefly |                                        |
| 1         | H                                   | S               | Res.      | 37       | 55                                                    | ~500           | ~500               | >100                | 8        |                                        |
| 2         | 4-CH <sub>3</sub>                   | S               | 67-70     | 32       | 30                                                    | 250            | 400                | ~100                | 4        | 40                                     |
| 3         | 2,5-(CH <sub>3</sub> ) <sub>2</sub> | S               | 47-50     | 26       | 12                                                    | >500           | >500               | >100                | <8       | 40                                     |
| 4a        | 2,2-(CH <sub>3</sub> ) <sub>2</sub> | S               | 67-72     | 48       | 25 (1)                                                | 15 (2)         | ~500               | ~100                | 8        | 45                                     |
| 4b        | 2,2-(CH <sub>3</sub> ) <sub>2</sub> | S               | 76-80     | 82       | 15                                                    | 32             | >500               | 90                  | 6        | 90                                     |
| 5         | 2,2-(CH <sub>3</sub> ) <sub>2</sub> | O               | 83-85     | 54       | >100                                                  | ~500           | ~500               | ~100                | 40       | 160                                    |
| 6         | 2-CH <sub>3</sub>                   | S               | Res.      | 75       | 25                                                    | >500           | >500               | >100                | 3        | 300                                    |
| 7         | 2-C <sub>2</sub> H <sub>5</sub>     | S               | 84-85     | 50       | 48                                                    | >500           | >500               | >100                | 50       | 100                                    |
| 8         | 2,2-(CH <sub>3</sub> ) <sub>2</sub> | SO              | 105-106   | 77       | 80                                                    | <30            | 250                | 50                  | 15       |                                        |
| 9         | 2,2-(CH <sub>3</sub> ) <sub>2</sub> | SO <sub>2</sub> | 131-132.5 | 86       | >100                                                  | ~500           | ~500               | >100                | 60       | 23                                     |
| 10        | H                                   | CH <sub>2</sub> |           |          | 100                                                   | ~500           | >500               | >500                | 110      | 500                                    |

| R = |                                                   | R' =            |  |
|-----|---------------------------------------------------|-----------------|--|
| 11  | CH <sub>3</sub> SCH <sub>2</sub>                  | H               |  |
| 12  | CH <sub>3</sub> SCH(CH <sub>3</sub> )             | H               |  |
| 13  | CH <sub>3</sub> SC(CH <sub>3</sub> ) <sub>2</sub> | H               |  |
| 14  | 13 (sulfoxide)                                    |                 |  |
| 15  | 13 (sulfone)                                      |                 |  |
| 16  | CH <sub>3</sub> OC(CH <sub>3</sub> ) <sub>2</sub> | H               |  |
| 17  | CH <sub>3</sub> SCH <sub>2</sub>                  | CH <sub>3</sub> |  |
| 18  | CH <sub>3</sub> SCH(CH <sub>3</sub> )             | CH <sub>3</sub> |  |
| 19  | CH <sub>3</sub> OCH(CH <sub>3</sub> )             | CH <sub>3</sub> |  |
| 20  | CH <sub>3</sub> SC(CH <sub>3</sub> ) <sub>2</sub> | CH <sub>3</sub> |  |
| 21  | CH <sub>3</sub> OC(CH <sub>3</sub> ) <sub>2</sub> | CH <sub>3</sub> |  |

<sup>a</sup> Systemic LD<sub>50</sub> in parentheses.**Table II. Elemental Analyses of Compounds 1-9 (Table I)**

| Compd no. | Carbon |       | Hydrogen |       | Nitrogen |       |
|-----------|--------|-------|----------|-------|----------|-------|
|           | Calcd  | Found | Calcd    | Found | Calcd    | Found |
| 1         | 40.83  | 41.38 | 5.99     | 5.79  | 15.91    | 16.09 |
| 2         | 44.68  | 44.38 | 6.43     | 6.54  | 14.88    | 14.81 |
| 3         | 47.52  | 47.01 | 6.98     | 6.70  | 13.86    | 13.95 |
| 4a        | 47.52  | 47.29 | 6.98     | 7.20  |          |       |
| 4b        | 47.52  | 47.00 | 6.98     | 7.17  |          |       |
| 5         | 51.60  | 51.31 | 7.58     | 7.30  | 15.04    | 15.37 |
| 6         | 44.68  | 43.90 | 6.43     | 6.17  | 14.88    | 15.00 |
| 7         | 47.52  | 47.56 | 6.98     | 7.11  |          |       |
| 8         | 44.03  | 43.90 | 6.47     | 6.72  | 12.84    | 12.75 |
| 9         | 41.02  | 40.96 | 6.03     | 5.98  | 12.96    | 11.88 |

In the case of the 2-ethyl homolog 7 of 6 a combination of the procedures outlined in Schemes II and III was employed; the dicarboxylic acid of Scheme III was esterified with methanol-hydrochloric acid and the resulting diester was cyclized and subsequently treated as shown in Scheme II.

The thiophan-3-one ring system is well known. Buiter *et al.* (1964) have described the preparation of the parent compound and its 4,4-dimethyl derivative by pyrolysis of the corresponding 3-thiaadipic acid in the presence of barium hydroxide after the method of Acheson *et al.* (1961). The general procedure described in Scheme II has been used by Berezhovskii *et al.* (1963) to prepare certain 4-aminothiophan-3-one derivatives.

As shown in Scheme I, two isomeric  $\beta$ -keto esters are possible in the cyclization of 3-thiaadipic acid diethyl ester. Woodward and Eastman (1946) and, later, Kolchin and Vul'fon (1962) showed that these isomers may be formed relatively selectively by temperature control, (a) being favored by a reaction temperature of 18-20° and (b) by a temperature of 80-120°. In the present work no effort was made to control the isomer distribution in the cycli-

zation step since both give rise to the same ketone in the subsequent decarboxylation reaction.

The structures of the compounds shown in Table I are supported by infrared and nmr studies in addition to the reported elemental analyses. In some cases syn-anti oxime mixtures were encountered (see Experimental Section).

#### BIOLOGICAL ACTIVITY

The overall insecticidal-miticidal properties of the present series (Table I) are generally typical of carbamoyloximes—moderate to good activity against aphids and flies; marginal activity at best against the southern armyworm; moderate activity against the Mexican bean beetle; and a wide range in miticidal activity. No significant nematocidal effect was observed, although primary screening results suggested slight activity for several of these compounds.

Substituting a sulfur atom for the third methylene group of cyclopentanone *O*-(methylcarbamoyl)oxime (10) imparts significant toxicity to the housefly (compare 1 with 10). Introduction of a single methyl at the 2 (6) or the 4 (2) position has little overall effect on insecticidal activity. The effect of a second methyl substituent depends upon its position. Location of both methyl groups at the 2 position provides the only highly miticidal compound (4) in the series but there is little effect on insect toxicity in comparison to the 2-methyl compound 6. Note that the addition of a second methyl at the analogous position in the aldicarb series (compare 12 and 13) markedly increases the aphid as well as the miticidal effectiveness. Except for a possible increase in aphid toxicity, the 2,5-dimethyl compound 3 appears to be no more active than its monomethyl homolog 6. Substitution of an ethyl group at the 2 position (compound 7) markedly reduces the aphid and housefly toxicity relative to 6. As with the aldicarb series (13, 14, and 15), the sulfoxide 8 is roughly comparable to its parent 4 in overall activity and the sulfone 9 demonstrates a diminished effectiveness.

The diminished activity of 5 relative to 4 is much more dramatic than, but consistent with, that observed with the acyclic sulfur-oxygen pairs: 13 and 16, and 18 and 19.

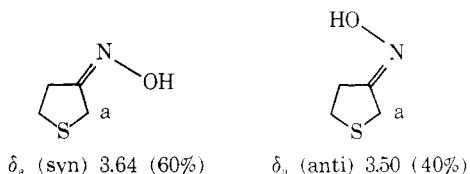
The insecticidal properties of 4, the optimum compound in the cyclic series, are clearly diminished in comparison with the activity of aldicarb 13. The cyclic compounds 1-9 appear to fall between their acyclic aldoxime (11-16) and ketoxime (17-21) analogs in insect toxicity and in their ability to inhibit housefly acetylcholinesterase (AChE,  $I_{50}$ ). Substitution of a methyl (ketoximes) or methylene groups (cyclic compounds) for the aldehydic proton (aldoximes) would increase steric hindrance at, and diminish electron withdrawal from, the oximino carbon. In terms of acetylcholinesterase inhibition, the latter effect would diminish the effectiveness of the carbamoyloxime as a carbamylating agent by a reduction of the "leaving-group" potential of the oximate anion and the former may restrict the formation of the transition state which leads to transcarbamylation. These considerations are consistent with the observed order of activity of these three classes of compounds as exemplified in this study.

As shown in Table I, compound 4 exhibits systemic properties similar to those of aldicarb. It is surprising that, as a group, these cyclic compounds lack significant nematocidal activity. In contrast, the acyclic aldicarb is an effective nematicide.

## EXPERIMENTAL SECTION

All products and intermediates have been characterized by nmr and ir spectral studies; in a few cases these data are detailed. The melting points are uncorrected.

**Thiophan-3-one Oxime.** To 9.1 g (0.13 mol) of hydroxylamine hydrochloride in 75 ml of ethanol was added a solution of 3.0 g (0.13 g-atom) of sodium metal in 510 ml of ethanol. After removal of sodium chloride by filtration the hydroxylamine solution was treated with 10 g (0.096 mol) of thiophan-3-one (Woodward and Eastman, 1946) and the resulting solution was heated at 50-60° for 2 hr. After evaporation *in vacuo* the residue was dissolved in 40 ml of hot ethyl acetate, treated to the cloud-point with hexane, and cooled to give, after chilling, 8 g (71%) of product, mp 38-43° (Karrer and Kieso, 1944, lit. mp 36°). The nmr spectrum of this oxime showed the following isomeric composition.



**Thiophan-3-one *O*-(Methylcarbamoyl)oxime (1).** A solution of 8 g (0.07 mol) of the oxime from the previous reaction in 50 ml of acetone was treated with 4.8 g (0.08 mol) of methyl isocyanate and one drop of dibutyltin diacetate. After 24 hr the mixture was concentrated *in vacuo* and the resulting oil was dissolved in ether and washed with 5 × 20 ml of water. After drying over sodium sulfate the ether solution was evaporated *in vacuo* to a residue which could not be induced to solidify. There was thus obtained 4.5 g of 1 as a residual oil (Tables I and II).

**2-Methylthiophan-3-one *O*-(Methylcarbamoyl)oxime (6).** To a solution of 124 g (3.1 mol) of sodium hydroxide in 600 ml of water was added with stirring 212 g (2.0 mol) of 3-mercaptopropionic acid. This mixture was added to 217 g (2.0 mol) of 2-chloropropionic acid in 400 ml of water. The resulting solution was stirred at 50° for 1 hr and was then stirred at ambient temperature for 2.5 hr. The reaction mixture was acidified and saturated with sodium chloride after which it was extracted with 5 × 100 ml of ethyl ether. The ether solution was dried over sodium sulfate and finally distilled to give 221 g (62%) of 2-methyl-3-thiaadipic acid, bp 218-223° (1 mm).

A mixture of 100 g (0.28 mol) of the acid from the preceding reaction and 10 g of barium hydroxide was heated with stirring at 250° under a Dean-Stark trap where the water-ketone mixture was collected during pyrolysis. The distillate was extracted thoroughly with ether. The ether solution was dried over sodium sulfate and finally distilled on an 18-in. spinning band column (Nester-Faust) to give, after a small forecut, 26 g (80%) of 2-methylthiophan-3-one, bp 87-97° (40 mm).

Using a procedure analogous to that reported above for 3-thiophanone oxime, 16 g (0.14 mol) of 2-methyl-3-thiophanone gave 14 g (76%) of its oxime as a residual oil. This, upon reaction with methyl isocyanate, after the general procedure reported for 1, gave the product 6 (Tables I and II) as a residual oil whose infrared spectrum indicated the possibility of a trace of *sym*-dimethylurea being present.

**2-Ethylthiophan-3-one *O*-(Methylcarbamoyl)oxime (7).** Using a procedure analogous to that reported for 2-methyl-3-thiaadipic acid (above), 167 g (1.0 mol) of 2-bromobutyric acid and 106 g (1.0 mol) of 3-mercaptopropionic acid in a solution of 120 g (3.0 mol) of sodium hydroxide in 750 ml of water gave a residue product which was dissolved in 250 ml of dry methanol. The resulting solution was treated with 10 g of anhydrous hydrogen chloride and, after heating at reflux for 6 hr, was distilled to give 104 g (47%) of dimethyl 2-ethyl-3-thiaadipate.

Using the general procedure of Woodward and Eastman (1946), 104 g (0.48 mol) of the diester from the previous reaction gave, upon treatment with 52 g (0.96 mol) of sodium methylate in 300 ml of anhydrous ether, 55 g (61%) of 2-ethyl-2(or 4)-carbomethoxythiophan-3-one.

The  $\beta$ -keto ester from the previous reaction (55 g, 0.29 mol) was decarboxylated after the method of Woodward and Eastman (1946) to give 2-ethylthiophan-3-one, bp 73° (1 mm), in 60% yield. This was converted to the corresponding oxime, bp 100-102° (1 mm), in 29% yield using the method described above. The nmr of this oxime showed it to be about 22% anti, based on the chemical shifts of the methylene proton in the two forms ( $\delta$ (syn) 4.22;  $\delta$ (anti) 3.73; see preceding assignments for thiophan-3-one oxime). Carbamoylation in acetone using a slight excess of methyl isocyanate and no catalyst produced 7 (Tables I and II).

**4-Methylthiophan-3-one *O*-(Methylcarbamoyl)oxime (2).** Using the procedure as described for 1 and outlined in Scheme I, 20 g (0.2 mol) of methyl methacrylate and 22 g (0.2 mol) of methyl thioglycolate were brought together with 2 ml of triethylamine to give 33 g (75%) of dimethyl 2-methyl-4-thiaadipate, bp 115-117° (1 mm).

*Anal.* Calcd for  $C_8H_{14}O_4S$ : C, 46.60; H, 6.84. Found: C, 46.82; H, 7.19.

This diester (33 g, 0.174 mol) was allowed to react with 19 g (0.35 mol) of sodium methoxide in 250 ml of anhydrous ether to produce 20 g (66%) of 4-methyl-2(or 4)-carbomethoxythiophan-3-one, bp 115-117° (1 mm). Preparation of this keto ester directly from the one-step addition-cyclization of the reactants in the previous step gave a 55% yield (bp 99-101° (1 mm)).

The 4-methylthiophan-3-one (bp 73-74° (10 mm)) was produced in 44% yield by the hydrolysis of 19 g (0.109 mol) of the keto ester with 100 ml of 10% sulfuric acid.

This ketone (5.5 g, 0.047 mol) was converted to the oxime in 39% yield (mp 55-57°) by treatment with 7 g (0.1 mol) of hydroxylamine hydrochloride and 7.8 g (0.1 mol) of sodium acetate in a mixture of 50 ml of ethanol and 55 ml of water. Using hydroxylamine in methanol (from 10 g (0.15 mol) of hydroxylamine hydrochloride and 8.1 g (0.15 mol) of sodium methylate in 75 ml of methanol) from 11 g (0.094 mol) of ketone there was obtained 6.6 g (53%) of a semicrystalline oxime which was a mixture of the syn and anti isomers.

The semicrystalline oxime (6.6 g, 0.05 mol) was con-

verted to 2 (Tables I and II) by reaction with 3 ml (excess) of methyl isocyanate in 25 ml of acetone containing 1 drop of dibutyltin diacetate. The carbamate was crystallized from a heptane-isopropyl ether mixture.

**2,5-Dimethylthiophan-3-one O-(Methylcarbamoyl)oxime (3).** The addition-cyclization of 27 g (0.2 mol) of ethyl 2-thiopropionate with 22.8 g (0.2 mol) of ethyl crotonate in 150 ml of anhydrous tetrahydrofuran using 4.78 g (0.2 mol) of sodium hydride (from 9 g of 53% sodium hydride in mineral oil) gave 21 g (48.6%) of 2,5-dimethyl-2-(or 4)-(carboethoxy)thiophan-3-one, bp 73–74° (0.5 mm). This keto ester (21 g, 0.097 mol) was decarboxylated by heating at reflux in 100 ml of 10% sulfuric acid for 6 hr to give 7 g (55.5%) of 2,5-dimethylthiophan-3-one, bp 33–35° (1 mm). This ketone (7 g, 0.054 mol) was converted to its oxime, isolated as a residual oil (6 g, 77%), by treatment with hydroxylamine (from 4.15 g (0.06 mol) of hydroxylamine and 3.25 g (0.06 mol) of sodium methylate) in 75 ml of methanol. Treatment of this residual oil (0.039 mol) with 2.5 ml (excess) of methyl isocyanate in 25 ml of acetone containing 1 drop of dibutyltin diacetate produced 3 (Tables I and II) from 1:1 hexane-isopropyl ether.

**2,2-Dimethylthiophan-3-one O-(Methylcarbamoyl)oxime (4).** The general procedure outlined in Scheme II was employed. To a solution of 11.5 g (0.5 g-atom) of sodium metal in 500 ml of absolute ethanol was added 60 g (0.5 mol) of methyl 3-mercaptopropionate, with stirring, followed by 99 g (0.5 mol) of ethyl 2-bromo-2-methylpropionate. When addition was complete (solid had begun to separate) the mixture was stirred and heated at reflux for 5 hr. After cooling and filtering, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in ether, filtered, and, finally, washed thoroughly with water. After drying over sodium sulfate the ether solution was distilled to give 100 g (80%) of diethyl 2,2-dimethyl-3-thiaadipate, bp 109–110° (0.5 mm). The structure was confirmed by nmr studies; alkoxy interchange took place during the reaction.

Anal. Calcd for  $C_{11}H_{20}O_4S$ : C, 53.21; H, 8.12. Found: C, 53.15; H, 8.14.

Treatment of the above diester (71 g, 0.38 mol) in 300 ml of anhydrous ethyl ether with 34.5 g of sodium methoxide with stirring with subsequent heating at reflux for 5 hr produced a suspension of white solid, which, upon cooling, was poured into a solution of 40 g of acetic acid in ice water. The oil which separated was extracted into ether. After drying over sodium sulfate, the ether solution was concentrated to yield 62 g (96%) of 2,2-dimethyl-4-(carboethoxy)thiophan-3-one as a residue product. This residue material (0.306 mol) was hydrolyzed with 200 ml of 10% sulfuric acid to give 30 g (75%) of 2,2-dimethylthiophan-3-one, bp 87–89° (30 mm). Reaction of this ketone (30 g, 0.23 mol) with hydroxylamine (from 17.5 g (0.25 mol) of hydroxylamine hydrochloride and 13.5 g (0.25 mol) of sodium methoxide) in 100 ml of methanol produced 6 g of solid product, mp 53–55°, and a liquid product in two equal fractions, bp 93 and 93–94° (1 mm), respectively, which crystallized to give material, mp 43–47 and 39–45°, respectively (total, 11 g). Infrared spectra indicated that these fractions were various mixtures of syn-anti oximes. The lowest melting fraction was examined by elemental analysis. The total yield was 17 g (51%).

Anal. Calcd for  $C_6H_{11}NOS$ : C, 49.64; H, 7.65. Found: C, 49.20; H, 7.73.

Reaction of the portion of oxime mp 53–55° (6 g, 0.041 mol) with 2.35 g (0.041 mol) of methyl isocyanate in 40 ml of acetone produced 4a (Tables I and II) (from isopropyl ether).

The remaining 11 g (0.054 mol) of oxime was converted to the methylcarbamate 4b (Tables I and II).

**2,2-Dimethylthiophan-3-one O-(Methylcarbamoyl)oxime 1-Oxide (8).** A solution of 4a (3 g, 0.015 mol) in 25 ml of ethyl acetate was treated with 4.5 g of 24% peracetic

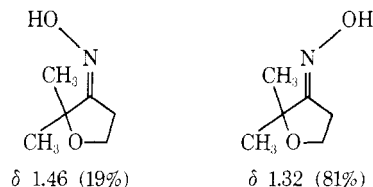
acid (1.15 g, 0.015 mol) at room temperature with stirring. After standing overnight the mixture was washed until neutral with sodium bicarbonate solution and, after drying over sodium sulfate, was evaporated *in vacuo* to a residue. Recrystallization from a 1:1 mixture of hexane-ethyl acetate produced 8 (Tables I and II).

The sulfone 9 (Tables I and II) was produced by a similar procedure using 10 g (excess) of peracetic acid.

**2,2-Dimethylfuran-3-one O-(Methylcarbamoyl)oxime (5).** To a suspension of 4.68 g (0.2 mol) of sodium hydride (from 9 g of 52% sodium hydride in mineral oil washed with hexane) in 150 ml of tetrahydrofuran was added dropwise with stirring 26.4 g (0.2 mol) of ethyl 2-hydroxy-2-methylpropionate and the resulting mixture was stirred until no more hydrogen was evolved. Then 17.2 g (0.2 mol) of methyl acrylate was added in one lot and the resulting mixture was stirred for 1.5 hr after which the THF was evaporated *in vacuo*. The resulting residue was taken up in water, and this solution was added with stirring to 100 ml of 15% sulfuric acid. The resulting solution was extracted with 1:1 chloroform-hexane (2 × 100 ml and then 4 × 50 ml) and the extracts were washed with dilute sodium bicarbonate solution and then dried over sodium sulfate. Distillation through an 18-in. spinning band column produced 10 g (29%) of 2,2-dimethyl-4-(carboethoxy)furan-3-one, bp 61–64° (10 mm), of questionable purity. A mass spectrum showed the major component to be *m/e* 172 (calcd for product, mol wt 172).

This product (0.058 mol) was decarboxylated in 50 ml of 10% sulfuric acid by boiling at reflux for 5 hr to give 3.5 g (52.5%) of 2,2-dimethylfuran-3-one as a residue product: nmr ( $CCl_4$ , TMS as internal standard)  $\delta$  1.15 (6 H, s,  $(CH_3)_2C$ ), 2.42 (2 H, t,  $J = 7.5$  Hz,  $C(O)CH_2$ ), 4.08 (2 H, t,  $J = 7.5$  Hz,  $OCH_2$ ).

Treatment of the dimethylfuranone (3.5 g, 0.03 mol) with 0.05 mol of hydroxylamine in 50 ml of methanol produced 3.1 g (78%) of oxime: mp 39–40°; nmr ( $CCl_4$ , TMS internal standard)  $\delta$  1.32 and 1.46 (6 H, two singlets taken together,  $C(CH_3)_2$ , indicative of a syn-anti mixture), 2.74 (2 H, t,  $J = 7$  Hz,  $CH_2CH_2O$ ), 3.95 (2 H, t,  $J = 7$  Hz,  $CH_2CH_2O$ ), 8.22 (br, 1 H, s,  $=NOH$ ).



Reaction of the above oxime (0.023 mol) with 1 ml of methyl isocyanate in 15 ml of acetone containing 1 drop of dibutyltin diacetate produced 5 (Tables I and II) whose infrared and nmr spectra indicate the possibility of a trace of *sym*-dimethylurea.

Test methods for determining insecticidal activity and fly-head acetylcholinesterase  $I_{50}$  values have been described (Payne *et al.*, 1966).

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## Overcrowding Factors of Mosquito Larvae. V. Synthesis and Evaluation of Some Branched-Chain Fatty Acids against Mosquito Larvae

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Overcrowding factors of mosquito larvae contained minute quantities of branched-chain fatty acids. Seven 2- and 3-substituted fatty acids were synthesized and evaluated for their biological activity against larvae of *Culex pipiens quinquefasciatus* Say, *C. tarsalis* Coquillett, *Anopheles albimanus* Wiedemann, and *Aedes aegypti* (L.). 2-Methylnonanoic acid (**1b**) and 2-methyloctadecanoic acid (**2b**) showed weak activity. 3-Methyloctadecanoic acid (**3b**) and 2,3-dimethyloctadecanoic acid (**4b**) possessed potent activity. 2-Butyldodecanoic acid (**5b**), 2-butyldodecanoic acid (**6b**), and 2-butyl-4-methylundecanoic acid (**7b**) showed considerable activity. A methyl group at the 3 position or an *n*-butyl group at the 2 position of long-chain carboxylic acids seemed essential in obtaining good activity.

Mosquito larvae overcrowded in laboratory cultures showed increased mortality and slow development. Emergence of smaller adults from overcrowded larvae was also observed (Ikeshoji, 1965). The autoregulating properties of chemical factors in the culture water of overcrowded larvae of *Culex pipiens quinquefasciatus* Say were demonstrated, and these chemical factors were designated as *overcrowding factors of mosquito larvae* (Ikeshoji and Mulla, 1970).

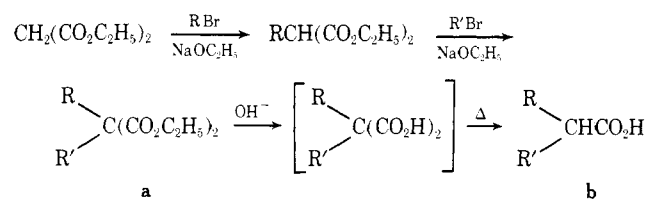
During the isolation and identification of these overcrowding factors, the mass spectra of the crude natural products indicated the presence of branched-chain fatty acids in minute amounts (Ikeshoji and Mulla, 1974). Along with the studies on the isolation and identification of overcrowding factors, attempts were made to synthesize a series of substituted long-chain fatty acids. The biological activity of these acids as related to their structures was investigated. This report presents the synthesis of these branched-chain fatty acids and their biological activity against mosquito larvae.

### EXPERIMENTAL SECTION

**Synthesis.** The compounds synthesized and evaluated for activity are shown in Scheme I. The malonic ester condensation was used to prepare these fatty acids. Alkyl bromides were prepared and treated with diethyl malonate in absolute ethanol in the presence of sodium ethoxide to yield monosubstituted malonic esters which, upon further alkylation with alkyl bromides under the same conditions, afforded disubstituted malonic esters. Saponification and subsequent thermal decarboxylation of these mono- and disubstituted malonic esters yielded the desired branched-chain fatty acids.

Scheme II shows the method for preparing 2-bromoheptadecane which is not readily available. 2-Heptadecanone (**9**) was previously prepared by Cason *et al.* (1949) through the condensation of dimethylcadmium and palmitoyl

### Scheme I. Synthesis of Various Branched-Chain Fatty Acids



1. R = CH<sub>3</sub>; R' = *n*-C<sub>7</sub>H<sub>15</sub>
2. R = CH<sub>3</sub>; R' = *n*-C<sub>16</sub>H<sub>33</sub>
3. R = H; R' = *n*-C<sub>15</sub>H<sub>31</sub>C(CH<sub>3</sub>)H
4. R = CH<sub>3</sub>; R' = *n*-C<sub>15</sub>H<sub>31</sub>C(CH<sub>3</sub>)H
5. R = *n*-C<sub>4</sub>H<sub>9</sub>; R' = *n*-C<sub>8</sub>H<sub>17</sub>
6. R = *n*-C<sub>4</sub>H<sub>9</sub>; R' = *n*-C<sub>10</sub>H<sub>21</sub>
7. R = *n*-C<sub>4</sub>H<sub>9</sub>; R' = *n*-C<sub>7</sub>H<sub>15</sub>C(CH<sub>3</sub>)HCH<sub>2</sub>

chloride in dry benzene; however, the yield of the pure ketone was only 55%. In the present report, a method of forming methyl ketone *via*  $\beta$ -keto sulfoxide was adopted (Corey and Chaykovsky, 1964). A nearly quantitative yield was obtained in following this method. Thus, methyl palmitate was treated with methylsulfinyl carbanion in dimethyl sulfoxide to give methylsulfinylmethyl *n*-pentadecyl ketone (**8**) which upon hydrogenolysis with aluminum amalgam in aqueous tetrahydrofuran yielded the ketone **9**. Reduction of **9** with lithium aluminum hydride afforded 2-heptadecanol (**10**). In order to avoid the formation of isomeric secondary bromides during the conversion of the secondary alcohol **10** into the corresponding bromide **12**, **10** was first treated with *p*-toluenesulfonyl chloride to form 2-heptadecyl tosylate (**11**) which was then allowed to react with sodium bromide in dimethylformamide to give 2-bromoheptadecane (**12**).

**Methylsulfinylmethyl *n*-Pentadecyl Ketone (8).** Methylsulfinyl carbanion solution was prepared from sodium hydride (9.6 g, 0.4 mol) and anhydrous dimethyl sulfoxide (200 ml) under dry nitrogen. Into this solution, anhydrous tetrahydrofuran (200 ml) was added. The resulting solution was cooled in an ice bath and kept stirring during the addition of methyl palmitate (54.1 g, 0.2 mol). The ice

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