SYNTHESIS AND STRUCTURE OF TETRAHYDRO-1,2-OXAZINE-N-DITHIOCARBOXYLIC ACID ESTERS

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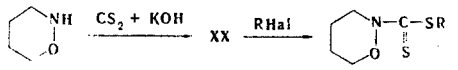
UDC 547.867.1.07:543.422.25.4

New tetrahydro-1,2-oxazine-N-dithiocarboxylic acid esters were synthesized, and their structures were investigated by IR and PMR spectroscopy and mass spectrometry.

The biological activity of compounds containing a 1,2-oxazine ring is well known [1]. In order to search for new pesticides we synthesized substances containing, in addition to the indicated structural fragment, a dithiocarbamate group, which is responsible for the fungicidal, acaricidal, and herbicidal activity of compounds of other classes.

We used the condensation of tetrahydro-1,2-oxazine (XIX) with carbon disulfide and alkali, which leads to the potassium salt of this acid (XX), for the synthesis of tetrahydro-1,2-oxazine-N-dithiocarboxylic acid esters (I-XVIII). Treatment of XX with alkyl halides readily converts it to esters I-XVIII.



XIX I-XVIII

XX R=K

The preparation of starting oxazine XIX includes the condensation of 1,4-dibromobutane with N-hydroxyethylurethane and saponification and decarboxylation of the resulting N-carbethoxytetrahydro-1,2-oxazine (XXI). Free base XIX was isolated by neutralization of the hydrochloride of XIX with potassium carbonate.

However, the literature [2] does not contain proof for the structure of XXI, and the method used to prepare it permits the probability of the formation of noncyclic structure $C_2H_5OOC-NH(CH_2)_4OH$. We therefore studied the spectral properties of I-XIX to confirm the presence of an O—N bond in the synthesized compounds.

Direct information regarding the existence of this bond in the tetrahydro-1,2-oxazine molecule could not be obtained from the IR spectral data because of the noncharacteristic nature of the stretching vibration of the O—N bond in compounds of this type. However, the IR and PMR spectral data indirectly confirm the presence of this bond in oxazine XIX. Thus the presence in the IR spectrum of a narrow band of medium intensity at 3316 cm^{-1}, which is due to the stretching vibrations of a secondary amino group, excludes the possibility of cleavage of the O—N bond to give 4-aminobutanol (XXII). The presence of a one-proton singlet at 5.0 ppm in the PMR spectrum (Table 1, XIX) also constitutes evidence for the presence of a secondary amino group in the compound. The fact that not only the signal of the protons of the methylene group attached to the nitrogen atom (from 3.08 to 3.45 ppm) but also the signal of the protons of the methylene group attached to the oxygen atom (from 3.84 to 4.40 ppm) experience a paramagnetic shift on passing from free base XIX to the hydrochloride also makes it possible to exclude structure XXII.

The PMR spectral data for tetrahydro-1,2-oxazine-N-dithiocarboxylic acid esters are in complete agreement with the structures of these compounds. The assignments of the signals in the PMR spectra of esters I-XVIII are presented in Table 1.

Shchelkovo Branch, All Union Scientific-Research Institute of Chemical Agents for the Protection of Plants. Patrice Lumumba International-Friendship University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 454-458, April, 1976. Original article submitted April 28, 1975.

TABLE 1. Data from the PMR Spectra of Tetrahydro-1,2-hydrazine and Tetrahydro-1,2-oxazine-N-dithiocarboxylic Acid Esters

Compound	Solvent	Assignments, δ, ppm (multiplicity; J, Hz)											
		NCH_2	OCH_2	$OC(CH_2)_2CN$	NH	SCH_2	SCH_2CH_2	$C(CH_2)_nCH_3$	CCH_3	CH-	CH_2-	aromatic H	aromatic CH_3
I	CCl_4	4,12 (m)	4,42 (m)	1,88 (m)		2,43 (s)							
II	CCl_4	4,08 (m)	4,39 (m)	1,88 (m)		3,10 (q; 7,5)			1,28 (t; 7,5)				
III	CCl_4	4,13 (m)	4,43 (m)	1,90 (m)		3,12 (t; 7,4)	1,70 (m)		1,04 (t; 7,0)				
IV	CCl_4	4,10 (m)	4,40 (m)	1,89 (m)		3,12 (t; 7,5)	1,58 (m)		0,98 (m)				
V	CCl_4	4,06 (m)	4,38 (m)	1,88 (m)		3,07 (t; 7,0)	1,68 (m)	1,48 (m)	0,93 (m)				
VI	CCl_4	4,09 (m)	4,42 (m)	1,88 (m)		3,12 (t; 7,0)	1,69 (m)	1,38 (m)	0,92 (m)				
VII	CCl_4	4,08 (m)	4,38 (m)	1,85 (m)		3,09 (t; 7,0)	1,65 (m)	1,33 (us)‡	0,88 (m)				
IX	CCl_4	4,08 (m)	4,40 (m)	1,88 (m)		3,08 (t; 7,0)	1,67 (m)	1,29 (us)	0,90 (m)				
XI	CCl_4	4,08 (m)	4,42 (m)	1,88 (m)		3,10 (t; 7,5)	1,61 (m)	1,25 (s)	0,88 (m)				
XII	CCl_4	4,01 (m)	4,38 (m)*	1,80 (m)		4,28 (s)						7,21 (m)	
XIII	CCl_4	4,03 (m)	4,38 (m)*	1,82 (m)		4,26 (s)						7,07 (m)	2,28 (s)
XIV	CCl_4	4,00 (m)	4,37 (m)	1,80 (m)		3,15 (m)†						7,18 (m)	
XV	CCl_4	4,02 (m)	4,37 (m)*	1,82 (m)		4,31 (s)						7,64—7,05 (m)	
XVI	CCl_4	4,08 (m)	4,40 (m)*	1,87 (m)		4,33 (s)						7,20—7,37 (m)	
XVII	CCl_4	4,02 (m)	4,37 (m)	1,83 (m)		4,48 (s)						7,72—7,05 (m)	
XVIII	CCl_4	4,07 (m)	4,35 (m)	1,83 (m)		3,78 (d; 7,0)‡				5,90 (m; 17,0; 10,0 7,0)	5,47—4,97 (m)		
XIX	$CDCl_3$	3,08 (m)	3,84 (m)	1,67 (m)	5,0 (s)								
XIX Hydrochloride	$CDCl_3$	3,45 (t; 6,0)	4,40 (t; 6,0)	2,13 (m) 1,89 (m)	10,04 (bs)								

*The singlet from the SCH_2 group is superimposed on this signal.

†The SCH_2CH_2Ph grouping is a four-spin AA'BB' system and is responsible for the mirror-image symmetrical multiplet centered at 3.15 ppm.

‡A doublet with additional splitting due to allylic coupling; bs indicates a broad signal, and us indicates an unresolved or poorly resolved signal that shows up as a singlet.

TABLE 2. Tetrahydro-1,2-oxazine-N-dithiocarboxylic Acid Esters

Compound	R	bp, °C (mm)	mp, °C	d_4^{20}	n_D^{20}	Found, %					Empirical formula	Calculated, %					Yield, %
						C	H	Hal	N	S		C	H	Hal	N	S	
I	CH_3	100,0—100,5 (0,22)	48—49 (hexane—ethanol)			40,7	6,1		7,8	36,3	$C_6H_{11}NOS_2$	40,7	6,3		7,9	36,2	92
II	C_2H_5	107—108 (0,22)		1,1838	1,5954	43,7	7,0		7,1	33,6	$C_7H_{13}NOS_2$	43,9	6,8		7,3	33,5	92
III	n-C_3H_7	111—112 (0,1)		1,1447	1,5830	47,0	7,3		7,0	31,3	$C_8H_{15}NOS_2$	46,8	7,4		6,8	31,2	87
IV	n-C_4H_9	122—123 (0,18)		1,1148	1,5713	49,5	8,0		6,3	29,1	$C_9H_{17}NOS_2$	49,3	7,8		6,4	29,2	89
V	n-C_5H_{11}	130,5—131,0 (0,18)		1,0950	1,5645	51,5	8,0		6,2	27,6	$C_{10}H_{19}NOS_2$	51,5	8,2		6,0	27,5	71
VI	n-C_6H_{13}	128—129 (0,08)		1,0746	1,5579	53,4	8,8		5,7	26,1	$C_{11}H_{21}NOS_2$	53,4	8,6		5,7	25,9	75
VII	n-C_7H_{15}	146—147 (0,18)		1,0571	1,5501	54,9	8,8		5,2	24,6	$C_{12}H_{23}NOS_2$	55,1	8,9		5,3	24,5	76
VIII	n-C_8H_{17}	159 (0,1)		1,0438	1,5461	56,7	9,2		5,2	23,4	$C_{13}H_{26}NOS_2$	56,7	9,2		5,1	23,3	76
IX	n-C_9H_{19}	174 (0,14)		1,0313	1,5408	58,2	9,4		4,8	21,9	$C_{14}H_{27}NOS_2$	58,1	9,4		4,8	22,2	67
X	n-$C_{10}H_{21}$	187—188 (0,17)		1,0170	1,5339	59,4	9,6		4,8	20,9	$C_{15}H_{29}NOS_2$	59,4	9,6		4,6	21,1	66
XI	n-$C_{12}H_{25}$		37—38			61,8	10,0		4,3	19,4	$C_{17}H_{33}NOS_2$	61,6	10,3		4,2	19,3	59
XII	$C_6H_5CH_2$		88,5—90,0			56,7	5,7		5,4	25,4	$C_{12}H_{15}NOS_2$	56,9	6,0		5,3	25,3	97
XIII	3-$CH_3C_6H_4CH_2$		48,5—49,0			58,6	6,5		5,3	24,2	$C_{13}H_{17}NOS_2$	58,4	6,4		5,2	24,0	78
XIV	$C_6H_5CH_2CH_2$		55,5—56,0			58,5	6,5		5,0	23,6	$C_{13}H_{17}NOS_2$	58,4	6,4		5,2	24,0	78
XV	3-$BrC_6H_4CH_2$		45,5—46,5			42,8	4,1	24,2	4,4	19,4	$C_{12}H_{14}BrNOS_2$	43,4	4,2	24,0	4,2	19,3	73
XVI	3-$ClC_6H_4CH_2$		36,0—37,0			50,1	4,9	12,5	5,1	22,2	$C_{12}H_{14}ClNOS_2$	50,1	4,9	12,3	4,9	22,3	50
XVII	2-$ClC_6H_4CH_2$		51,5—52,0			50,1	4,9	12,3	5,0	22,3	$C_{12}H_{14}ClNOS_2$	50,1	4,9	12,3	4,9	22,3	68
XVIII	$CH_2{=}CHCH_2$	121—122 (0,1)			1,6038	47,2	6,6		6,9	31,2	$C_8H_{13}NOS_2$	47,3	6,4		6,9	31,5	67

It should be noted that the shift to weak field (by ~0.51-0.59 ppm) of the signals of the O-methylene protons as compared with the spectrum of unsubstituted tetrahydro-1,2-oxazine serves as an additional confirmation of the presence of an O–N bond in the molecules of the investigated substances. The introduction of a $C(S)SCH_2$ grouping increases the chemical shift of the methylene protons attached to the nitrogen atom by 0.92-1.05 ppm (Table 1). As indicated by an examination of Stuart models, in the latter case the effect of the sulfur atoms through space may play a substantial role. In addition to the tetrahydro-1,2-oxazine ring, a common structural element in I-XVIII is the α-methylene group of the $N-C(S)SCH_2R$ fragment, for which chemical shifts of 3.08-3.12 ppm (when R = alkyl) and 4.26-4.28 ppm (when R = aryl are characteristic.

The mass spectra of I-XIX give a definitive confirmation of their structure. If the ring had been broken, one should have expected an increase in the molecular weight by two mass units, but this is not observed. Thus the mass spectrum of oxazine XIX is characterized by the presence of an intense molecular ion peak (here and subsequently, the m/e values for the corresponding ions are presented) of 87 rather than 89, which would have occurred in the case of XXII.

The mass spectra of esters I-XVIII also have molecular ion peaks containing a cyclic fragment. In addition, all of the mass spectra contain peaks in common corresponding to ions formed as a result of detachment of the substituents attached to the CS bonds – ions with m/e 163 $(M - R + H)^+$ and, in the case $R = CH_3$, 162 $(M - R)^+$ and 130 $(M - SR)^+$, as well as ions with m/e 171 formed during subsequent fragmentation.

The synthesized compounds have fungicidal and acaricidal activity, as well as weak insecticidal and herbicidal activity.

EXPERIMENTAL METHOD

The PMR spectra of CCl_4 or $CDCl_3$ solutions of the compounds were recorded with T-60 and HA-100D spectrometers (at 100 MHz for the hydrochloride of XIX) with tetramethylsilane as the internal standard. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The mass spectra were recorded with an MKh-1309 mass spectrometer at an ionizing-electron energy of 70 eV.

Potassium Tetrahydro-1,2-oxazine-N-dithiocarboxylate (XX). A solution of 4.02 g (0.29 mole) of potassium carbonate in 39 ml of water was added at 18-22° in the course of 20 min to 7.2 g (0.58 mole) of tetrahydro-1,2-oxazine hydrochloride, and the mixture was then stirred at 18-20° until carbon dioxide evolution had ceased completely. A solution of 3.26 g (0.58 mole) of potassium hydroxide in 13 ml of water and 4.6 g (0.61 mole) of carbon disulfide were then added successively to the mixture in the course of 15 min, after which the mixture was stirred at 37-38° for another 1.5 h. The unchanged carbon disulfide was removed by distillation, the residual solution was cooled and filtered, and the filtrate was diluted with 1500 ml of acetone. The resulting precipitate was removed by filtration, the solvent was removed by vacuum distillation to dryness, and the residue was recrystallized from ethanol to give 8.4 g (60.8%) of XX in the form of the hydrate with mp 113-114° (dec.). Found: C 25.3; H 5.1; N 5.9; S 27.0%. $C_5H_8NOS_2K \cdot 2H_2O$. Calculated: C 25.3; H 5.1; N 5.9; S 27.0%.

Methyl Tetrahydro-1,2-oxazine-N-dithiocarboxylate (I). A 4.45-g (0.31 mole) sample of methyl iodide was added at 18-22° in 10-12 min to a suspension of 7.1 g (0.30 mole) of XX in 70 ml of absolute ethanol, after which the mixture was stirred at 35-40° for 1.5 h. The end of the reaction was determined from the disappearance of starting XX by means of a qualitative reaction with 2% aqueous silver nitrate (a yellow precipitate is formed when XX is present). The mixture was cooled and filtered, and the filtrate was diluted with water (1 : 1). The product was extracted with three 50-ml portions of ether, and the extract was dried with sodium sulfate. The solvent was removed by distillation, and the residue was fractionated to give 5.1 g (92%) of ester I with bp 100.0-100.5° (0.22 mm) and mp 48-49°.

Compounds II-XVIII were similarly obtained. Compounds XI and XIII were purified, without fractionation, by crystallization from alcohol–hexane. Compounds XII and XIV-XVII were crystallized by cooling the reaction mixtures. The precipitated potassium bromide in these experiments was removed by filtration from the hot mixture. The products were recrystallized from ethanol. Data with respect to all of the experiments are presented in Table 2.

LITERATURE CITED

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