excluded, in particular, inactivation through reversible binding to a protein (*15*).

Turning to the analogs of (I), (V) is highly toxic to mammals both orally and by skin application; obviously, penetration and transport are adequate to deliver sufficient compound to overwhelm the detoxification mechanisms and cholinesterase. compound III is toxic orally but relatively safe dermally, suggesting that cuticular penetration limits the availability of compound III. Compound II is safer than (III), slightly more toxic than (I). As usual for a diethyl analog, compound II is less soluble in water than (I) but more soluble in organic solvents; it is also more stable to hydrolysis and, presumably, to metabolism. Apparently, penetration and transport are also limiting for (II), but detoxification by metabolism is probably not so effective as with (I). Turning to the insect data, obviously (I), (II), and (III) can readily penetrate and move to the cholinesterase-active sites of a number of species of insects because of smaller size or different type of cuticle, tissues, and transport system. The lack of toxicity to aphids and mites might be associated with poor penetration and transport; differences in sensitivity of the different insect cholinesterases have, however, not been excluded.

The authors, therefore, tentatively conclude that the penetration and transport factors are critical in the low toxicity of (I) to mammals, and that poor solubility or partition properties may be the limiting factors. This same situation may apply to other insecticidal phosphates with low mammalian toxicity; the principles obviously have general applicability in the design of safe new insecticides.

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INSECTICIDE SYNTHESIS

The Synthesis and Insecticidal Properties of Some Cholinergic Trisubstituted Acetaldehyde O-(Methylcarbamoyl)oximes

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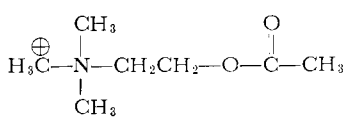
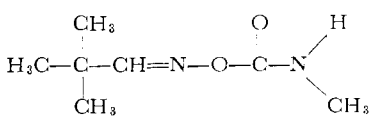
A series of trisubstituted acetaldehyde O-(methylcarbamoyl)oximes, bearing strong structural similarities to acetylcholine, has been shown to possess good insecticidal properties. The most active compounds were those in which one of the substituents was an electronegative group. 2-Methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl)-oxime was the most generally effective contact and systemic insecticide.

THE intrinsic insecticidal activity of aryl carbamates generally is correlated with their ability to inhibit acetylcholinesterase (*11*). Among *O*-(methylcarbamoyl)oximes screened for pesticidal activity in these laboratories in recent years, butanone and acetone *O*-(methylcarbamoyl)oximes (I and I*a*, respectively) possessed modest insecticidal properties, although they were only weak inhibitors of fly-head cholinesterase (Table I).

In an effort to improve acetylcholinesterase inhibition, and thus possibly enhance insecticidal activity, *O*-(methylcarbamoyl)oximes were synthesized which structurally resembled acetylcholine (II), thus offering a more exacting fit for the acetylcholinesterase surface. Two model compounds were trimethylacetaldehyde *O*-(methylcarbamoyl)oxime (III) and *tert*-butyl methyl ketone *O*-(methylcarbamoyl)oxime (IV). The *tert*-butyl portion of each of these molecules is isosteric with the trimethylammonium portion of acetylcholine and



II



III

should complement the so-called anionic surface of acetylcholinesterase. In addition, the sum of the interatomic distances from quaternary carbon to carbonyl carbon in III and IV is approximately 5.6 A. while in acetylcholine, the analogous distance from quaternary nitrogen to carbonyl carbon is about 5.9 A. These steric similarities are further confirmed by an examination of molecular models of II and III. *O*-(Methylcarbamoyl)oximes of this type should, therefore, offer considerable opportunity for simultaneous interaction with the anionic and esteratic sites of acetylcholinesterase (*11, 22*).

A marked increase in insecticidal activity, accompanied by an enhanced inhibition of acetylcholinesterase, was

indeed obtained with III (Table I). The acetate of trimethylacetaldoxime was a very efficient substrate for acetylcholinesterase, thereby supporting the proposed complementarity of III for the enzyme. The failure of the closely related ketoxime derivative, IV, was, therefore, all the more disappointing. Recent studies suggest that the detrimental effect of the methyl group attached to the azomethine carbon is predominantly an inductive influence rather than steric.

A preference for trimethyl substitution on the 2-carbon atom was shown by a comparison of III and VI. When one of the 2-methyl groups of III was replaced by hydrogen to form 2-methylpropionaldehyde *O*-(methylcarbamoyl)oxime (VI) a significant reduction in activity occurred. An analogous comparison in a substrate-specificity study with acetylcholinesterase showed that 3,3-dimethylbutyl acetate was hydrolyzed more rapidly than 3-methylbutyl acetate (*1*). Conversely, at least one of the substituents at the quaternary carbon may be larger than methyl. Thus, replacement of a 2-methyl group by an allyl group to form VII, resulted in a small increase in anticholinesterase activity, although insecticidal activity was somewhat reduced.

Supporting evidence for limitations on the interatomic distance from quaternary carbon to carbonyl carbon was obtained with 3,3-dimethylbutyraldehyde *O*-(methylcarbamoyl)oxime (V), which was less active in inhibiting acetylcholinesterase and had no insecticidal activity at the highest concentration tested (Table I).

In an attempt to enhance insecticidal activity further, several relatively polar analogs of III were synthesized, having approximately the same geometry as III but with one of the 2-methyl groups replaced by an electron-withdrawing group. It was postulated that these compounds would have a greater attraction for the anionic site of acetylcholinesterase as a result of the inductive effect on the neighboring methyl groups, and that perhaps biotransportation to the site of action would be improved with the more polar analogs. In addition to increasing activity against the aphid and the fly, this structural manipulation expanded the spectrum of activity and increased systemic properties in many cases (Table II).

A study of the relationship of general insecticidal activity to chemical structure, using XII as a prototype, indicated a high degree of specificity for the parent molecule. Replacement of the methyl group bonded to the sulfur atom with a variety of other substituents generally resulted in a reduction in over-all activity (Table III). Substitution of a 2-methyl group with hydrogen or larger alkyl or aryl groups also diminished activity (Table IV). Thus, the combination of two methyl groups and a methylthio bonded to the quaternary carbon atom appeared to be optimum for insecticidal activity in this series.

The data presented in Table V demonstrate more fully the detrimental effect, already observed with trimethylacetaldoxime, of replacing the aldehydic hydrogen with an alkyl group. All of the ketoxime derivatives, whether aliphatic or alicyclic, were virtually inactive when compared with the aldoxime derivative, XII. Compound LI, an aldoxime derivative, was included in Table V to again demonstrate the importance of the proper placement of substituents on the 2-carbon atom.

Table VI shows the influence of substitution at the carbamate nitrogen on insecticidal activity. As previously observed with phenyl carbamates—e.g., Ref. *8*— a single methyl substituent on the carbamate nitrogen was most effective for insecticidal activity.

Compounds XII, XIII, XV, and XVI (Table II) were generally equivalent in insecticidal activity, yet XII was markedly different in two respects. Its I_{50} was significantly greater than the others; it was a stable compound while the others decomposed under laboratory storage conditions. Since the metabolic conversion of sulfides to sulfoxides and sulfones has been demonstrated for other insecticides (*6*), it is inferred that the sulfoxide (XIII) is actually the active agent in vivo. The water solubility of XIII is greater than 25% while the

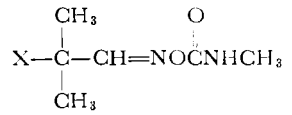
Table I. Properties and Biological Activities of Aliphatic *O*-(Methylcarbamoyl)oximes

$$R{=}N{-}O\overset{\overset{O}{\|}}{C}NHCH_3$$

No.	R	n_D^{30} (M.P., ° C.)	Analysis		Bean Aphid LD_{50}	Housefly, P.P.M.	I_{50} (Molar)[a]
			Calcd.	Found			
I	$CH_3CH_2C(CH_3)=$	1.4601	N, 19.4	N, 19.5	50	100	6×10^{-4}
Ia	$CH_3C(CH_3)(CH_3)=$	(49–50°)	N, 21.5	N, 21.4	100	100	ca. 10^{-3}
III	$CH_3C(CH_3)(CH_3)-CH=$	(70–73°)	N, 17.7	N, 17.6	10	30	1×10^{-5}
IV	$CH_3C(CH_3)(CH_3)-C(CH_3)=$	(33–36°)	N, 16.3	N, 16.5	>100	500	3×10^{-4}
V	$CH_3C(CH_3)(CH_3)-CH_2CH=$	1.4653	N, 16.3	N, 16.0	>100	>1000	3×10^{-4}
VI	$CH_3C(H)(CH_3)-CH=$	1.4674	N, 19.4	N, 19.6	>100	210	3×10^{-4}
VII	$CH_2=CHCH_2C(CH_3)(CH_3)-CH=$	1.4712	N, 15.2	N, 15.1	20	68	5×10^{-6}

[a] Housefly-head cholinesterase inhibition; manometric determination.

Table II. Physical Properties and Biological Activities of 2-Substituted 2-Methylpropionaldehyde O-(Methylcarbamoyl)oximes



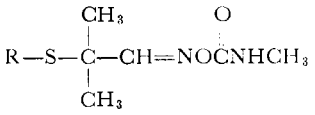
No.	X	M.P., ° C.	Calcd.	Found	LD_{50}, P.P.M. BA[a]	M[a]	[M][a]	AW[a]	BB[a]	HF[a]	I_{50} (Molar)[b]
VIII	CH_3O	71–73	C, 48.3 H, 8.1 N, 16.1	C, 48.2 H, 7.9 N, 16.4	23	95	23	275	100	6	6×10^{-6}
IX	C_2H_5O	Oily residue	C, 51.0 H, 8.6	C, 51.2 H, 8.6	50	700	125	500	100	82	...
X	H—C(=O)—O	Oily residue	C, 44.7 H, 6.4	C, 44.7 H, 6.7	20	1000		325	>100	26	...
XI	$CH_3C(=O)O$	Oily residue	C, 47.5 H, 7.0 N, 13.8	C, 47.6 H, 7.2 N, 14.1	15	150	40	500	>100	40	2×10^{-5}
XII	CH_3S	100–101	C, 44.2 H, 7.4 N, 14.7	C, 44.1 H, 7.5 N, 14.5	4	15	5	500	70	4	1×10^{-5}
XIII	CH_3SO	108–110	C, 40.8 H, 6.8	C, 40.5 H, 6.6	3	12	15	600	40	5	9×10^{-7}
XIV	CH_3SO_2	134.5–135.5	C, 37.8 H, 6.3	C, 38.2 H, 6.2	>100	100	150	>1000	80	8	5×10^{-6}
XV	CN	80–82	C, 49.7 H, 6.5 N, 24.8	C, 49.9 H, 6.4 N, 24.6	10	45	45	55	65	3	1.5×10^{-6}
XVI	NO_2	87–88	C, 38.2 H, 5.8 N, 22.2	C, 38.3 H, 6.1 N, 22.5	6	10	10	55	80	3	5×10^{-7}
XVII	N_3	Oily residue	C, 38.9 H, 6.0 N, 37.8	C, 38.9 H, 6.3 N, 38.1	40	125	...	>1000	>100	20	
XVIII	$(CH_3)_2N$[c]	65–67	C, 51.3 H, 9.1	C, 51.3 H, 9.6	...	...	...	...	...	...	...

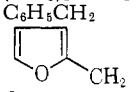
[a] BA = bean apid (*aphis fabae* Scopoli); M = two-spotted mite (*Tetranychus telarius*); [M] = two-spotted mite systemic; AW = southern armyworm (*Prodenia eridania*); BB = Mexican bean beetle (*Epilachna varivestria*); HF = housefly (*Musca domestica*); ... indicates not evaluated.

[b] Housefly-head cholinesterase inhibition, manometric method.

[c] This compound was so unstable that a reliable bioassay could not be obtained.

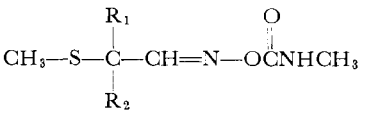
Table III. Properties and Insecticidal Activities of Various S-Substituted 2-Methyl-2-mercaptopropionaldehyde O-(Methylcarbamoyl)oximes



No.	R	M.P., ° C.	Analysis Calcd.	Analysis Found	D_{50}, P.P.M. BA[a]	M[a]	[M][a]	AW[a]	BB[a]	HF[a]
XII	CH_3	100–101	N, 14.7	N, 14.5	4	15	5	500	70	4
XIX	C_2H_5	78–79.5	N, 13.7	N, 13.6	1	75	15	>1000	>100	27
XX	n-C_3H_7	77–79	N, 12.8	N, 12.6	4	200	..	>1000	>100	90
XXI	i-C_3H_7	90–92	N, 12.8	N, 12.8	20	180	60	>1000	>100	150
XXII	CH_2=CH—CH_2	74–76	N, 13.0	N, 12.7	2	35	6	>1000	>100	60
XXIII	n-$C_{12}H_{25}$	60–65	N, 8.1	N, 7.7	>100	>1000	..	>1000	>100	>1000
XXIV	$CH_3CH_2SCH_2CH_2$	Oily residue	N, 10.6	N, 10.4	>100	1000	..	1000	>100	700
XXV	$(CH_3)_2NCH_2CH_2$	60–63	N, 17.0	N, 16.7	50	>1000	..	>1000	>100	>1000
XXVI	$C_6H_5CH_2$	94–98	N, 10.5	N, 10.7	8	>1000	..	>1000	>100	1000
XXVII		95–98	C, 51.5 H, 6.3	C, 51.7 H, 6.2	5	>1000	..	>1000	>100	>1000
XXVIII	$C_2H_5OCOCH_2$	n_D^{30} = 1.4987	C, 45.8 H, 6.9	C, 45.9 H, 6.9	100	>1000	..	>1000	>100	1000
XXIX	C_2H_5OCS	84–85	N, 10.6	N, 10.8	>100	>1000	..	>1000	>100	>1000
XXX	CH_3CO	Oily residue	N, 12.8	N, 12.9	...	>1000	..	>1000	>100	1000
XXXI	C_6H_5	79–84	N, 11.1	N, 11.1	>100	>1000	..	>1000	>100	>1000
XXXIII	CH_3NHCO_2N=CHC(CH$_3$)$_2$—S	112–114	N, 16.0	N, 16.0	...	>1000	..	>1000	>100	1000
XXXIV	p-Cl—C_6H_5	82–85	N, 9.8	N, 9.6	>100	>1000	..	>1000	>100	500
XXXV	$(CH_3)_2NCS$	91–92	N, 16.0	N, 15.8	>100	>1000	..	>1000	>100	>1000

[a] See Table II for definition of abbreviations.

Table IV. Properties and Insecticidal Activities of Various 2,2-Disubstituted (Methylthio)acetaldehyde O-(Methylcarbamoyl)oximes



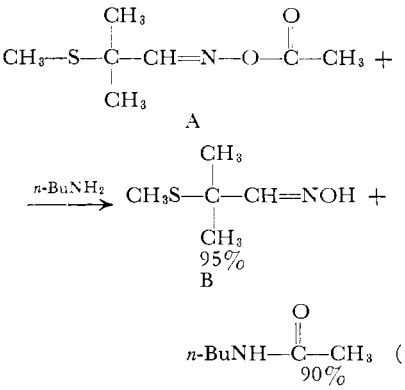
No.	R_1	R_2	M.P., ° C.	Analysis Calcd.	Analysis Found	LD_{50}, P.P.M. BA[a]	M[a]	AW[a]	BB[a]	HF[a]
XXXVI	H	H	Oily residue	C, 37.0 H, 6.2 N, 17.3	C, 37.0 H, 6.5 N, 16.9	>100	>1000	>1000	>100	>1000
XXXVII	H	CH_3	Oily residue	C, 40.9 H, 6.9	C, 41.3 H, 6.7	50	200	>1000	>100	8
XII	CH_3	CH_3	100–101	C, 44.2 H, 7.4 N, 14.7	C, 44.1 H, 7.5 N, 14.5	4	15	500	70	4
XXXVIII	CH_3	C_2H_5	68–70	C, 47.1 H, 7.9 N, 13.7	C, 46.8 H, 8.0 N, 13.4	12	70	>1000	>100	125
XXXIX	CH_3	n-C_3H_7	57–58	C, 49.5 H, 8.3 N, 12.8	C, 49.5 H, 8.3 N, 12.8	100	80	>1000	>100	150
XL	CH_3	C_6H_5	Oily residue	N, 11.1	N, 10.8	>100	1000	>1000	>100	1000
XLI	CH_3	neo-C_5H_{11}	75–76	C, 53.7 H, 8.9 N, 11.4	C, 53.6 H, 8.9 N, 11.6	>100	>1000	>1000	>100	1000
XLII	C_2H_5	C_2H_5	Oily residue	C, 49.6 H, 8.3 N, 12.9	C, 49.6 H, 8.4 N, 12.9	100	150	>1000	>100	100

[a] See Table II for definition of abbreviations.

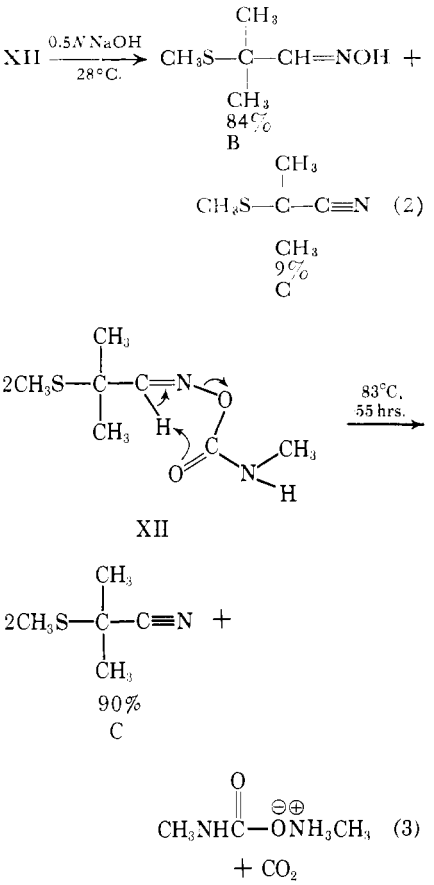
sulfide, XII, is only about 0.6%. This may, in part, account for the excellent systemic properties of XII if this sulfide is rapidly converted in vivo to XIII. Both XII and XIII are highly toxic to mammals by the oral route; the oral LD_{50} to rats being in the order of 1 mg. per kg. The higher oxidation product, XIV, is a less effective insecticide (Table II) and only one tenth as toxic to the rat. The water solubility of this sulfone, XIV, is approximately 0.7%.

An examination of the chemical and biological properties of the compounds shown above indicated that XII, 2-methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime (Union Carbide 21149; Temik), had the best potential as a commercially useful insecticide (*20*). This compound has been subjected to extensive laboratory and field tests (*7*, *13*, *19*) under the designations UC 21149 and TEMIK.

Although the above relationships between structure and activity are in good agreement with current ideas on the steric nature of the active site of acetylcholinesterase, some of the inferences on the molecular complementarity of 2-substituted 2,2-dimethylacetaldehyde *O*-(methylcarbamoyl)oximes for acetylcholinesterase must remain tentative until the isomeric configurations (*syn* and *anti*) have been completely established for this series of compounds. In this regard, the existing evidence indicates that XII has the *syn* configuration. Hauser and Jordan (*5*) have demonstrated that *O*-(acetyl-)*syn*-aldoximes react with *n*-butylamine to form the aldoxime while the *anti* isomers give the corresponding nitrile. In addition, these investigators showed that phenylcarbamates of *syn*-aldoximes were hydrolyzed by dilute sodium hydroxide to give the aldoxime as the major product while the *anti* isomer afforded the corresponding nitrile or carboxylic acid. The reaction of 2-methyl-2-(methylthio)propionaldehyde *O*-(acetyl)oxime (A) with *n*-butylamine proceeds vigorously to afford 2-methyl-2-(methylthio)-propionaldoxime (B) in near quantitative yield (Equation 1) while the hydrolysis of XII with 0.5*N* sodium hydroxide at 28° C. also yields the oxime (B) as the major product (Equation 2). 2-Methyl-2-(methylthio)propionitrile (C) is obtained as a minor product in the hydrolysis of the carbamate, XII, but could not be detected as a product of the reaction of *n*-butylamine with the oxime acetate (A).



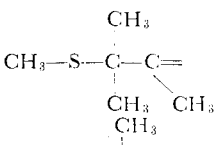
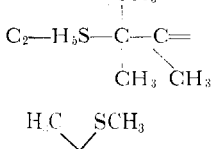
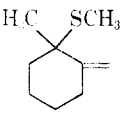
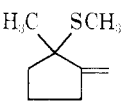
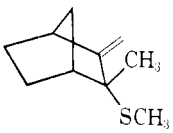
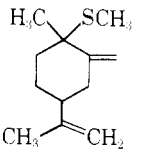
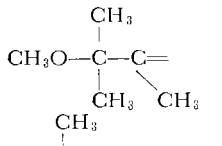
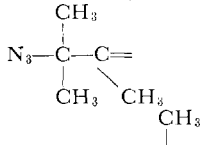
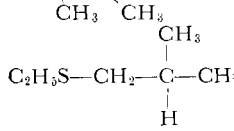
The thermal decomposition of XII, however, in boiling benzene (Equation 3) affords the nitrile (C) in 90% yield and the oxime as a minor product.



In addition to complementing the steric features of the enzyme, certain methylcarbamate inhibitors of acetylcholinesterase have been shown to carbamoylate the esteratic site (*23*, *24*). With the exception of the sulfone derivative (XIV), the increasing inductive effects of the electronegative substituent

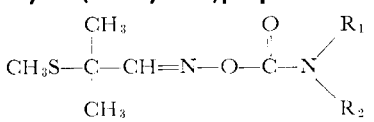
Table V. Properties and Insecticidal Activities of 2-Substituted Ketoxime O-Methylcarbamates

$$R{=}NO\overset{O}{\overset{\|}{C}}NHCH_3$$

No.	R	M.P., ° C.	Analysis Calcd.	Analysis Found	LD_{50}, P.P.M. BA[a]	M[a]	AW[a]	BB[a]	HF[a]
XLIII		77–79	C, 47.0 H, 7.9 N, 13.7	C, 47.4 H, 8.0 N, 13.7	100	>1000	>1000	>100	400
XLIV		71–73	C, 49.5 H, 3.3 N, 12.8	C, 49.6 H, 8.2 N, 12.9	>100	>1000	>1000	>100	700
XLV		81–83	C, 52.1 H, 7.9 N, 12.2	C, 52.2 H, 8.2 N, 12.5	100	>1000	1000	>100	>1000
XLVI		110–111	C, 49.9 H, 7.5 N, 13.0	C, 50.1 H, 7.6 N, 12.6	50	1000	>1000	>100	260
XLVII		115–117	C, 54.5 H, 7.5 N, 11.5	C, 54.3 H, 7.7 N, 11.2	100	>1000	>1000	>100	>1000
XLVIII		128–130[b]	C, 57.7 H, 8.2 N, 10.4	C, 58.0 H, 8.2 N, 10.0	>100	>1000	>1000	>100	>1000
		71–73[b]	C, 57.7 H, 8.2 N, 10.4	C, 57.9 H, 8.4 N, 10.7	>100	>1000	>1000	>100	>1000
XLIX		55–57	C, 51.0 H, 8.6 N, 14.9	C, 50.9 H, 8.6 N, 14.8	>100	>1000	>1000	>100	250
L		Oily residue	C, 42.2 H, 6.6 N, 35.2	C, 42.2 H, 6.9 N, 34.9	>100	1000	>1000	>100	150
LI		Oily residue	C, 47.0 H, 7.9 N, 13.7	C, 47.4 H, 8.0 N, 13.4	>100	1000	>1000	>100	>1000

[a] See Table II for definition of abbreviations.
[b] Isomeric products.

Table VI. Physical Properties and Biological Activities of Carbamates Derived from 2-Methyl-2-(methylthio)propionaldoxime



No.	R_1	R_2	M.P., ° C.	Analysis Calcd.	Analysis Found	LD_{50}, P.P.M. BA[a]	M[a]	AW[a]	BB[a]	HF[a]	I_{50} (Molar)
LII	H	H	92–93	N, 15.9	N, 15.7	12	400	1000	100	10	ca. 10^{-3}
XII	H	CH_3	100–101	N, 14.7	N, 14.5	4	15	500	70	4	1×10^{-5}
LIII	H	C_2H_5	83–84	N, 13.7	N, 13.8	75	300	1000	125	30	5×10^{-5}
LIV	H	n-C_3H_7	72–73	N, 12.8	N, 13.0	100	500	1000	100	60	2×10^{-4}
LV	H	C_6H_5	52–55	N, 11.1	N, 11.2	100	1000	1000	100	400	4×10^{-5}
LVI	H	$CH_2{=}CH{-}CH_2$	55–56	N, 12.9	N, 12.9	12	500	1000	80	30	...
LVII	H	$C_6H_5CH_2$	88–89	N, 10.5	N, 10.7	100	1000	1000	100	1000	...
LVIII	H	$C_6H_5CH_2CH_2$	51–52	N, 10.0	N, 9.9	100	300	1000	100	1000	...
LIX	CH_3	CH_3	47–48	C, 47.1 H, 7.9	C, 46.9 H, 7.9	12	500	1000	100	25	1×10^{-4}

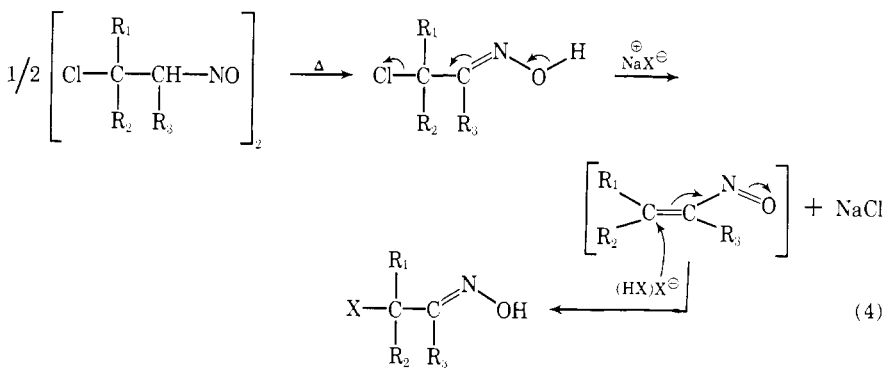
[a] See Table II for definition of abbreviations.

for the 2-substituted-2,2-dimethylacetaldehyde *O*-(methylcarbamoyl)oximes (Table II) result in increased acetylcholinesterase inhibition and a corresponding decrease in chemical stability. The relationship between the electronegativity of these substituents and the activity of the respective methylcarbamates suggest that, within this limited series of compounds, this inductive effect directly influences the carbamoylation mechanism.

Synthesis and Reactions

The simple aliphatic oximes were obtained by the conventional reaction of hydroxylamine with the appropriate carbonyl compound (*2*). The carbonyl compounds were obtained from commercial sources or by techniques described in the literature.

Other oximes described herein, were synthesized by the reaction of an appropriate nucleophile with a dimeric 2-chloronitroso compound. Ogloblin (*14*) demonstrated that in such reactions isobutylene nitrosochloride dimer is first rearranged to 2-chloro-2-methylpropionaldoxime which is extremely reactive towards nucleophiles. A mechanism for the reaction of 2-chlorooximes with nucleophiles has been postulated by Dornow and Jordan (*1*) and later by Lemieux *et al.* (*9*), and by Pritzkow *et al.* (*18*) as proceeding by an elimination-addition reaction through a nitrosoolefin. Such a mechanism is applicable here as illustrated by Equation 4.

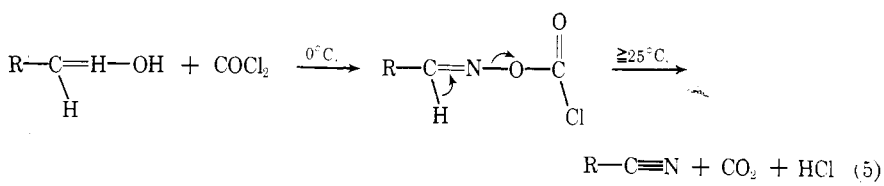


In general, the reaction proceeds exothermically with a wide variety of nucleophiles in alcoholic medium to afford high yields of alpha-substituted oximes, provided the chlorine is attached to a tertiary-carbon atom. When the chlorine was attached to a secondary carbon, poorer yields of the substitution products were obtained.

When $X^{\ominus}$ was cyanide or nitrite, the desired product was isolated in good yield only when a dipolar aprotic solvent such as dimethyl sulfoxide was used.

The oximes were readily converted to monosubstituted carbamates by reaction with an appropriate isocyanate, with or without a suitable catalyst such as a tertiary amine or a tin salt (*16*).

The monosubstituted carbamates, as well as unsubstituted and disubstituted carbamates, were also synthesized by converting the oxime to a chloroformate through reaction with phosgene, using *N*,*N*-dimethylaniline as a hydrogen chloride acceptor, and allowing the oxime chloroformate to react with two equivalents of the desired amine (*16*). Some care must be exercised, however, in the synthesis of the aldoxime chloroformates as they tend to decompose at room temperature and above with the formation of the corresponding nitrile (Equation 5). This is indeed a very clean method for converting the aldoximes to nitriles in good yield.



$$R{-}C{\equiv}N + CO_2 + HCl \quad (5)$$

The poor stability of the amino analog, XVIII (Table II), was apparently related to the strongly basic nature of the compound. The major decomposition products were a nitrile, presumably 2-dimethylamino-2-methylpropionitrile, carbon dioxide, and methylamine. The compound could be stabilized by conversion to an amine salt which was devoid of insecticidal properties.

Experimental. Melting points were obtained in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Microanalyses are by the Analytical Laboratories, Chemicals Division, Union Carbide Corporation. The assigned structures were supported by infrared spectra obtained in KBr pellets on a Baird Atomic Model 4-55. Characteristic absorption bands were observed for the *O*-(methylcarbamoyl)oximes as indicated: C=O, 5.82 microns; C—O, 8.1 microns; N—H, 2.99 microns, and 6.63 microns; N—O, 10.6 microns; C=N, 6.1 microns. The NMR spectra were obtained on a Varian 60 Mc Spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard.

Many of the novel oximes needed for this work are shown in Table VII along with physical properties and elemental analyses. Others were necessarily isolated as oily residues, characterized by infrared and elemental analysis, and were omitted from this paper.

2 - Methyl - 2 - (methylthio)propionaldoxime. The α-(alkylthio)oximes were synthesized by the method of Payne (*15*). The synthesis of this oxime will illustrate the general method.

Isobutylene nitrosochloride (97 grams; 0.4 mole) dimer, prepared by the method of Yakubovich and Lemke (*20*), was added in small portions to a well stirred solution of methyl mercaptan (48 grams; 0.8 mole) and sodium hydroxide (32 grams; 0.8 mole) in 350 ml. of ethanol. The reaction was exothermic and the temperature was maintained at 35° to 40° C. with the aid of an ice bath.

When the nitrosochloride addition was complete the mixture was warmed to 50° and stirred for 30 minutes. The salt was removed by filtration and the alcohol evaporated in vacuo. The residue was dissolved in a small amount of benzene, filtered, and the solvent evaporated. Distillation of the residue afforded 84 grams (80% yield): b.p. 82–3° C. 8 mm., n_D^{30} = 1.4991. Anal. Calcd. for $C_5H_{11}NOS$: C, 45.1; H, 8.3; N, 10.5. Found: C, 44.9; H, 8.3; N, 10.6. NMR: singlet at 1.39 p.p.m. (6H); singlet at 1.93 p.p.m. (3H); singlet 7.29 p.p.m. (1H) and broad singlet at 9.06 p.p.m. (1H).

2 - Methyl - 2 - (methylthio)propionaldehyde *O*-(Methylcarbamoyl)oxime (XII). A solution of 2-methyl-2-(methylthio)propionaldoxime (67 grams; 0.5 mole) in 150 ml. of anhydrous acetone was treated with methyl isocyanate (34.2 grams; 0.6 mole) and three drops of triethylamine. The reaction was exothermic and the temperature rose to 50° C., then subsided. External heat was required to maintain the reaction temperature at 50° for a total of 6 hours. The mixture was then cooled and the solvent evaporated in vacuo. The resulting solid was purified by recrystallization from isopropyl ether affording 81 grams (85% yield) of 2-methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime; m.p. 99–100° C. Anal. Calcd for $C_7H_{14}N_2O_2S$: C, 44.2; H, 7.4; N, 14.7; S, 16.9; O, 16.8. Found: C, 44.1; H, 7.6; N, 14.5; S, 16.9; O, 17.2.

NMR: singlet 1.45 p.p.m. (6H); singlet at 1.97 p.p.m. (3H); doublet at 2.90 p.p.m. (3H); broad singlet at 6.13 p.p.m. (1H) and a singlet at 7.50 p.p.m. plus a very small singlet at 7.34 p.p.m. which combined integrate for 1H.

The signal at 7.50 p.p.m. (96.6%) and 7.34 p.p.m. (3.4%) are assigned to the aldehydic proton and suggest, as does chemical evidence, that XII exists predominately in the *syn* form (*10*, *17*).

2 - Methyl - 2 - (methylthio)propionaldehyde *O*-(Allylcarbamoyl)oxime (LVI). The synthesis of this compound will serve to illustrate the general method for carbamoyloximes via the oxime chloroformate route.

Phosgene (22 grams; 0.22 mole) was collected in 200 ml. of anhydrous ether at 0° C. and the well-stirred solution treated dropwise with *N*,*N*-dimethylaniline (24 grams; 0.2 mole). The mixture was then treated dropwise with 2 - methyl - 2 - (methylthio)propionaldoxime (27 grams; 0.2 mole) dissolved in 200 ml. of ethyl ether and the reaction temperature maintained at 0° to −5° C. for a total of 2 hours.

The dimethylaniline hydrochloride was removed by filtration and about 200 ml. of solvent evaporated from the ether filtrate under reduced pressure without heating.

The ether solution of the chloroformate was charged to a stirred flask and allylamine (28 grams; 0.5 mole) dissolved in 100 ml. of water was added dropwise at 0° C. with vigorous stirring. After a 30-minute reaction period, the ether layer was separated and the solvent evaporated under reduced pressure. The residue was washed thoroughly with water and purified by recrystallization from *n*-heptane. There was obtained 35 grams (81% yield) of 2-methyl-2-(methylthio)propionaldehyde *O*-(allylcarbamoyl)oxime; m.p. 55–6° C. Anal. Calcd. for $C_9H_{20}N_2O_2S$: C, 49.7; H, 7.9; N, 12.9. Found: C, 50.0; H, 7.9; N, 12.9.

2 - Methyl - 2 - (methylsulfinyl)propionaldehyde *O*-(Methylcarbamoyl)oxime (XIII). To 9 grams (0.048 mole) of 2-methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime (XII) dissolved in 50 ml. of ethyl acetate was added 17.5 grams of 20.6% peracetic acid (0.048 mole) in ethyl acetate over a 30-minute period. The solution was stirred during the addition and the reaction temperature maintained at 32–7° C. by gentle cooling.

After standing at room temperature for 16 hours, the pale green solution was diluted to 500 ml. with hexane and cooled to −10° C. The precipitate was collected by filtration and was washed with isopropyl ether to afford 9 grams (92% yield) of a white solid; m.p. 99–102° C. Recrystallization from benzene–ethyl acetate (95:5) raised the melting point to 108–10° C.

The infrared spectrum showed a strong S=O stretching vibration at 9.55 microns in addition to the other expected bands.

2 - Methyl - 2 - (methylsulfonyl)propionaldehyde *O*-(Methylcarbamoyl)oxime (XIV). This compound was synthesized by the procedure described for the sulfoxide except that two equivalents (plus a 10% excess) of peracetic per equivalent of XII were employed.

The reaction mixture was stirred at 30° C. for 4 hours after completion of the peracetic acid feed. The slurry was cooled to 15° C. and filtered to afford the sulfone in 88% yield; m.p. 133–5° C. Recrystallization from ethyl acetate raised the melting point to 134.5–5.5° C.

The infrared spectrum was characterized by strong SO_2 absorption at 7.75 and 8.95 microns.

2 - Methyl - 2 nitropropionaldehyde *O*-(Methylcarbamoyl)oxime (XVI). 2-Methyl-2-nitropropionaldoxime was synthesized by dissolving 24.2 grams (0.35 mole) of sodium nitrite and 24.1 grams (0.2 mole) of 2-chloro-2-methyl-1-nitrosopropane dimer in 175 ml. of dimethyl

Table VII. Physical Properties of Oximes

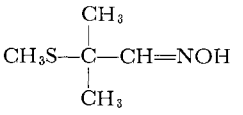
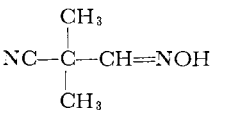
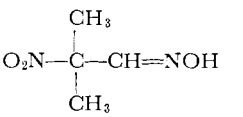
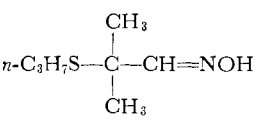
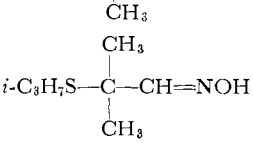
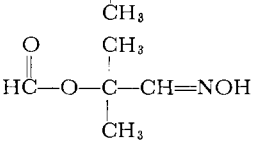
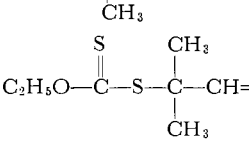
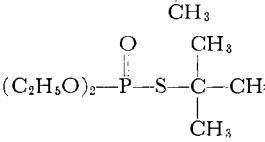
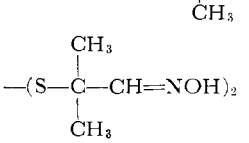
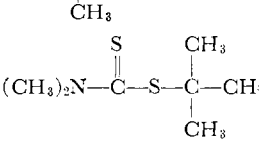
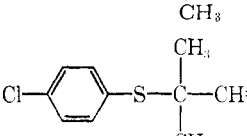
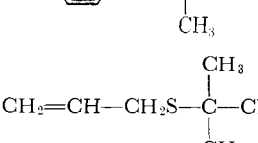
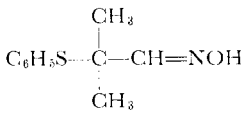
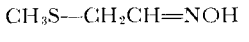
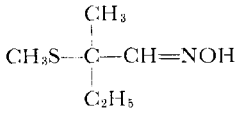
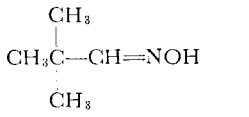
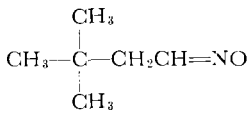
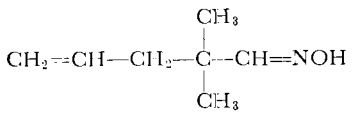
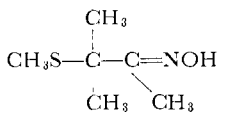
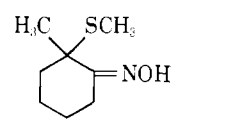
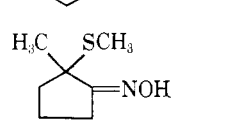
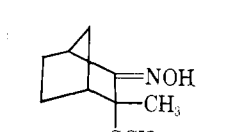
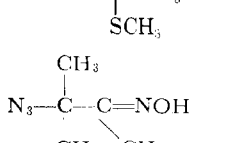
Oxime	B.P., ° C. (M.P.)	Analysis Calcd.	Analysis Found
	57°/0.8 mm. (19–21°)	C, 45.1 H, 8.3 N, 10.5	C, 44.9 H, 8.2 N, 10.6
	(90–93°)	C, 53.6 H, 7.1 N, 25.0	C, 53.6 H, 6.9 N, 25.2
	70–71°/2 mm. (44–46°)	C, 36.4 H, 6.1 N, 21.2	C, 36.4 H, 6.2 N, 21.4
	74–75°/0.9 mm.	C, 52.1 H, 9.4 N, 8.7	C, 51.6 H, 9.2 N, 8.6
	74–76°/2 mm.	C, 52.1 H, 9.4 N, 8.7	C, 51.9 H, 9.1 N, 8.3
	70–71°/2 mm.	C, 45.8 H, 6.9 N, 10.7	C, 46.0 H, 6.9 N, 11.0
	(51–52°)	C, 40.6 H, 6.3 N, 6.8	C, 40.7 H, 6.4 N, 6.8
	(60–63°)	N, 5.2	N, 5.1
	(130–132°)	C, 40.7 H, 6.8 N, 11.9	C, 41.1 H, 6.9 N, 11.9
	(75–76°)	N, 13.5	N, 13.3
	(45–49°)	C, 52.3 H, 5.3 N, 6.1	C, 52.7 H, 5.2 N, 5.7
	75–77°/1 mm.	C, 52.8 H, 8.4	C, 52.9 H, 8.7

Table VII. Continued

Oxime	B.P., ° C. (M.P.)	Analysis Calcd.	Analysis Found
	(82–85°)	C, 62.0 H, 6.7 N, 7.2	C, 61.7 H, 6.8 N, 6.9
	56–58°/1 mm.	C, 34.3 H, 6.7 N, 14.0	C, 34.6 H, 6.8 N, 14.4
	61–62°/0.5 mm.	C, 49.0 H, 8.8 N, 9.5	C, 49.3 H, 9.0 N, 9.4
	50°/10 mm. (36–38°)	N, 13.9	N, 13.6
	46°/2 mm.	C, 62.6 H, 11.4	C, 62.5 H, 11.2
	73–74°/8 mm. n_D^{28} = 1.4550	N, 11.0	N, 11.3
	(75–76°)	C, 48.9 H, 8.9 N, 9.5	C, 49.1 H, 9.2 N, 9.8
	(78–80°)	C, 55.4 H, 8.7 N, 8.1	C, 55.6 H, 8.8 N, 7.8
	104–106°/1.8 mm.	N, 8.8	N, 8.5
	(75–76°)	C, 54.5 H, 7.5 N, 11.5	C, 54.3 H, 7.7 N, 11.2
	(34–35°)	N, 39.4	N, 39.4

sulfoxide and allowing the solution to stir at room temperature for 3 days. The mixture was then poured into 200 ml. of iced water and 200 ml. of ethyl ether. After thorough agitation, the layers were separated, and the aqueous layer was extracted four times with 75 ml. of ether. The combined ether extracts were washed with water, dried, and the solvent was evaporated. The residue was distilled through a short column yielding 12 grams of a colorless oil; b.p. 85° C./2 mm. Upon redistillation through a 36-inch spinning-band column there was obtained 10 grams of the desired oxime boiling at 65° C./1 mm.

The oxime solidified and melted at 44–6° C. after recrystallization from xylene. Anal. Calcd. for $C_4H_8N_2O_3$: N, 21.2. Found: 21.4.

Infrared: In addition to the characteristic oxime bands, strong absorption was observed at 6.47 and 7.45 microns for NO_2 and 7.21 and 7.32 microns for $C(CH_3)_2$.

Reaction of the oxime (9 grams; 0.076 mole) with methyl isocyanate (5 grams, 0.088 mole) in 50 ml. of anhydrous ether, using dibutyltin diacetate as a catalyst, afforded the desired methylcarbamate. After recrystallization from isopropyl alcohol there was obtained 8 grams of a white solid; m.p. 87–8° C.

2 - Cyano - 2 - methylpropionaldehyde *O*-(Methylcarbamoyl)oxime (XV). 2-Cyano-2-methylpropionaldoxime was synthesized by the addition of isobutylene nitrosochloride dimer (24.2 grams; 0.2 mole) in small portions to a slurry of sodium cyanide (9.8 grams; 0.2 mole) in 150 ml. of dimethyl sulfoxide at 60° C. After 2 hours at 60° C., the mixture was cooled and poured into 200 ml. of iced water. The aqueous solution was extracted four times with 100 ml. of ether, and the combined ether extracts were washed with water and dried. Upon evaporation of the solvent a solid residue was obtained which was purified by recrystallization from a benzene-hexane mixture. There were obtained 4 grams of the cyanooxime; m.p. 91–3° C. Anal. Calcd. for $C_5H_8N_2O$: C, 53.6; H, 7.1; N, 25.0. Found: C, 53.6; H, 6.9; N, 25.2.

The methylcarbamate was obtained in 92% yield by reaction of the oxime with methyl isocyanate as described for XII. Recrystallization from ethyl ether afforded 2-cyano-2-methylpropionaldehyde *O*-(methylcarbamoyl)oxime; m.p. 80–2° C.

2 - Methoxy - 2 - methylpropionaldehyde *O*-(Methylcarbamoyl)oxime (VIII). 2-Methoxy-2-methylpropionaldoxime was prepared by the method of Butterbaugh (*3*).

The oxime was converted to the methylcarbamate in 60% yield by the method described for XVI. The compound was purified by recrystallization from isopropyl ether; m.p. 71–3° C.

2 - Dimethylamino-2-methylpropionaldehyde *O*-(Methylcarbamoyl)oxime (XVIII). 2-Dimethylamino-2-methylpropionaldoxime was synthesized by adding isobutylene nitrosochloride dimer (36.5 grams; 0.3 mole), dissolved in warm toluene, to 45 grams (1.0 mole) of dimethylamine in 200 ml. of ethanol. The reaction temperature quickly rose to 75° C. and cooling was required to control the reaction. When all of the nitrosochloride dimer had been added, the mixture was heated to reflux for 1 hour, filtered, and the solvents were evaporated in vacuo. The residue was recrystallized from isopropyl ether to afford 24 grams of the aminooxime; m.p. 94–6° C. Anal. Calcd. for $C_6H_{14}N_2O$: C, 55.4; H, 10.8; N, 21.5. Found: C, 55.4; H, 10.9; N, 21.7.

The aminooxime was allowed to react with methyl isocyanate and the methylcarbamate isolated as described for XII. Purification was effected by recrystallization from isopropyl ether to give a white solid; m.p. 65–7° C.

After several days at room temperature the *O*-(methylcarbamoyl)oxime began to decompose with the liberation of a gas having an ammoniacal odor and form-

ing an oily residue. The gas was identified by mass spectrographic analysis as predominately carbon dioxide with a small amount of methylamine. An infrared spectrum of the residual oil showed a strong C≡N absorption at 4.47 microns, $(CH_3)_2N$— at 3.57 microns and $(CH_3)_2C$= at 7.25 microns, and 7.35 microns. Strong bands at 6.35 microns and 6.80 microns suggest COO^- and a band at 6.10 microns indicates acid carbonyl.

2-Dimethylamino-2-methylpropionaldehyde *O*-(methylcarbamoyl)oxime (3 grams; 0.16 mole) was converted to a maleate salt by reaction with 2 grams of maleic acid in 200 ml. of ethyl ether. The solid which precipitated was collected by filtration, washed with ether and recrystallized from ethanol; m.p. 81–3° C. Anal. Calcd. for $C_{12}H_{21}N_3O_6$: C, 47.5; H, 7.0; N, 13.9. Found: C, 47.7; H, 7.1; N, 14.1.

This salt was stable indefinitely under normal laboratory conditions of storage.

Hydrolysis of XII with 0.5*N* NaOH. 2 - Methyl - 2 - (methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime (95 grams; 0.5 mole) was added to a well stirred 0.5*N* NaOH solution prepared by dissolving 20 grams (0.5 mole) of NaOH in 250 ml. of methanol and sufficient distilled water to give 1000 ml. of solution.

After being stirred at 25–8° C. for 36 hours, the mixture was neutralized to pH 7 with dilute hydrochloric acid. The mixture was extracted with 500 ml. of isopropyl ether, the organic layer was separated, and the aqueous phase was extracted three times with 150 ml. of isopropyl ether. The combined organic extracts were concentrated in vacuo to about 300 ml. and filtered at 0° C. to remove the unreacted starting material. The filtrate was stripped to a residue under reduced pressure without heat. The residue was stirred with 400 ml. of pentane and filtered. The recovered starting carbamate amounted to 27.5 grams (0.145 mole); m.p. 96–8° C.

The pentane was evaporated and the residue distilled. A low-boiling forerun weighing 5 grams was collected and analyzed by vapor-phase chromatography using a 10% UCON 50HB5100 on 80/100 Chromosorb W column. This forerun was 71% 2-methyl-2-(methylthio)propionitrile (3.55 grams; 0.031 mole) and 29% 2-methyl-2-(methylthio)propionaldoxime (1.45 grams; 0.011 mole). An additional 38 grams (0.286 mole) of oxime was collected using a 36-inch spinning band column; b.p. 57° C./0.8 mm. Thus the yield of oxime, based on methylcarbamate consumed, was 84%, the yield of nitrile was 8.7% and 92.7% of the reacted 2-methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime was accounted for.

2-Methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime (XII) was not attacked by 2% sodium bicarbonate at room temperature. A 98% recovery was effected after stirring a 10% slurry for 4 days.

Thermal Decomposition of XII. 2-Methyl - 2 - (methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime (57 grams; 0.3 mole) was mixed with 150 ml. of benzene and heated at reflux for 55 hours. At 69° C., bubbles of carbon dioxide were observed, and this bubbling effect continued for 48 hours. The reaction temperature was 83° C.

Filtration of the mixture afforded 14 grams (88% yield) of the methylammonium salt of methylcarbamic acid. The salt was very volatile (*21*, *25*). It melted at about 100° C., depending upon the rate of heating, and left no residue after melting. No satisfactory elemental analysis could be obtained, and recrystallization from isopropyl alcohol did not improve the stability or sharpen the melting point of the salt. The salt, which dissolved in water to give an alkaline solution, possessed a very strong ammoniacal odor and completely volatilized upon exposure to the atmosphere overnight. The infrared spectrum supported the structural assignment with a strong N—H band at 2.98 microns; NH_3^+ at 3.0 microns to 4.0 microns and at 4.47 microns; COO^- at 6.35 microns and 7.45 microns, and strong absorption at 6.65 microns was assigned to NH_3^+ and N—H.

The benzene was evaporated from the filtrate, and the residue was distilled to afford 31 grams (90% yield) of 2-methyl-2-(methylthio)propionitrile; b.p. 73° C./40 mm. and 58° C./19 mm. n_D^{25} = 1.4546. Anal. Calcd. for C_5H_9NS: C, 52.1; H, 7.9; S, 27.8. Found: C, 52.4; H, 8.0; S, 27.9.

Infrared: C≡N at 4.5 microns; $(CH_3)_2C$= at 7.2 microns and 7.3 microns, and CH_3—S at 7.55 microns.

NMR: singlet (6H) at 1.62 p.p.m. for the *gem*-dimethyl function and a singlet (3H) at 2.28 p.p.m. for the S—CH_3.

2 - Methyl - 2 - (methylthio)propionaldehyde *O*-(Acetyl)oxime. Reaction with *n*-Butylamine. Acetic anhydride (71 grams; 0.7 mole) was added during 10 minutes to 67 grams (0.5 mole) of 2 - methyl - 2 - (methylthio)propionaldoxime. The reaction mixture was held at 40° C. with the aid of an ice bath during the addition, then transferred to flask equipped with a 36-inch spinning band distillation column. The acetic acid was stripped from the product under reduced pressure, along with the excess acetic anhydride, and the residue distilled to afford 73 grams (83% yield) of 2-methyl-2-(methylthio)propionaldehyde *O*-(acetyl)oxime; b.p. 60–1° C./0.33 mm. Anal. Calcd. for $C_7H_{13}NO_2S$: C, 48.0; H, 7.5; O, 18.3. Found: C, 48.2; H, 7.7; O, 18.0.

Infrared: 5.65 microns (ester C=O); 6.15 microns (C=N); 7.51 microns (S—CH_3) and 8.3 microns (C—O).

NMR: singlet at 7.50 p.p.m. (1H); singlet 2.09 p.p.m. (3H); singlet 1.95 p.p.m. (3H) and singlet 1.43 p.p.m. (6H).

To 56 grams (0.32 mole) of 2-methyl-2-(methylthio)propionaldehyde *O*-(acetyl)oxime was slowly added 44 grams (0.6 mole) of *n*-butylamine. The reaction mixture was swirled and cooled in an ice bath to keep the reaction temperature below 55° C. At the conclusion of the reaction, the excess *n*-butylamine was evaporated under reduced pressure, and the residue was distilled on a 36-inch spinning band still. A fraction weighing 40.5 grams was collected which boiled at 50–1° C./0.6 mm. This product was identified as 2-methyl-2-(methylthio)propionaldoxime by its infrared and nuclear magnetic resonance spectra. Vapor-phase chromatography indicated a purity of at least 99%. This represents a 95% yield of oxime based on acetate charged. Continued distillation afforded 33 grams (90% of yield) of *n*-butylacetamide; b.p. 82° C. / 0.75 mm.

Insecticidal Test Methods

Formulation. A stock solution was formulated at the rate of 100 mg. of compound and 10 mg. of Triton X-155 in 10 ml. of acetone. An initial dilution to 100 ml. with water followed by a 1 to 1 serial dilution provided a dosage series beginning at 1000 p.p.m. In a few cases, it was necessary to increase the amount of surfactant-acetone to provide a satisfactory test suspension. For the fly-bait test, 10% aqueous sucrose was the dilution medium.

Insects. Using standard procedures the bean aphid (*Aphis fabae* Scop.) was reared on potted-dwarf nasturtium plants; the two-spotted spider mite [*Tetranychus telarius* (L.)], the southern armyworm [*Prodenia eridania* (Cram.)], and the Mexican-bean beetle (*Epilachna varivestis* Muls.) on Tendergreen-bean plants; and the housefly (*Musca domestica* L.) by the CSMA technique.

Treatments. Bean plants infested 24 hours previously with mites and aphid-infested nasturtiums were sprayed to run-off on a modified Campbell turntable. Two mite-infested bean plants in a 2.5-inch clay pot at the primary leaf stage were used for the systemic test. The pot was placed in a wax paper container and 20 ml. of the aqueous preparation was drenched around the plant. Third instar larvae of the bean beetle and fourth instar larvae of the armyworm were exposed to dip-treated bean leaves in Petri dishes lined with moistened filter paper. Mixed sexes of 5-day-old flies were

exposed in hemispherical screen cages to the bait soaked onto cotton wads in waxed paper containers 3.5 cm. in diameter. The aphids were reared and held at 68 ± 5° F. and 50 ± 10% RH; the others at 80 ± 5° F. and 50 ± 10% RH. Mortality counts were made in 24 hours, 5 to 7 days, 72 hours, 72 hours, and 24 hours for the aphids, mites, armyworm, bean beetle, and fly, respectively. Armyworm and bean beetle larvae were considered dead if unable to move the length of their body when prodded. Results for aphids and mites were corrected for check mortality by means of Abbott's formula. Dosage mortality curves were plotted on log-probit paper and the LD_{50} read from an eye-fitted line.

Anticholinesterase Determination

Fly-head cholinesterase molar I_{50}'s were measured by the manometric method as described by Moorefield and Tefft (*12*). Final ACh concentration was 0.02*M*.

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STRUCTURE AND TOXICITY

The Fungitoxicity of Compounds Containing a Trichloromethylthio-Group

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The R-group can affect fungitoxicity of compounds of the type R—$SCCl_3$ in two areas, that of permeation of fungal cells, and that of chemical reactivity of the R—$SCCl_3$ molecule with cellular constituents. Potential hydrophilicity and ionization of the R-group may decrease permeation while potential lipophilicity of the R-group may increase permeation. High levels of fungitoxicity of compounds of the type R—$SCCl_3$ necessitate a reactive sulfur linkage. The R-group may influence reactivity at this site and direct the mode of chemical reactions of compounds of the type R—$SCCl_3$ with cellular constituents.

FUNGITOXICITY has been reported for a wide variety of compounds containing the trichloromethylthio-group (—$SCCl_3$) (*2, 7, 5, 8, 9, 18–21*). Captan [(*N*-trichloromethylthio)-4-cyclohexene-1,2-dicarboximide, Figure 1, *C*-5] is a highly successful agricultural fungicide. Because many compounds containing the —$SCCl_3$ group are fungitoxic, the —$SCCl_3$ group has been considered to be the toxic reaction center or toxophore. However, not all compounds of the type R—$SCCl_3$ are fungitoxic. A few are weak toxicants and each varies in its specificity toward fungi. In addition to altering fungitoxicity, the R-group controls other chemical and physical properties. An attempt will be made to relate these effects to biological activity.

Some compounds of the type R—$SCCl_3$ have been reported nontoxic simply because testing procedures did not allow for volatility or instability. According to Block (*1*), fungitoxicity of trichloromethylthiomethane sulfonate (Figure 1, *A*-4) was missed by Johnston *et al.* (*8*) because the compound vaporized from their testing system. Uhlenbroek and Koopmans (*19*) may have reported trichloromethyl-methyl disulfide (Figure 1, *A*-1) as nontoxic for the same reason.

O-n-butyl trichloromethane sulfenate (Figure 1, *A*-3) may be unstable. Sosnovsky (*18*) reported it as nontoxic. Many simple amine derivatives of trichloromethylmercaptan decompose on standing (*3, 7*). The isobutyl analog is toxic to certain fungi and boils at a lower temperature than does *O-n*-butyl trichloromethane sulfenate. Hence, the lack of activity of the *n*-butyl analog is not due to volatility.

Some compounds containing two —$SCCl_3$ groups have been reported as nontoxic. Analogs of 1,4-di(trichloro-