



**HAL**  
open science

## Synthesis and anticholinesterasic activity of some $\alpha$ -thio-substituted O-(methylcarbamoyl)oximes

G rard Vilarem, Georges Merlina, Jean-Pierre Calmon

### ► To cite this version:

G rard Vilarem, Georges Merlina, Jean-Pierre Calmon. Synthesis and anticholinesterasic activity of some  $\alpha$ -thio-substituted O-(methylcarbamoyl)oximes. *Journal of Agricultural and Food Chemistry*, 1989, 37 (1), pp.173-177. <10.1021/jf00085a040>. <hal-03486851>

**HAL Id: hal-03486851**

**<https://hal.science/hal-03486851v1>**

Submitted on 17 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destin e au d p t et   la diffusion de documents scientifiques de niveau recherche, publi s ou non,  manant des  tablissements d'enseignement et de recherche fran ais ou  trangers, des laboratoires publics ou priv s.



HAL Authorization



## Open Archive Toulouse Archive Ouverte (OATAO)

OATAO is an open access repository that collects the work of Toulouse researchers and makes it freely available over the web where possible.

This is an author-deposited version published in: <http://oatao.univ-toulouse.fr/>  
Eprints ID: 5886

**To link to this article:** DOI: 10.1021/jf00085a040

URL: <http://dx.doi.org/10.1021/jf00085a040>

**To cite this version:** Vilarem, Gérard and Merlina, Georges and Calmon, Jean-Pierre *Synthesis and anticholinesterasic activity of some  $\alpha$ -thio-substituted O-(methylcarbamoyl)oximes*. (1989) *Journal of Agricultural and Food Chemistry*, vol. 37 (n°1). pp. 173-177. ISSN 0021-8561

Any correspondence concerning this service should be sent to the repository administrator: [staff-oatao@listes.diff.inp-toulouse.fr](mailto:staff-oatao@listes.diff.inp-toulouse.fr)

# Synthesis and Anticholinesterasic Activity of Some $\alpha$ -Thio-Substituted *O*-(Methylcarbamoyl)oximes

Gérard Vilarem,<sup>1</sup> Georges Mrlina, and Jean Pierre Calmon\*

A series of six oxime *N*-methylcarbamates,  $C_6H_5C(R)=NOCONHCH_3$  [ $R = SCH_3, CH_2SCH_3, (Z)$ - and  $(E)$ - $CH(CH_3)_2SCH_3, C(CH_3)_2SCH_3, C(CH_3)_3$ ], analogues of commercial compounds such as aldicarb, butocarboxim, methomyl, and thiofanox, was synthesized for potential anticholinesterasic activity. NMR, IR, and UV were used to assign the configurations. The kinetic study of the inhibition of acetylcholinesterase from bovine erythrocyte and the determination of the dissociation constant  $K_d$  and of the carbamylation rate constant  $k_2$  allowed discussion of the importance of the number of methyl groups on the carbon  $\alpha$  to the imine group. The insertion of the phenyl group generally did not improve the activity but yielded compounds, one isomer of which had a potential activity close to that of the commercial compounds.

In 1965, Weiden et al. first described the *O*-(methylcarbamoyl)oximes as cholinesterase inhibitors. The replacement of the weakly acidic phenol by another weakly acidic group, such as an aliphatic or alicyclic oxime, in the synthesis broadened the family of the insecticidal carbamates. Further, in order to obtain an optimized acetylcholinesterase inhibition, structure-activity studies showed that conformational similarity to acetylcholine, mono-methylation of the carbamate nitrogen, and  $\alpha$ -alkylthio substitution were essentials (Fridinger et al., 1971).

The compounds described in this work belong to the group of the  $\alpha$ -substituted *O*-(methylcarbamoyl)acetophenoximes studied by Fukuto et al. (1969) and Jones et al. (1972).

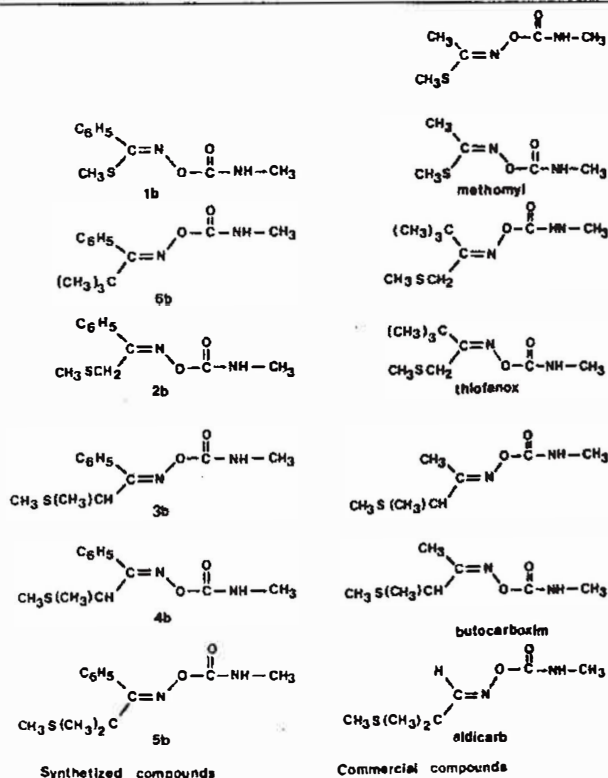
Mrlina and Calmon (1980a,b) characterized the mechanism of hydrolysis for this group and discussed the anticholinesterasic activity versus physicochemical parameters. Following those previous studies, a new series of *O*-(methylcarbamoyl)oximes was synthesized with a structure resembling those of commercial compounds as aldicarb, butocarboxim, methomyl, and thiofanox (Table I). These new molecules retained the main structure of the commercial analogue to which a phenyl group was added on the carbon bearing the imine bond. This transformation might increase their lipophilic character, thereby promoting the penetration of these molecules in the insect integument (Gerolt, 1970, 1972).

The effects induced by this modification were determined by measuring acetylcholinesterase inhibition *in vitro*, which is a good estimation of insecticidal activity for those molecules.

## MATERIALS AND METHODS

The commercial oxime *N*-methylcarbamates submitted to the *in vitro* anticholinesterase activity test are the following: aldicarb or 2-methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime; aldoxycarb or 2-methyl-2-(methylthio)butanaldehyde *O*-(methylcarbamoyl)oxime; butocarboxim or 3-(methylthio)butanone *O*-(methylcarbamoyl)oxime; butoxycarboxim or 3-(methylsulfonyl)-2-butanone *O*-(methylcarbamoyl)oxime; oxamyl or *S*-methyl *N,N'*-dimethyl-*N*-[(methylcarbamoyl)oxy]-1-thioxamimidate; methomyl or methyl *N*-[(methylcarbamoyl)oxy]thioacetimidate; thiofanox or 3,3-di-

Table I. Structures and Names of Studied Compounds



methyl-1-(methylthio)-2-butanone *O*-(methylcarbamoyl)oxime.

The high-grade pesticides were provided by the Cluzeau Info Labo Co. (33220 Ste. Foy La Grande, France), and their purity was checked by NMR and thin-layer chromatography.

## SYNTHESIS

The  $\alpha$ -thio-substituted ketones (starting molecules for compounds 2b, 3b, 4b, and 5b) were prepared by reacting thiomethane with the corresponding  $\alpha$ -bromo ketone according to Prelog et al. (1944). The intermediate oximes, 2a, 3a, 4a, and 5a were obtained by the addition of hydroxylamine to the ketones as described by Grob and Ide (1974). The procedure described by Benn (1964) permitted us to synthesize molecule 1a by chlorination of the benzaldoxime on the  $\alpha$ -position and substitution of the chlorine atom by the thiomethyl group. Isobutyrophenoxime was synthesized following the conditions used by Nef (1900). The melting points and the configuration of the oximes

Laboratoire d'Agrochimie et Chimie Organique Biologique, Ecole Nationale Supérieure Agronomique de Toulouse, 145 Avenue de Muret, 31076 Toulouse Cedex, France.

**Table II. Melting Points and Configuration of Oximes:  $C_6H_5(R)C=NOH$**

no.	R	isomer	mp, °C	lit. mp, °C
1a	SCH <sub>3</sub>	Z	83-84	85 <sup>a</sup>
2a	CH <sub>2</sub> SCH <sub>3</sub>	Z	58	59-60.5 <sup>b</sup>
3a	CH(CH <sub>3</sub> )SCH <sub>3</sub>	E <sup>d</sup>	100	102-103 <sup>b</sup>
4a	CH(CH <sub>3</sub> ) <sub>2</sub> SCH <sub>3</sub>	Z <sup>e</sup>	76	94-95 <sup>b</sup>
5a	C(CH <sub>3</sub> ) <sub>2</sub> SCH <sub>3</sub>	E	130	130-130.5 <sup>b</sup>
6a	C(CH <sub>3</sub> ) <sub>3</sub>	E	166-167	165 <sup>c</sup>

<sup>a</sup>Benn (1964). <sup>b</sup>Grob and Ide (1974). <sup>c</sup>Nef (1900). <sup>d</sup>90% E isomer. <sup>e</sup>90% Z isomer.

converted to the carbamate by addition of a stoichiometric quantity of methyl isocyanate in anhydrous ethyl ether with triethylamine as catalyst.

**$\alpha$ -(Methylthio)acetophenone (Grob and Ide, 1974).** To 0.12 mol of thiomethane dissolved in 50 mL of sodium methanolate at 0 °C was added 0.095 mol of  $\alpha$ -bromoacetophenone. Stirring was continued for 2 h at that temperature and then stopped; the solution was left at room temperature for 12 h. After extraction with ethyl ether, the oily fraction was distilled under reduced pressure.

**$\alpha$ -(Methylthio)acetophenoxime (2a) (Grob and Ide, 1974).** A solution containing 0.056 mol of  $\alpha$ -(methylthio)acetophenone and 0.17 mol of hydroxylamine hydrochloride in 53 mL of pyridine was stirred for 24 h at room temperature. The reacting medium was washed with a cold solution of hydrochloric acid (0 °C) and extracted with ethyl ether. The final product was recrystallized from hexane.

**$\alpha$ -(Methylthio)acetophenone *O*-(Methylcarbamoyl)oxime (2b).** Methyl isocyanate (0.023 mol) was allowed to react with 0.022 mol of  $\alpha$ -(methylthio)acetophenone oxime in 50 mL of anhydrous ethyl ether containing catalytic quantities of triethylamine. After 12 h, the *N*-methylcarbamate was filtered and then recrystallized from a mixture of hexane and toluene (30/50).

**Benzohydroxamoyl Chloride (Benn, 1964).** Benzaldoxime (0.099 mol) was dissolved in chloroform (200 mL) and the resultant mixture cooled to 0 °C in an ice salt bath. A fairly slow stream of dry chlorine was bubbled through the solution until the starting blue solution turned yellow.

***S*-Methyl Benzothiohydroximate (Benn, 1964).** To a mixture of benzohydroxamoyl chloride (0.05 mol) and

methanethiol (0.042 mol) dissolved in anhydrous ethyl ether (200 mL) was added triethylamine (0.1 mol). A white precipitate of triethylamine hydrochloride appeared instantaneously. The reaction medium was washed with a cold 0.5 N sulfuric acid first and then extracted with ethyl ether. The final product was recrystallized from an ethyl ether/petroleum ether mixture (1/1).

**Isobutyrophenoxime (Nef, 1900).** The oxime was obtained by reacting two molecules of hydroxylamine hydrochloride with one molecule of isobutyrophenone in a mixture of ethanol and water (15/25). The oxime crystals were recrystallized in hexane and in ethanol.

The two last oximes were converted into the *N*-methylcarbamate in the same way as described for compound 2b.

In every case, except for compound 3a, a single isomer was obtained for the oxime and the configurations were in agreement with those previously described. The chromatographic method used by Grob and Ide (1974) did not lead to a good separation of the two isomers *E* and *Z*. After repeated recrystallizations from hexane, two fractions, each containing a single isomer of 90% purity, could be obtained. A complete separation of the carbamate derivatives could be achieved by flash chromatography (Still et al., 1978). In a 40-cm-high column (4-cm i.d.) containing 15 cm of 230-400-mesh silica gel (Merck 9385), the isomers were eluted with a mixture of ethyl acetate/petroleum ether (45/55) at a rate of 10 cm/min. Thin-layer chromatography (Merck 5526) of the isomers, using as eluant ethyl acetate/petroleum ether (50/50), ensures an isomeric purity of 99% ( $\Delta R_f = 0.16$ ) for the carbamic derivatives.

The structures were confirmed by elemental analysis and by their IR, UV, and NMR spectra. The results are shown in Tables III-V. The infrared spectra were taken on a Perkin-Elmer Model 783 either in solution (chloroform or carbon tetrachloride) or as a KBr pellet. The UV spectra were obtained in ethanol with a Cary 210 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A 56/60 spectrometer with tetramethylsilane as internal standard and deuteriated chloroform or dimethyl sulfoxide as solvents.

#### ACETYLCHOLINESTERASE INHIBITION

The anticholinesterase activity was measured with purified bovine erythrocyte acetylcholinesterase, XII S 0.4-1

**Table III. Physicochemical Characteristics of Oxime *N*-Methylcarbamates:  $C_6H_5(R)C=NOC(=O)NHCH_3$**

no.	R	mp, °C	isomer	elemental analyses							
				calculated, %				found, %			
				C	H	N	S	C	H	N	S
1b	SCH <sub>3</sub>	119 <sup>a</sup>	Z	53.56	5.40	12.49	14.29	53.52	5.43	12.67	14.83
2b	CH <sub>2</sub> SCH <sub>3</sub>	92-94	Z	55.44	5.92	11.75	13.45	55.30	5.72	12.01	13.19
3b	CH(CH <sub>3</sub> )SCH <sub>3</sub>	102	E	57.12	6.39	11.10	12.70	57.24	6.39	10.84	13.40
4b	CH(CH <sub>3</sub> ) <sub>2</sub> SCH <sub>3</sub>	98	Z	57.12	6.39	11.10	12.70	57.03	6.34	11.63	12.62
5b	C(CH <sub>3</sub> ) <sub>2</sub> SCH <sub>3</sub>	205	E	58.62	6.81	10.51	12.03	58.61	6.69	10.36	12.62
6b	C(CH <sub>3</sub> ) <sub>3</sub>	158	E	66.66	7.69	11.96		66.18	7.76	11.86	

<sup>a</sup>Lit. mp 119 °C (Fukuto et al., 1969).

**Table IV. NMR and UV Spectra of Oximes  $C_6H_5(R)C=NOH$**

no.	$C_6H_5$	<sup>1</sup> H NMR <sup>a</sup>							UV <sup>b</sup>			
		H(C <sup>α</sup> )	SCH <sub>3</sub>	OH	HC(C <sup>α</sup> ) (d <sup>c</sup> )	OH (d <sup>c</sup> )	HC(C <sup>α</sup> ) (d <sup>c</sup> )	OH (d)	$\lambda_{max}$	lit. <sup>c</sup> $\lambda_{max}$	$\epsilon$	lit. <sup>c</sup> $\epsilon$
1a	7.43 (s)	2.09 (s)					11.55	219		10320		
2a	7.56 (m)	3.86 (s)	2.15 (s)	8.23 (s)	3.81 (s)	11.36 (s)	3.84 (s)	249	250	10560		10964
3a	7.43 (s)	3.66 (q)	2.10 (s)	8.33 (s)	3.80 (q)	10.63 (s)	3.86 (q)	221	221	6080 (sh)		6918 (sh)
4a	7.50 (m)	4.81 (q)	2.16 (s)	9.08 (s)	4.73 (q)	11.16 (s)	4.74 (q)	236.7	236.5	7760		7762
5a	7.39 (s)		2.06 (s)	7.86 (s)		10.53 (s)						
6a	7.19 (m)			8.13 (s)		10.26 (s)						

<sup>a</sup>Chemical shifts in ppm; (CH<sub>3</sub>)<sub>4</sub>Si internal standard; CDCl<sub>3</sub> solvent since DMSO was used (d). Key: s, singlet; d, doublet; q, quartet; m, multiplet; sh, shoulder. <sup>b</sup>Wavelengths in nm; EtOH solvent. <sup>c</sup>Grob and Ide (1974).

Table V. NMR and UV Spectra of Oxime *N*-Methylcarbamates:  $C_6H_5(R)C=NOC(=O)NHCH_3$

no.	$^1H$ NMR <sup>a</sup>						UV <sup>b</sup>	
	$C_6H_5$	H(C <sup>α</sup> )	H(C <sup>β</sup> )	NH	NCH <sub>3</sub>	SCH <sub>3</sub>	$\lambda_{max}$	$\epsilon$
1b	7.45 (s)			6.10 (br)	2.83 (d)	2.06 (s)	215	9920
2b	7.53 (m)	3.89 (s)		6.39 (br)	2.93 (d)	2.13 (s)	248.7	12080
3b	7.43 (s)	3.81 (q)	1.33 (d)	6.06 (br)	2.89 (d)	2.16 (s)	222	6400 (sh)
4b	7.56 (m)	4.86 (q)	1.43 (d)	6.39 (br)	2.93 (d)	2.16 (s)	234.6	7600
5b	7.35 (s)		1.46 (s)	5.93 (br)	2.86 (d)	2.10 (s)		
6b	7.26 (m)		1.25 (s)	6.16 (br)	2.86 (d)			

<sup>a</sup>Chemical shifts in ppm;  $(CH_3)_4Si$  internal standard;  $CDCl_3$  solvent. Key: s, singlet; d, doublet; q, quartet; m, multiplet; br, broad; sh shoulder. <sup>b</sup>Wavelengths in nm; EtOH solvent.

unit/mg of solid, purchased from Sigma Chemical Co. and acetylcholinesterase, XII S 0.4–1 unit/mg of solid, purchased from Sigma Chemical Co. and acetylcholine hydrochloride provided by Koch Light Laboratories as substrate. The residual activity was determined by the method of pH-stat as described by Nishioka et al. (1976). Both enzyme and substrate were dissolved in a phosphate buffer, 10 mM, pH 7.6, containing 0.1 M NaCl (13.9 mg of AChE, activity 0.54 unit/mg of solid in 1 mL of buffer). The inhibitors, commercial or previously described oxime carbamates, were added to the reaction medium as freshly prepared ethanolic solutions. The final concentration of ethanol in the enzyme reaction medium did not exceed 2.5%.

To 2 mL of phosphate buffer were added first 10–50  $\mu L$  of the ethanolic solution of the inhibitor and then only 50  $\mu L$  of the enzymatic solution. After 3 min of incubation time, the pH was adjusted to its initial value of 7.6 with a  $2 \times 10^{-2}$  N NaOH solution and then the substrate added (0.5 mL of 10 mM acetylcholine). The reaction was followed by an automatic titrator (Radiometer pHM 64, combined with a TTT60 titrator and Autoburet ABU13) with a  $2 \times 10^{-2}$  N NaOH carbonate-free solution as the titrant. Incubation and reaction temperatures were held at  $25 \pm 0.2$  °C.

## RESULTS AND DISCUSSION

Prior to any activity interpretation, synthesized oxime *N*-methylcarbamates were checked for their structure and, in some cases, their configurations could be confirmed.

**NMR Spectra.** The chemical shifts concerning the oximes (series a) and the corresponding carbamates (series b) are reported in Tables IV and V. The results observed for the oximes are close to those observed by Grob and Ide (1974). For the hydroxyl proton, the difference in the chemical shifts between those obtained in dimethyl sulfoxide and those in chloroform fluctuates from 1.68 to 3.21 ppm. Such a difference could be explained by a solvent effect. Dimethyl sulfoxide used by Grob and Ide seems to be more effective for the disrupting of the intermolecular hydrogen bond than the deuterated chloroform. Thereby, the protons beared by the hydroxyl group are more protected and resonate at higher fields (7.8–9 ppm) than in dimethyl sulfoxide (10.7–11.4 ppm). A similar phenomenon was earlier described by Karabatsos and Taller (1968). For that series of oximes, the chemical shift observed in deuterated dimethyl sulfoxide is typical of the configuration; the hydroxyl proton of the *E* isomer appears at lower fields than that of the *Z* isomer (over 10.63 ppm).

For both oximes and carbamates, a difference appeared in the behavior of the phenyl protons that could give either a singlet or a multiplet. The bulkiness of the substituents neighboring the carbon  $\alpha$  to the imine bond disturbs the coplanarity of the phenyl ring with the imine bond, modifying the spatial interactions between the protons of the substituent and those of the phenyl ring. The singlet seems to be linked to the noncoplanar position. The in-

fluence on the protons belonging to the carbon  $\alpha$  to the  $C=N$ , owed to the position of the hydroxyl group on one or on the other side of the imine double bond, is well shown by the spectra of compounds 3a and 4a. The proton in  $\alpha$ -position resonates as a quartet at 4.81 ppm for molecule 4a and 3.66 ppm for molecule 3a. According to Karabatsos and Taller (1968) and Berlin and Rengaraju (1971), the protons on the carbon  $\alpha$  to the imine bond *cis* to the hydroxyl group resonate at lower fields than the corresponding protons in *trans* position. So we can conclude that molecule 4a is really the *Z* isomer and molecule 3a the *E* isomer. For those protons, the variation between the chemical shifts due to isomerism is smaller for the carbamate series than for the oxime series. In the same way, protons of the aromatic ring resonate under 7.43 ppm for the *E* isomers and over 7.50 ppm for the *Z* isomers. For the proton on the carbamoyl nitrogen, the effects of the oximino function are expressed by higher chemical shifts for the *Z* isomer (6.39 ppm) than for the *E* isomer (below 6.16 ppm).

**Infrared Spectrophotometry.** In the infrared spectrum of molecule 4a, done in a KBr pellet, the O–H stretching band appears at  $3160\text{ cm}^{-1}$  for the isomer *trans* (phenyl and OH in *trans* position) and at  $3200\text{ cm}^{-1}$  for its *cis* homologue (molecule 3a). This change in frequencies of the absorption of the OH bond is in agreement with the observations of Palm and Werbin (1953, 1954) who found this difference in the frequencies for oximes between *E* and *Z* forms.

In chloroform solution as in carbon tetrachloride diluted solution, the oximes are characterized by a strong, sharp band at  $3580\text{ cm}^{-1}$  for the absorption of the "free" OH and by a medium-broad band at  $3280\text{--}3300\text{ cm}^{-1}$  due to the absorption of the bonded OH itself. The aromatic band is slightly shifted to  $3000\text{ cm}^{-1}$  because of the conjugation of the phenyl group with the  $C=N$  double bond. The absorption of this last bond appears at  $1620$  and  $1500\text{ cm}^{-1}$  as sharp, medium bands. For molecule 1a, the absorption at  $1620\text{ cm}^{-1}$  is in agreement with the observations of Goulden (1953). The *N*-methylcarbamates corresponding to those oximes stand out by the stretching band of free N–H bond at  $3425$  or  $3440\text{ cm}^{-1}$  (strong and very sharp), a very strong vibration of the carbonyl group at  $1740\text{ cm}^{-1}$ , a bending band at  $1500\text{--}1530\text{ cm}^{-1}$  for the N–H bond, and a strong absorption of C–O bond of the carbamoyl function near  $1200\text{--}1240\text{ cm}^{-1}$  (Nyquist, 1973).

**Ultraviolet Spectrophotometry.** The UV spectrophotometry can contribute to the configurational assignment of the isomers: For example, isomer 3a, possessing a phenyl group *trans* to the oxygen atom, exhibits an absorption maximum at a lower wavelength with a smaller extinction coefficient than its isomer 4a (*cis* isomer), results in agreement with those of Karabatsos and Hsi (1967).

**Acetylcholinesterase Inhibition.** As acetylcholine is the synaptic mediator of neurotransmission in the central nervous system in insects and vertebrates, the *N*-methylcarbamates act as substrates whose biological cycle



- Cohen, S. G.; Chishti, S. B.; Elkind, J. L.; Reese, H.; Cohen, J. B. Effects of charge, volume and surface on binding of inhibitor and substrate moieties to acetylcholinesterase. *J. Med. Chem.* 1985, 28, 1309-1313.
- Durden, J. A.; Weiden, M. H. J. Insecticidal 2-(methylcarbamoyloxyphenyl)-1,3-dioxolanes, -oxathiolanes, and -dithiolanes. *J. Agric. Food Chem.* 1969, 17, 94-100.
- Felton, J. C. Insecticidal activity of some oxime carbamates. *J. Sci. Food Agric.* 1968, 19 (Suppl), 32-38.
- Fridinger, T. L.; Mutsch, E. L.; Bushong, J. W.; Matteson, J. W. Synthesis and biological activity of  $\alpha$ -mercaptol O-(carbamoyl)oximes. *J. Agric. Food Chem.* 1971, 19, 422-431.
- Fukuto, T. R.; Metcalf, R. L.; Jones, R. L.; Myers, R. O. Structure, reactivity and biological activity of O-(diethyl phosphoryl)oximes and O-(methylcarbamoyl)oximes of substituted acetophenones and  $\alpha$ -substituted benzaldehydes. *J. Agric. Food Chem.* 1969, 17, 923-930.
- Gerolt, P. The mode of entry of contact insecticides. *Pestic. Sci.* 1970, 1, 209-212.
- Gerolt, P. The mode of entry of oxime carbamates into insects. *Pestic. Sci.* 1972, 3, 43-55.
- Goulden, J. D. S. Infrared spectra of quaternary methiodides of N,N-disubstituted thioamides. *J. Chem. Soc.* 1953, 997-998.
- Grob, C. A.; Ide, J. Beckmann fragmentation and rearrangement. Part VII. Fragmentation and cyclization of  $\alpha$ -methylthio-ketoximes. *Helv. Chim. Acta* 1974, 57, 2571-2583.
- Hart, G. J.; O'Brien, R. D. Recording spectrophotometry method for determination of dissociation and phosphorylation constants for the inhibition of acetylcholinesterases by organophosphates in the presence of substrate. *Biochemistry* 1973, 12, 2940-2945.
- Hastings, F. L.; Main, A. R.; Iverson, F. Carbamylation and affinity constants of some carbamate inhibitors of acetylcholinesterase and their relation to analogous substrate constants. *J. Agric. Food Chem.* 1970, 18, 497-502.
- Jones, R. L.; Fukuto, T. R.; Metcalf, R. L. Structure, reactivity and biological activity of O-(methylcarbamoyl)oximes of substituted benzaldehydes. *J. Econ. Entomol.* 1972, 65, 28-32.
- Karabatsos, G. J.; Hsi, N. Structural studies by nuclear magnetic resonance—XI. Conformations and configurations of oxime O-methyl ethers. *Tetrahedron* 1967, 23, 1079-1095.
- Karabatsos, G. J.; Taller, R. A. Structural studies by nuclear magnetic resonance—XV. conformation and configuration of oximes. *Tetrahedron* 1968, 24, 3347-3360.
- Mrlina, G.; Calmon, J. P. Kinetics and mechanism of hydrolysis of insecticidal O-(methylcarbamoyl)oximes. *J. Agric. Food Chem.* 1980a, 28, 605-609.
- Mrlina, G.; Calmon, J. P. Inhibition of acetylcholinesterase by O-(methylcarbamoyl)oximes. Structure-activity relationships. *J. Agric. Food Chem.* 1980b, 28, 673-675.
- Nef, J. U. Ueber die alkylierung der ketone. *Annalen* 1900, 310, 316-321.
- Nishioka, T.; Kitamura, K.; Fujita, T.; Nakajima, M. Kinetic constants for the inhibition of acetylcholinesterase by phenylcarbamates. *Pestic. Biochem. Physiol.* 1976, 6, 320-337.
- Nishioka, T.; Fujita, T.; Kamoshita, K.; Nakajima, M. Mechanism of inhibition reaction of acetylcholinesterase by phenyl N-methylcarbamates. Separation of hydrophobic, electronic, hydrogen bonding and proximity effects of aromatic substituents. *Pestic. Biochem. Physiol.* 1977, 7, 107-121.
- Nyquist, R. A. Infrared spectra-structure correlations of carbamic acid: aryl-, alkyl esters. *Spectrochim. Acta* 1973, 29A, 1635-1641.
- Palm, A.; Werbin, H. The infrared spectra of alpha and beta oximes. *Can. J. Chem.* 1953, 31, 1004-1008.
- Palm, A.; Werbin, H. Infrared study of the N-OH group in alpha and beta oximes. *Can. J. Chem.* 1954, 32, 858-863.
- Prelog, V.; Hahn, V.; Brauchli, H.; Beyerman, H. C. Ueber alkyl-( $\beta$ -oxy- $\beta$ -aryl-aethyl)-sulfide und dialkyl-( $\beta$ -oxy- $\beta$ -aryl-aethyl)-sulfonium-salze. *Helv. Chim. Acta* 1944, 27, 1209-1217.
- Still, C. W.; Kahn, M.; Mitra, A. Rapid chromatography technic for preparative separations with moderate resolution. *J. Org. Chem.* 1978, 43, 2923-2925.
- Weiden, M. H. J.; Moorefield, H. H.; Payne, L. K. O-(methylcarbamoyl)oximes: a new class of carbamate insecticides-acaricides. *J. Econ. Entomol.* 1965, 58, 154-155.