SYNTHESIS AND MASS SPECTRA OF 4-MONO- AND 4,4-DISUBSTITUTED 5,6-TETRAMETHYLENETETRAHYDRO-1,3-OXAZINE-2-THIONES

A. V. Peretokin, A. S. Moskovkin, I. V. Miroshnichenko,
M. Ya. Botnikov, Yu. F. Malina, and B. V. Unkovskii

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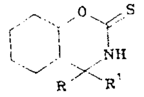
The syntheses and mass spectra of 5,6-tetramethylenetetrahydro-1,3-oxazine-2-thione and its 4-mono- and 4,4-disubstituted analogs are reported. The primary decay processes under electron impact are loss of the 1,3-oxazine ring, formation of hydrocarbon ions, and rearrangement of the $[M - C_6H_9]^+$ ion.

The present work is a continuation of earlier studies on the synthesis and decay under electron impact of substituted tetrahydro-1,3-oxazine-2-thiones [1-3]. We have now synthesized and examined the mass spectra of bicyclic analogs of these compounds, 5,6-tetramethylenetetrahydro-1,3-oxazine-2-thione(I) [4] and the previously unknown 4-mono- and 4,4-disubstituted 5,6-tetramethylenetetrahydro-1,3-oxazine-2-thiones (II-VI).



I-VI

I $R=R^1=H$; II $R=H$, $R^1=CH_3$; III $R=H$, $R^1=C_2H_5$; IV $R=R^1=CH_3$; V $R+R^1=$ $-(CH_2)_5-$; VI $R=H$, $R^1=C_6H_5$

Compound (I) was prepared earlier [4-6] by reaction of 2-aminomethyl-1-cyclohexanol (VII) with carbon disulfide in the presence of aqueous sodium hydroxide. Mouserron, Winternitz, and Mousseron-Canet [5, 6] suggested that the 1,3-aminoalcohol VII [7] was the trans-isomer. However, it was shown later [8, 9] that it was in fact a mixture of the cis- and trans-isomers. Thus, a mixture of the cis- and trans-isomers of oxazinethione I was prepared in [5, 6].

We synthesized the pure trans-isomer of I in [4-6] starting with the trans-2-aminomethyl-1-cyclohexanol [10] and carbon disulfide (method A; in [4], the experimental method and yield were not given. Analogously, reaction of the cis-2-(α-aminobenzyl)-1-cyclohexanol with carbon disulfide gives cis-4e-phenyl-5,6-tetramethylenetetrahydro-1,3-oxazine-2-thione (VI, method A). The starting aminoalcohol was prepared from cis-3-phenyl-4,5-tetramethyleneisoxazoline, which was synthesized by 1,3-dipolar cycloaddition of benzonitrile oxide to cyclohexene [11]. The isoxazoline formed was reduced with lithium aluminum hydride as in [12, 13].

In contrast to I and VI, oxazinethiones II-V were synthesized by reductive cyclization of the corresponding 2-(1-isothiocyanatoalkyl)-1-cyclohexanones [14, 15] (method B). This method as a rule gives mixtures of oxazinethione stereoisomers differing in the cis- and trans-configurations at the point of fusion of the rings, and in the case of II and III in the orientation of the alkyl substituent at $C_{(4)}$ of the oxazine ring. Oxazinethiones II-V with predominantly cis-fusion of rings were crystallized from mixtures of stereoisomers in alcohol. The properties and yields of oxazinethiones II-VI are given in Table 1. The configurations and preferred conformations of stereoisomers of II-V, established from PMR spectra, will be reported later.

The structures of II-VI were confirmed by IR spectra. The strong absorption band of the thioamide group ν_{CSNH} at 1540-1560 $msec^{-1}$ and the broad band with maximum at 3150-3170 cm^{-1} due to deformation of the N—H bond are present.

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TABLE 1. Properties of 4-Mono- and 4,4-Disubstituted 5,6-Tetramethylenetetrahydro-1,3-oxazine-2-thiones

Compound	Substituents		Empirical formula	mp, °C* (from alcohol)	Synthesis method	Yield†, %
	R	R'				
II	H	CH_3	$C_9H_{15}NOS$	204 ... 204,5	B	40,6
III	H	C_2H_5	$C_{10}H_{17}NOS$	173 ... 174	B	82,0
IV	CH_3	CH_3	$C_{10}H_{17}NOS$	204 ... 205	B	99,0
V	$-(CH_2)_5-$		$C_{13}H_{21}NOS$	167 ... 168	B	87,8
VI	H	C_6H_5	$C_{14}H_{17}NOS$	252 ... 254‡	A	48,6

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*Constants of the individual cis-isomers are shown.

†Yield of the cis- and trans-isomers is shown.

‡From isopropanol.

TABLE 2. Mass Spectra of I-VI

Compound	m/z (relative intensity, %)
I	171 (100), 95 (37), 94 (55), 82 (37), 81 (39), 79 (49), 67 (49), 55 (26), 54 (18), 43 (37), 41 (74)
II	185 (100), 109 (36), 104 (31), 81 (38), 79 (45), 67 (70), 55 (56), 54 (35), 43 (59), 42 (35), 41 (87)
III	199 (100), 118 (62), 110 (34), 93 (31), 81 (64), 67 (55), 58 (80), 57 (38), 56 (60), 55 (37), 41 (61)
IV	199 (100), 123 (72), 118 (51), 81 (42), 69 (26), 67 (36), 58 (60), 57 (35), 55 (25), 42 (48), 41 (40)
V	239 (100), 163 (33), 158 (31), 136 (33), 98 (48), 95 (31), 81 (62), 67 (48), 55 (39), 54 (45), 41 (79)
VI	247 (100), 171 (32), 166 (62), 129 (28), 106 (74), 105 (79), 104 (70), 91 (45), 79 (30), 77 (32), 41 (24)

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*Peaks for M^+ and the ten strongest ion peaks in the mass spectra are given.

TABLE 3. Peak Heights for Characteristic Ions in the Mass Spectra of I-VI (% Σ_{27})

Fragment	Compound					
	I	II	III	IV	V	VI
W_M	13,2	8,4	10,4	12,5	9,8	10,2
$[M-HS]^+$	1,3	1,0	0,8	0,2	1,5	0,5
Φ_1	4,9	3,0	1,8	7,6	2,6	3,2
Φ_2	6,5	3,2	1,0	1,0	—	0,9
Φ_3	1,2	2,6	5,4	5,4	2,5	6,3
Φ_4	2,9	2,1	7,0	6,3	3,9	7,6
Φ_5	2,7	5,0	3,3	3,7	2,4	8,0
Φ_6	1,8	2,9	3,9	5,1	1,6*	7,1
81	5,2	Φ_2	5,6	4,4	5,0	1,5
79	6,5	3,8	1,8	1,8	2,4	3,1
67	Φ_2	5,8	4,8	3,8	3,9	2,0
55	3,4	4,7	3,2	2,6	3,1	1,0
41	9,8	7,3	5,3	4,2	6,4	2,5

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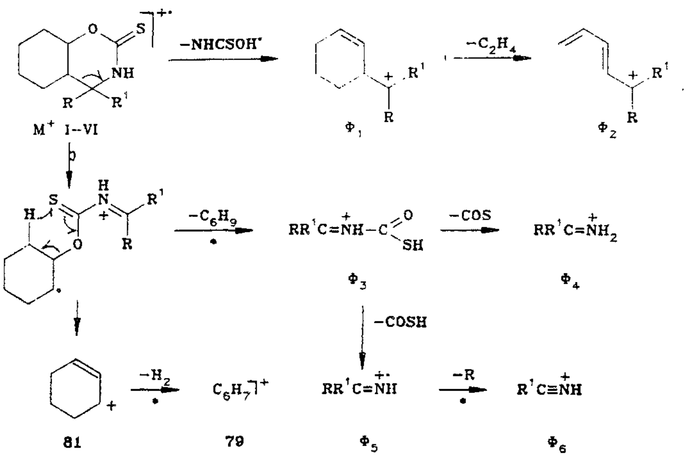
*Ion $[\Phi_5 - H]^+$.

The peak intensities of the molecular and fragment ions in the mass spectra of the trans-isomer of I and the cis-isomers of II-VI (Tables 2 and 3) reflect the relative stability of their molecular ions (M^+, W_M values in the ranges 8.4-13.2). These are the base peaks. The M^+ for I has the highest stability of the studied compounds. Introduction of alkyl and phenyl substituents into the oxazine ring (II-VI) slightly reduces the W_M value (Table 3).

The bicyclic structure of I-VI largely directs their fragmentation under electron impact. The cyclic system of M^+ for these compounds splits by a mechanism similar to that for alkyl-substituted bicyclo[4.4.0]decanes [16-18], primarily by rupture of bonds at the tertiary carbon atoms, and is accompanied by appearance in the spectra of I-VI of strong ion peaks

Φ_1, Φ_3, and 81* (scheme). Decays giving metastable ion peaks in the spectra of I-III and V are denoted by asterisks.



The 81 ion is formed through homolytic rupture of the C–C bond at the point of fusion of the rings. Subsequent ordinary decay through a cyclic transition state leads to the cyclohexenyl cation 81. The ions $[M - C_6H_9]^+$ are also characteristic of the studied compounds (fragment Φ_3). These then lose a COS molecule or a COSH radical. Earlier [2], we demonstrated during a study of methylsubstituted tetrahydro-1,3-oxazine-2-thiones that the same ion results from migration of hydrogen from the methyl group located on $C_{(6)}$ of the oxazine ring to the sulfur. Introduction of alkyl and especially phenyl substituents at the α-position relative to the nitrogen for II-VI stabilizes ion Φ_3 (Table 3).

The mass number and strength of the peak for Φ_6 is an analytical marker for mass-spectrometric identification of the isomeric 4-ethyl- (III) and 4,4-dimethylsubstituted (IV) compounds. The 42 ion is characteristic for IV as well as for the monocyclic 4,4-dimethylsubstituted tetrahydro-1,3-oxazine-2-thiones [1, 2]. The 56 ion is characteristic for III. According to high-resolution mass spectra, the 42 ion (IV) consists of 98.7% $[C_2H_4N]^+$ and 1.3% $[C_2H_2O]^+$. The 56 ion (III) consists of 92% $[C_3H_6N]^+$ and 8% $[C_4H_8]^+$.

The ions $[C_5H_7]^+$ (67), $[C_4H_7]^+$ (55), and $[C_3H_5]^+$ (41) are also strong for I-VI besides the ions shown in the scheme. Metastable ions corresponding to the following decays are found in spectra of I-III: 82 ion → 67 ion (54.7); 67 ion → 41 ion (25.1); and 81 ion → 55 ion (37.3). Loss from the M^+ ion of the thiol radical leads to appearance of weak peaks for $[M - HS]^+$. Loss from M^+ of the alkyl substituent located in the α-position relative to the nitrogen is not characteristic for II-IV. Thus, the ion peak $[M - R^1]^+$ with relative strength 7% is found only in the spectrum of IV.

The elemental composition of all ions given in Table 3 for II and V were confirmed by high-resolution mass spectrometry.

EXPERIMENTAL

IR spectra for I-VI were taken on a UR-10 instrument as mineral oil mulls. PMR spectra were obtained on a Bruker WM (250 MHz) instrument using an internal standard of HMDS and $CDCl_3$ solvent. Mass spectra were recorded on a Varian MAT CH-6 instrument using direct sample insertion into the ion source, an ionizing electron energy of 70 eV, and an ionization chamber temperature of 120°C. High-resolution mass spectra were obtained on a Kratos MS-80 instrument using direct sample insertion into the ion source, an ionizing electron energy of 70 eV, an ionization chamber temperature of 150°C, and a standard of perfluorokerosene. The resolution was $M/\Delta M = 10{,}000$.

Elemental analyses (C, H, N, S) for II-VI correspond to those calculated.

trans-5,6-Tetramethylenetetrahydro-1,3-oxazine-2-thione (I, $C_8H_{13}NOS$). (Method A). To a solution of 8.5 g (0.005 mole) trans-2-aminomethyl-1-cyclohexanol [10] in 20 ml 25% aqueous sodium hydroxide cooled to 5°C were added dropwise with vigorous stirring over 20 min

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*Here and henceforth in the text, Table 3, and Scheme 1, the numbers characterizing the ion are the mass-to-charge ratio (m/z).

11.5 g (0.15 mole) carbon disulfide. The reaction mixture was heated for 4 h under gentle reflux. The crystalline product was filtered off, washed with 20 ml cold water, and dried in a vacuum desiccator over anhydrous calcium chloride. Yield 5.3 g (50%) I, mp 261-262°C (from alcohol; according to [4], mp 260-262°C from alcohol). IR spectrum: 1580 cm^{-1} (CSNH).

cis-4e-Phenyl-5,6-tetramethylenetetrahydro-1,3-oxazine-2-thione (VI) was prepared analogously (method A) by reaction of carbon disulfide and cis-2-(α-aminobenzyl)-1-cyclohexanol. Its properties are given in Table 1.

4,4-Dimethyl-5,6-tetramethylenetetrahydro-1,3-oxazine-2-thione (IV). (Method B). To a solution of 1.94 g (0.01 mole) 2-(2-isothiocyanatopropyl-2)-1-cyclohexanone in 20 ml alcohol were added with stirring over 1 h 0.22 g (0.006 mole) sodium borohydride at a temperature less than 25°C. After the addition was complete, the reaction mixture was stirred for 15 min and solvent was removed on a rotary evaporator. Ten ml water were added to the residue. The solution was extracted with chloroform (3 × 25 ml). The combined extracts were washed with water until neutral and dried with anhydrous magnesium sulfate. After removal of solvent, 1.94 g (99%) of a mixture of stereoisomers of 4,4-dimethyl-5,6-tetramethylenetetrahydro-1,3-oxazine-2-thione (IV) were obtained.

Mixtures of the erythro- and threo-isomers of the corresponding 1,3-isothiocyanatoketones 2-(1-isothiocyanatoethyl-1)-1-cyclohexanone, 2-(1-isothiocyanatopropyl-1)-1-cyclohexanone, and 2-(1-isothiocyanatocyclohexyl-1)-1-cyclohexanone reacted analogously (method B) with sodium borohydride in a reductive cyclization [14, 15] in yields of 40.6, 82.0, and 87.8%, respectively, to give crystalline mixtures of the cis- and trans-isomers of oxazinethiones II, III, and V with predominance of the cis-isomers (according to PMR spectra). The pure cis-isomers of II-V were isolated after two crystallizations from alcohol. Their properties are given in Table 1. The structure and stereochemical purity of the prepared compounds were confirmed using TLC and PMR.

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