SYNTHESIS AND MASS SPECTRA OF 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINE-2-THIONES

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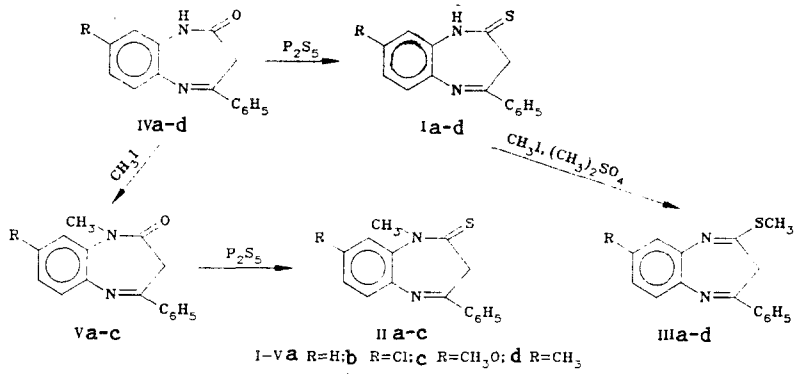
2,3-Dihydro-1H-1,5-benzodiazepine-2-thiones and their N-methyl and S-methyl derivatives were synthesized. It was demonstrated by means of the IR, UV, PMR, and mass spectra that in solutions with different polarities 1,5-benzodiazepine-2-thiones exist primarily in the thione form; the thione and enamino-thiol forms are the most probable forms in the gas phase.

1,2-Dihydro-1,4-benzodiazepine-2-thiones have psychotropic activity. In addition, they are valuable intermediates in the synthesis of annelated tricyclic 1,4-benzodiazepines [1]. Considerably less study has been devoted to their 1,5 analogs.

The synthesis of 2,3-dihydro-1H-1,5-benzodiazepine-2-thiones (I) and their N-methyl (II) and S-methyl (III) derivatives is described in the present paper. We also studied the thione–thiol tautomerism of I.

Diazepinethiones I were obtained by thionylation of 8-R-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones IV with phosphorus pentasulfide in anhydrous pyridine (Table 1).



1-Methyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones Va-c were isolated in the reaction of diazepines IVa-d with methyl iodide, i.e., alkylation takes place at the $N_{(1)}$ atom. The IR spectra of these compounds do not contain bands of stretching vibrations of free and associated NH groups; signals of a methyl group appear in the PMR spectra.

Compounds V readily undergo thionylation to give 1-methyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepine-2-thiones IIa-c. The alkylation of diazepinethiones I with dimethyl sulfate in methanol or with methyl iodide in benzene in the presence of an interphase-transfer catalyst does not take place at the $N_{(1)}$ atom but rather at the sulfur atom, and 2-methylmercapto derivatives III are formed. Compound IIIa has been previously described [2].

The UV spectra of I and II are similar to one another and differ from the absorption spectra of 2-methylmercapto derivatives III with respect to the hypsochromic shift of the short-wave absorption band.

A singlet of methylene protons at 3.4-4.0 ppm, which in the case of II is split to give an AB quartet, which is explained by the retarded character of the inversion of the heteroring [1, 3, 4], is observed in the PMR spectra of I and III.

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TABLE 1. Characteristics of I-III

Compound	Empirical formula	mp,* °C	R_f	PMR spectrum,** δ, ppm	UV spectrum, λ_{max}, nm (log ε)	Yield, %
Ia	$C_{15}H_{12}N_2S$	222...223 (222 [2])	0,69	3,92 (2H, s, CH_2); 7,20...8,25 (9H, m, arom. protons)	268 (4,39), 291 (4,28), 326 (4,00) sh., 350 (3,71) sh	83
Ib	$C_{15}H_{11}ClN_2S$	187...188	0,81	4,00 (2H, s, CH_2); 7,20...8,30 (8H, m, arom. protons)	269 (4,40), 291 (4,33), 316 (4,08) sh., 350 (3,83) sh	94
Ic	$C_{16}H_{14}N_2OS$	215...216	0,62	3,82 (3H, s, CH_3); 3,94 (2H, s, CH_2); 6,85...8,30 (8H, m, arom. protons)	268 (4,42), 292 (4,30), 318 (4,02) sh., 351 (3,68) sh	85
Id	$C_{16}H_{14}N_2S$	191...193	0,71	2,34 (3H, s, CH_3); 3,94 (2H, s, CH_2); 7,15...8,30 (8H, m, arom. protons)	268 (4,46), 290 (4,32), 316 (4,00) sh., 350 (3,70) sh	78
IIa	$C_{16}H_{14}N_2S$	102...103	0,80	4,04 (3H, s, CH_3); 3,28 4,74 (2H, 2 d, J=12 Hz, CH_2); 7,60...8,50 (9H, m, arom. protons)	268 (4,35), 315 (3,77)	89
IIb	$C_{16}H_{13}ClN_2S$	135...136	0,83	3,73 (3H, s, CH_3); 3,56, 4,98 (2H, 2 d J=12 Hz, CH_2); 7,60...8,50 (8H, m, arom. protons)	269 (4,54), 327 (4,03)	90
IIc	$C_{17}H_{16}N_2OS$	115...117	0,73	3,76, 3,85 (2×3H, 2 s, CH_3); 3,28, 4,75 (2H, 2 d J=12 Hz CH_2); 6,90...8,30 (8H, m, arom. protons)	269 (4,48), 326 (4,05)	78
IIIa	$C_{16}H_{14}N_2S$	87...88 (87...88 [2])	0,69	2,35 (3H, s, CH_3); 3,48 (2H, s, CH_2); 7,20...8,20 (9H, m, arom. protons)	257 (4,44), 316 (3,79)	86
IIIb	$C_{16}H_{13}ClN_2S$	126...127	0,70	2,36 (3H, s, CH_3); 3,48 (2H, s, CH_2); 7,10...8,15 (8H, m, arom. protons)	259 (4,46), 328 (3,85)	89
IIId	$C_{17}H_{16}N_2S$	118...119	0,66	2,34, 2,38 (2×3H, 2 s, CH_3); 3,43 (2H, s, CH_2); 7,00...8,15 (8H, m, arom. protons)	258 (4,40), 328 (3,79)	80

*The compounds were recrystallized: Ia-d from ethyl acetate, IIa and IIIb,d from aqueous alcohol, IIb,c from ethanol, and IIIa from hexane.

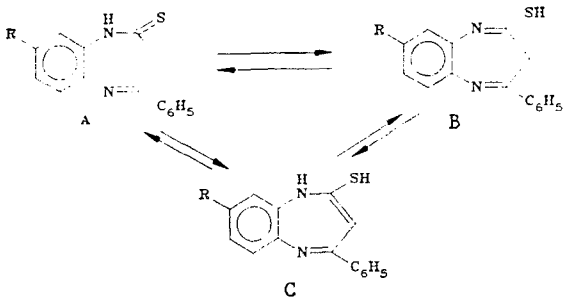
**The PMR spectrum of IIa was recorded in d_6-DMSO; the PMR spectra of the remaining compounds were recorded in d_6-acetone.

TABLE 2. Mass Spectra of Compounds Synthesized

Compound	m/z								
	M^+	M^+-H (F_1)	M^+-SH (F_1)	M^+-H_2S (F_2)	M^+-CH_2CS	$M^+-C_3H_4S$	M^+-CH_3CS	$M^+-C_3H_5S$	M^+-SCH_3 (F_1)
					F_3		F_4		
Ia	71,3	5,3	11,7	7,5	100	—	12,4	—	—
Ib	85,0	4,4	10,4	6,0	100	—	7,3	—	—
Ic	63,2	4,4	9,2	4,0	100	14,4	4,4	84,0	—
Id	65,6	6,8	15,8	6,9	100	7,3	34,7	—	—
IIa	100	10,9	16,5	5,2	93,0	3,7	94,2	16,9	—
IIb	76,5	4,2	6,6	2,0	100	4,2	73,2	9,3	—
IIc	97,1	6,1	5,0	2,0	100	10,8	18,6	60,0	—
IIIa	97,0	12,7	26,5	4,1	—	62,0	—	15,9	100
IIIb	100	10,4	20,8	5,2	—	37,0	9,2	5,2	54,0
IIId	100	11,1	23,1	2,6	—	25,0	—	11,8	48,0

In contrast to the IR spectra of II and III, the IR spectra of I contain strong absorption bands of NH groups. At the same time the absorption band of a C=N group, which undergoes splitting in the case of III, which contain two azomethine groups, is characteristic for I and II. The spectra of I and II recorded in chloroform contain a band of stretching vibrations of a C=S group at 1370-1375 cm^{-1}, which is absent in the case of III-V. The known (for lactams and thiones) $\nu_{C=O}/\nu_{C=S}$ ratio is 1.23, which corresponds to the data in [5, p. 505].

Compounds I theoretically can exist in different tautomeric forms (forms A, B, and C).



On the basis of the data obtained it may be assumed that in solutions with different polarities Ia-d exist primarily in the thione form.

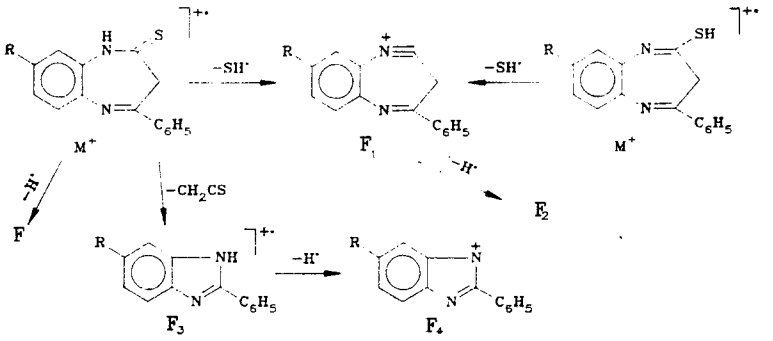
It is known that mass spectrometry is used to study thione–thiol tautomerism [6, 7]. In this connection we studied the behavior of the synthesized compounds under conditions of ionization of the molecules by electron impact.

We compared the mass-spectrometric behavior of I-III with the known fragmentation of 1,5-benzodiazepin-2-ones [8], 1,4-benzodiazepine-2-thiones [7], and imidazo[1,2,b]-1,2,4-triazepinethiones [6].

For all of the compounds the molecular-ion peaks (M^+) are characterized by increased intensity, which significantly exceeds the corresponding values for 4-aryl-1,5-benzodiazepin-2-ones [9]; this is associated with the participation of the p and d orbitals of sulfur in stabilization of the positive charge.

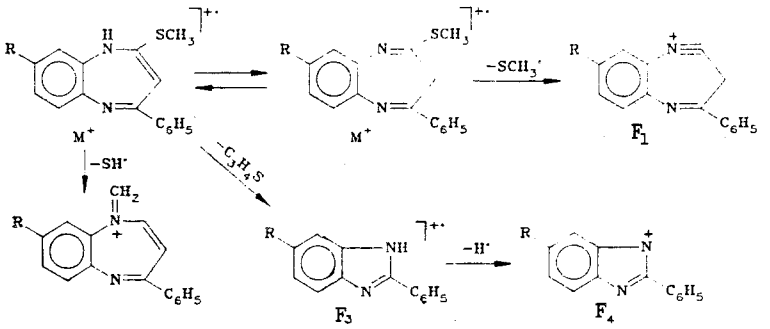
The principal pathway of the fragmentation of the M^+ ions of thiones Ia-d is cleavage of the thiolactam bond with subsequent elimination of a molecule of thioketene and the formation of the $[M - CH_2CS]^+$ ion (F_3). Similar fragmentation is also observed for 4-aryl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones [8]. In all cases the peaks of these ions are the maximum peaks in the mass spectra (Table 2). At the same time, however, cleavage of the $N_{(1)}$–$C_{(2)}$ bond and the $C_{(3)}$–$C_{(4)}$ bond may also lead to the ejection of an HC≡C–SH particle, which could correspond to the C structure in the enamino-thiol form.

Other fragmentation pathways – elimination of a hydrogen atom, an SH particle, etc. – are also observed for the M^+ ions. According to [7], the elimination of an SH radical by the molecular ion is due to the existence of a thione–enamino-thiol equilibrium (A ⇄ C), although in this case one evidently cannot exclude the existence also of thione–imino-thiol (A ⇄ B) tautomerism.



We then investigated the pathways of fragmentation of 1-methyl thiones IIa-c under electron impact. The fragmentation of these compounds also proceeds via several pathways. The principal pathway of the fragmentation of II is the formation of the F_3 ion. For IIa the peak of the signal of this ion amounts to 93%, while for IIb and IIc the peak of the F_3 ion is maximal. In addition, the formation of F_4 ions is observed in the mass spectra of these compounds. At the same time, there are $[M - SH]^+$ (F_1) ions in the mass spectra for all three compounds; this can evidently be explained by the A $\rightleftarrows$ C partial equilibrium.

The existence of a thione–imino-thiol equilibrium (A $\rightleftarrows$ B) in Ia-d could be confirmed by the mass-spectral fragmentation of methylmercapto derivatives IIIa-d. In the case of IIIb,d the M^+ peak, the intensity of the signal of which is 97% for IIIa, has the maximum intensity. The principal pathway of fragmentation of the M^+ ions of all of the compounds of this type is splitting out of a methylmercapto group. In the case of IIIa the peak of the $[M - SCH_3]^+$ (F_1) ion is maximal, while for IIIb and IIId its signal amounts to 54% and 48%, respectively.



We assumed that the relative intensities of the peaks of the $[M - SH]^+$ ions observed in the mass spectra of thiones I may definitively characterize the contribution of the thiol form; however, the peak of the $[M - SH]^+$ ion is also present in the mass spectra of S-methyl-substituted III, and the relative intensity of the peak of this ion exceeds by a factor of almost two the corresponding values obtained for unsubstituted and N-methyl-substituted thiones.

All of the S-methyl derivatives III lose a molecule of $CH{\equiv}C{-}SCH_3$ during fragmentation. The intensities of the peaks of the F_3 ions formed for IIIa, IIIb, and IIId are, respectively, 62%, 37%, and 25%. The formation of these ions is possible only from enamino-thiol form C.

The enamino-thiol form and the analogous fragmentation pathway for IIIa were presented in [10].

Thus thione form A and enamine-thiol form C are evidently the most probable forms for the molecular ions of Ia-d.

EXPERIMENTAL

The IR spectra of KBr pellets and solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol ($c = 10^{-4}$ mole/liter) were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in d_6-DMSO

and d_6-acetone were recorded with a Tesla BS-567A spectrometer (100 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were obtained with an MKh-1320 mass spectrometer using direct introduction of the samples into the ionization energy of 50 eV, a cathode emission current of 0.6 mA, and temperatures 30-40°C below the melting points of the samples.

The course of the reactions and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in an ether–hexane system (3:1).

The results of elementary analysis for C, H, and N were in agreement with the calculated values.

4-Phenyl-8-R-2,3-dihydro-1H-1,5-benzodiazepine-2-thiones Ia-d. A solution of 10 mmole of diazepinones IVa-d in 20 ml of absolute pyridine was stirred with heating until dissolving was complete, after which 12 mmole of phosphorus pentasulfide was added, and the mixture was heated to 100-110°C for 1 h. The reaction mass was poured into 100 ml of cold water, and the resulting precipitate was removed by filtration, washed with water, and purified.

1-Methyl-8-R-2,3-dihydro-1H-1,5-benzodiazepine-2-thiones IIa-c. These compounds were similarly obtained from benzodiazepinones Va-c.

2-Methylmercapto-4-phenyl-8-R-2,3-dihydro-1H-1,5-benzodiazepinones IIIa-d. A) A 3-ml sample of 50% NaOH solution was added with stirring to a mixture of 5 mmole of diazepines Ia-d, 7.5 mmole of methyl iodide, 0.3 mmole of tetrabutylammonium bromide, and 30 ml of benzene, and the mixture was heated for 40-50 min at 55-65°C. It was then cooled, and the aqueous layer was separated. The benzene solution was washed with water until the wash water was neutral, after which the solvent was evaporated, and the precipitate was separated.

B) A solution of 2.4 mmole of dimethyl sulfate in 2 ml of methanol was added to a stirred solution of 2 mmole of diazepines Ia-d in a mixture of 5 ml of 1 N aqueous NaOH and 10 ml of methanol, after which the mixture was heated at 50-55°C for 30-45 min. It was then diluted with water and made alkaline with a solution of alkali. The resulting precipitate was removed by filtration, dried, and recrystallized.

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