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MASS SPECTRA OF 1H-2,3-DIHYDRO-1,4-BENZODIAZEPINE-2-THIONES

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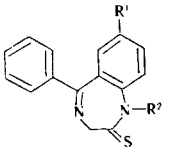
The mass-spectrometric fragmentation of 1H-2,3-dihydro-1,4-benzodiazepine-2-thiones differs substantially from the fragmentation of the corresponding oxo derivatives with respect to the presence of $[M - HCN]^+$ and $[M - SH]^+$ ions. This is due to the tautomeric transformation of the molecular ions of the thiones to enethiol and eniminothiol tautomeric forms. The approximate percentages of each of the tautomeric forms were estimated.

In order to compare the mass-spectrometric behavior of 1,4-benzodiazepin-2-ones [1, 2] with their thio analogs, we studied the mass spectra of the following 1,4-benzodiazepine-2-thiones:



I-VII

I R^1=H, R^2=H; II R^1=H, R^2=D; III R^1=CH_3, R^2=H; IV R^1=Cl, R^2=H; V R^1=Br, R^2=H; VI R^1=NO_2, R^2=H; VII R^1=Cl, R^2=CH_3

The investigated compounds were synthesized as previously described in [3, 4]. The m/e values and the relative intensities of the peaks of the principal ions in the mass spectra of I-VII are presented in Table 1. The W_M values (the fraction of the molecular ions in the total ion current, which characterizes the stability of the molecule with respect to electron impact [5]) for the corresponding oxo and thio derivatives are compared in Table 2, and the ratios of the intensities of the peaks of some of the characteristic fragment ions to the intensity of the molecular ion for the investigated thiones are also presented.

It follows from a comparison of the W_M values that the thiones have considerably higher stability with respect to electron impact than the corresponding oxo compounds. The W_M values for the thiones exceed the corresponding values for the benzodiazepinones by a factor of 2-2.5.

The free p and d orbitals of the sulfur atom evidently participate to a great extent in stabilization of the positive charge in the molecular ions of the thiones.

M. V. Lomonosov Moscow State University. I. I. Mechnikov Odessa State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1412-1417, October, 1976. Original article submitted September 19, 1975.

TABLE 1. m/e Values and Relative Intensities in Percent Relative to the Maximum Peaks of the Ions in the Mass Spectra of I-VII

I.	254	(4,8),	253	(23,1),	252	(100),	251	(41,4),	226	(5,1),	225	(30,4),	224	(17,0),
	223	(11,8),	222	(6,3),	219	(11,1),	218	(14,8),	207	(3,5),	206	(8,5),	205	(6,5),
	194	(4,2),	193	(6,5),	192	(3,2),	190	(6,5),	166	(3,8),	165	(17,5),	164	(4,7),
	163	(5,4),	152	(3,9),	121	(3,6),	117	(3,3),	116	(5,9),	104	(5,8),	91	(11,8),
	90	(4,9),	89	(7,0),	77	(15,8),	76	(3,5),	69	(3,3),	65	(4,0),	63	(4,5),
	51	(7,0)												
III.	268	(4,3),	267	(24,0),	266	(100),	265	(37,7),	240	(4,6),	239	(25,0),	238	(9,0),
	233	(7,5),	232	(7,4),	223	(9,9),	222	(3,2),	221	(3,2),	220	(5,4),	219	(4,9),
	208	(3,4),	207	(5,2),	206	(4,0),	205	(3,4),	190	(3,2),	178	(5,6),	165	(5,1),
	163	(3,1),	116	(4,4),	104	(3,7),	103	(3,2),	91	(9,9),	89	(4,6),	77	(11,0),
	51	(3,0)												
IV.	289	(5,4),	288	(33,2),	287	(35,4),	286	(100),	285	(39,8),	261	(6,4),	260	(4,9),
	259	(23,7),	258	(3,7),	254	(4,1),	253	(7,8),	252	(10,5),	240	(3,9),	224	(7,8),
	223	(25,4),	222	(7,8),	205	(3,1),	193	(4,5),	190	(5,8),	165	(8,0),	164	(5,2),
	163	(9,7),	151	(3,1),	150	(3,1),	104	(4,3),	91	(9,9),	89	(5,2),	77	(11,3),
	63	(3,7),	51	(4,7)										
V.	334	(4,6),	333	(26,9),	332	(100),	331	(67,5),	330	(98,5),	329	(35,8),	306	(4,0),
	305	(20,8),	304	(7,3),	303	(21,5),	299	(6,0),	298	(8,7),	297	(6,1),	296	(6,2),
	288	(3,2),	287	(6,2),	286	(13,5),	285	(8,9),	284	(4,4),	251	(4,4),	224	(16,5),
	223	(46,5),	222	(13,3),	218	(5,0),	205	(9,6),	194	(3,4),	193	(10,6),	192	(3,6),
	191	(7,2),	190	(13,2),	178	(4,2),	177	(6,6),	166	(5,2),	165	(18,8),	164	(15,1),
	163	(20,2),	152	(6,4),	151	(7,0),	150	(5,0),	139	(3,6),	126	(4,2),	125	(3,6),
	121	(4,6),	117	(4,0),	116	(5,8),	115	(4,8),	104	(11,4),	103	(5,8),	91	(22,8),
	90	(7,6),	89	(13,4),	77	(31,4),	76	(7,6),	75	(5,6),	63	(12,6),	51	(7,2)
VI.	299	(3,5),	298	(14,8),	297	(100),	296	(35,8),	270	(16,4),	267	(7,7),	266	(3,5),
	265	(3,2),	263	(3,1),	251	(5,9),	250	(16,1),	224	(3,1),	223	(8,1),	222	(5,5),
	218	(4,0),	205	(6,4),	191	(3,1),	190	(6,1),	165	(4,2),	164	(4,1),	163	(4,2),
	91	(8,9),	89	(3,2),	77	(9,7),	63	(4,0),	51	(4,0)				
VII.	303	(3,0),	302	(32,8),	301	(14,3),	300	(100),	299	(3,5),	285	(4,3),	275	(12,5),
	274	(5,7),	273	(51,0),	272	(3,1),	254	(4,0),	253	(4,9),	241	(6,0),	239	(5,1),
	238	(9,6),	237	(50,4),	229	(8,1),	228	(5,3),	227	(39,8),	226	(3,9),	223	(3,1),
	222	(6,9),	165	(10,0),	164	(5,8),	163	(7,7),	125	(7,9),	91	(8,0),	89	(6,4),
	77	(14,8),	75	(3,1),	74	(12,2),	51	(5,2)						

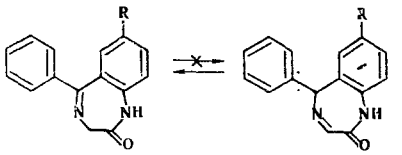
TABLE 2. W_M Values and Ratios of the Intensities of the Molecular and Fragment Ions in the Mass Spectra of I-VI

R_1	Benzodiazepinones			Benzodiazepinethiones		
	W_M	W_M	$\frac{J_{M-H}}{J_M}$	$\frac{J_{M-HCN}}{J_M}$	$\frac{J_{M-SH}}{J_M}$	$\frac{J_{M-SH_2}}{J_{M-H}}$
H	13.7	31.0	0.418	0,197	0.083	0,389
CH_3	16.8	33.2	0,391	0,209	0.066	0,215
Cl	15.6	32,1	0,421	0,222	0.059	0,266
Br	16.8	33.2	0,387	0.217	0.052	0,228
NO_2	8,6	26,6	0,410	0,163	0,029	0,056

The peaks of the molecular ions, which undergo fragmentation in three principal directions – with elimination of a hydrogen atom, an HCN molecule, and an SH radical – are the maximum peaks in the mass spectra of all of the investigated compounds. Calculation of the mass spectrum of II with correction for the isotope effect showed that as a result of elimination of a hydrogen atom, the deuterium label in the $[M - H]^+$ ion is retained completely. Consequently, it can be assumed that, as in the case of benzodiazepinones [1], the hydrogen atom is primarily eliminated from the ortho position of the 5-phenyl group. As seen from Table 2, the ratios of the intensities of the peaks of the $[M - H]^+$ and M^+ ions are approximately equal for the entire series of compounds ($J_{M-H}/J_M = 0.41 \pm 0.02$), and the electronic properties of the substituents in the 7 position consequently do not affect the rate of elimination of the H radical.

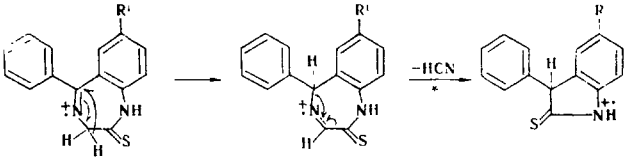
Splitting out of HCN by the molecular ions of the thiones in a number of cases (I and IV-VI) is confirmed by the corresponding metastable transitions and is one of the primary differences in their mass-spectrometric behavior from the behavior of benzodiazipinones, for which this process shows up only in the case of compounds with electron-acceptor substituents in the 7 position, and primarily elimination of the H_2CN radical is observed. On the other hand, in the case of the thiones the elimination of 28 amu shows up weakly and, in all likelihood, is associated with the two-step loss of H and HCN in a different sequence.

The elimination of HCN by the molecular ions of 7-nitro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one was explained [2] by migration of a hydride ion from 3-C to 5-C, promoted by the 7-nitro group, which induces a positive charge on the 5-C atom in the quasi-para position. Sadee [2] cites literature analogies, but data on isomerization of this sort under the influence of chemical reagents or UV irradiation are absent in the cited literature [6-8]. Reverse isomerization has been described, and it proceeds readily [9]:



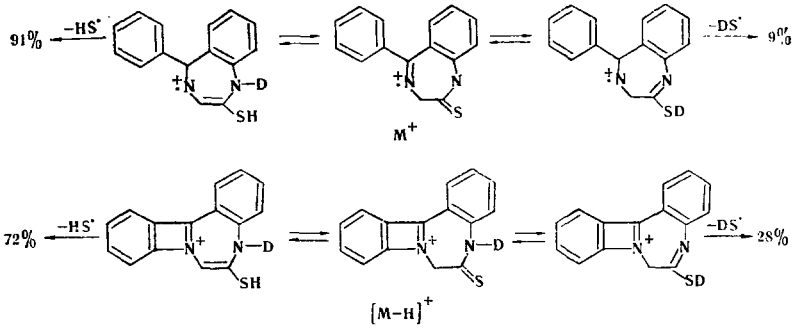
In addition, 1,2-dihydro-3H-1,4-benzodiazepine-2-thiones readily condense with electrophilic reagents (including benzaldehyde) at the methylene group. The thiones are more active in these reactions than their oxygen analogs.

It may be assumed that, in contrast to benzodiazepines [1, 2], the charge in the molecular ions of the benzodiazepinthiones is localized primarily on the 4-N atom. One of the hydrogen atoms of the 3-methylene group then migrates in the form of a radical to the 5 position, and a $\pi-3C-4N$ bond, which ensures conjugation of the positive charge with the C=S group, is formed simultaneously. This sort of rearrangement is possible only upon electron impact:



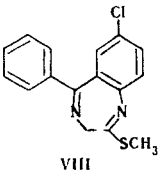
On the other hand, the elimination of an HCN molecule may be due to the presence of a thione–enethiol tautomeric equilibrium in the molecular ions, evidence for which is provided by the characteristic (for the entire series of compounds) elimination of an SH radical by the molecular ions.

We also note that the $[M-H]^+$ ions also eliminate an SH radical. On the basis of a calculation of the mass spectrum of II with correction for the natural percentage of heavy isotopes we were able to establish that the molecular ions lose 9% DS and 91% HS (based on 100% of the label), whereas the $[M-H]^+$ ions lose 28% DS and 72% HS. Considering that the deuterium label is attached to the thionamide nitrogen atom (the location of the label at the amide nitrogen atom was established by means of PMR spectra for two benzodiazepinones deuterated by the same method [1]) one may arrive at the conclusion that the molecular ions and the $[M-H]^+$ ions are found both in thione–enethiol and thione–eniminethiol tautomeric forms; the relative concentration of the enimine tautomer is somewhat higher in the $[M-H]^+$ ions than in the molecular ions.



Although we do not claim to have established the precise concentrations of all three forms, these data nevertheless make it possible to assert that the larger portion of the molecular ions exist in the enethiol form.

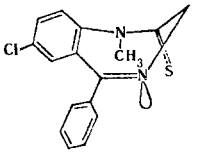
Whereas the introduction of a methyl group in the 1 position in the case of benzodiazepinones practically does not change the character of the mass-spectrometric fragmentation [2], in the case of thiones (VII) one observes a number of substantial changes: 1) the $[M-H]^+$ ions practically vanish; 2) elimination by the molecular ions of a methyl radical (5.5%) and a CH_3NCS molecule (40%) is observed; 3) rearranged $CH_3\overset{+}{N}\equiv CSH$ ions (12%) appear.



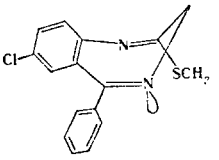
VIII

However, in the case of VIII the $[M - H]^+$ ion peak becomes a maximum in the mass spectrum, and the $[M - HCN]^+$ ion peak vanishes completely. Consequently, $[M - HCN]^+$ ions are formed only from the thione form of the molecular ions, and the process evidently takes place in conformity with the scheme presented above.

The absence of $[M - H]^+$ ion peaks in the mass spectrum of VII indicates that these ions can be formed only from the eniminethiol tautomeric form of the molecular ions. The sulfur atom, which has a larger atomic radius than the oxygen atom, evidently hinders interaction of the free sp orbital of the nitrogen atom in the 4 position with the ortho position of the 5-phenyl substituent. Elimination of a hydrogen atom by the molecular ions of VII is therefore not observed:



However, if the thiol configuration is fixed (VIII), the diazepine portion of the molecule becomes planar, and the C–S bond is directed from the 4-N atom:

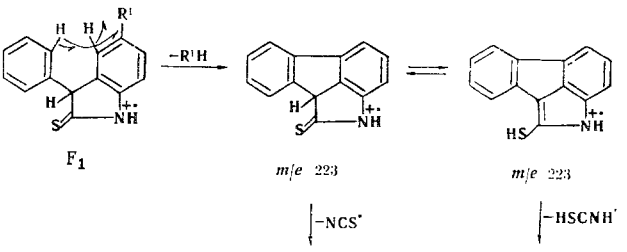


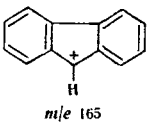
Interaction of the nitrogen atom with the ortho position of the phenyl ring is facilitated, and the $[M - H]^+$ ion peak is therefore the maximum peak in the mass spectrum of VIII, and its intensity exceeds the intensity of the molecular ion peak by a factor of 2.5. It is also possible that there is partial elimination of a hydrogen atom from the 3-methylene group during the formation of $[M - H]^+$.

On the basis of an analysis of the mass spectra of IV, VII, and IX and a comparison of the ratios of the ion peaks (J_M/J_{M-H} and J_M/J_{M-HCN}), it can be concluded that the molecular ions of IV are found in all three tautomeric forms and that the percentage of the thione form is lower by a factor of approximately two than in the case of VII, and the percentage of the eniminethiol form is lower by a factor of approximately six than in the case of VIII. The enethiol form of the molecular ions does not participate appreciably in the H and HCN elimination processes.

As seen from Table 2, the $M^+ - HCN$, $M^+ - SH$, and $[M - H]^+ - SH^\cdot$ processes for benzodiazepinethione VI are suppressed to a considerable degree as compared with the remaining compounds i.e., the nitro group in the 7 position hinders fragmentation of the molecular ions via this pathway. However, the W_M value for VI is appreciably lower than for the remaining series; this is due to the considerable contribution of the $[M - NO]^+$, $[M - NO_2]^+$, and $[M - H - NO_2]^+$ ions (4.1, 2.0, and 1.5%, respectively) to the total ion current.

The F_1 ions formed as a result of elimination of HCN (see the scheme above) subsequently eliminate substituents R_1 and H (or R_1 H in one step if R_1 is a halogen atom [2]), which is followed by the elimination of NCS· or HNCSH· to give characteristic ion peaks common to the entire series with m/e 223, 165, and 163, in conformity with the following scheme:





m/e 165

$[C_{13}H_7]^+$

m/e 163

Thus the mass-spectrometric behavior of 5-phenyl-1,4-benzodiazepine-2-thiones differs substantially from the fragmentation of the corresponding benzodiazepinones. This difference is due to the fact that, in contrast to benzodiazepinones, tautomerization to enethione and eniminethione tautomeric forms is characteristic for the molecular ions of the thiones.

EXPERIMENTAL

The mass spectra were obtained with an MKh-1303 spectrometer with a system for direct introduction of the samples at an ionizing voltage of 50 V, an emission current of 1.5 μA, and temperatures ranging from 140 to 170°. Compound II was obtained by repeated refluxing of I in deuteromethanol and subsequent evaporation of the solvent. The mass spectrum showed that II contains 34% of the deuterated derivative.

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STRUCTURE AND PROPERTIES OF 1- AND 3-HYDROXYTRIAZOLO[4,5-b]PYRIDINES

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UDC 547.821'791:543.422.4.6'.51

It is shown that 1-hydroxytriazolo[4,5-b]pyridine exists in alcohol solution primarily in the N-oxide form, whereas 3-hydroxytriazolo[4,5-b]pyridine exists in the hydroxy form. 4-Methyltriazolo[4,5-b]pyridine 1-oxide is formed in the methylation of 1-hydroxytriazolo[4,5-b]pyridine, whereas 3-methoxytriazolo[4,5-b]pyridine is formed in the methylation of 3-hydroxytriazolo[4,5-b]pyridine.

It has previously been reported [1] that two isomeric compounds corresponding to two tautomeric forms – the N-oxide (Ia) and the N-hydroxy form (Ib) – are formed in the methylation of 1-hydroxybenzotriazole. The Ia⇌Ib tautomerism was studied by comparison of the UV spectra of the starting compound and its methylation

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