ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 2, pp. 292–303. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © L.V. Klyba, N.A. Nedolya, O.A. Tarasova, E.R. Zhanchipova, 2009, published in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 2, pp. 301–312.

Mass Spectra of New Heterocycles: VII.* Main Fragmentation Channels of 2-(Methylsulfanyl)-4,5-dihydro-3*H*-azepines under Electronic Ionization

L. V. Klyba, N. A. Nedolya, O. A. Tarasova, and E. R. Zhanchipova

Faworsky Irkutsk Institute of Chemistry, Siberian Division, Russian Academy of Sciences, Irkutsk, 664033 Russia
e-mail: nina@irioch.irk.ru

Received April 23, 2008

Abstract—Mass spectra of 3,7-di- and 3,6,7-trisubstituted 2-(methylsulfanyl)-4,5-dihydro-3*H*-azepines were investigated for the first time. The fragmentation of molecular ions of 3-alkoxy-substituted dihydroazepines follows the rules characteristic of ethers. The fragmentation of $[M]^+$ of 3-phenyldihydroazepine occurred through a sequence of rearrangements; one of them led to the formation of a stable ion $[M - MeS]^+$. A specific feature of the fragmentation of 3-(pyrrol-1-yl)dihydroazepine under the electronic ionization consists in the formation of ion $[M - Me]^+$ with the charge mainly localized on the pyrrole ring. A partial decomposition at heating of 3-alkoxy-4,5-dihydro-3*H*-azepines (with alkanol elimination) resulted in 7-(methylsulfanyl)-3*H*-azepines. The latter under the electronic ionization give a stable molecular ion whose primary fragmentation involves the elimination of MeS group or its fragments.

DOI: 10.1134/S1070428009020237

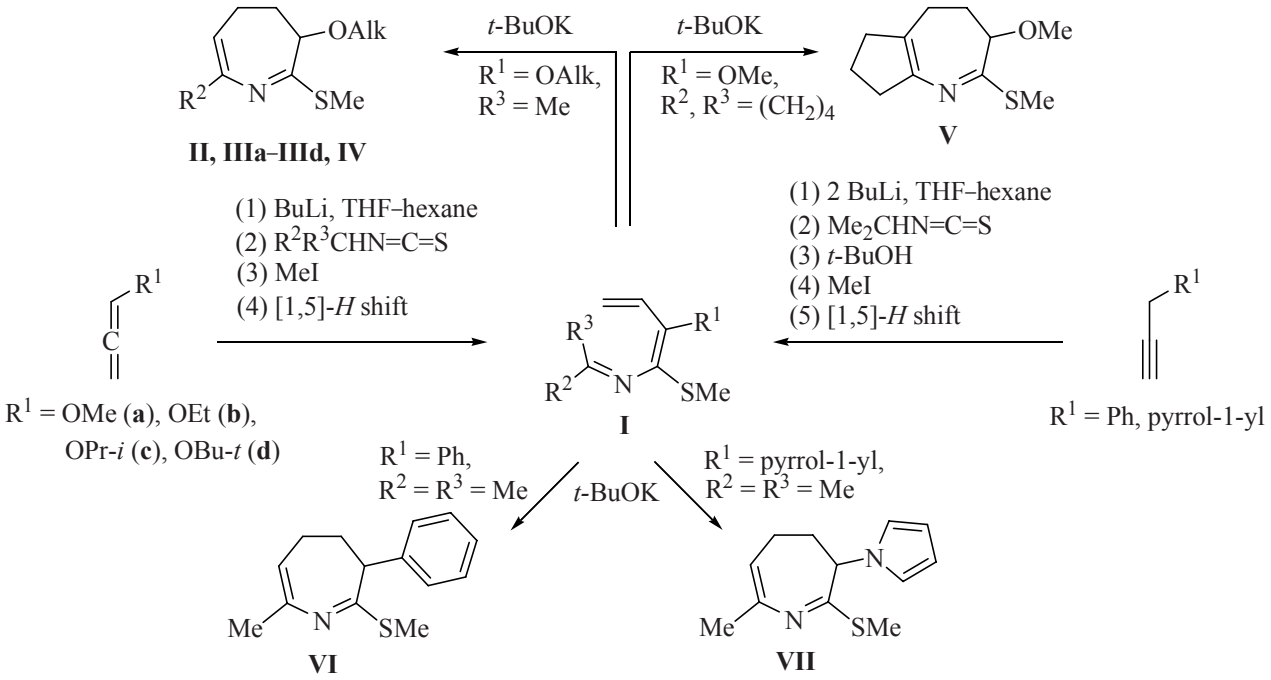
Seven-membered heterocycles, azepines, and their versatile derivatives attract strong interest first of all due to their spread in natural objects [2] and to their applications to medical practice and pharmacology [3]. These are both azepine alkaloids and unique drugs of psychotropic, antidepressant, anticonvulsive and other actions used in the treatment of grave diseases like epilepsy, schizophrenia, Alzheimer's disease, and also cancer, AIDS and many others. Besides this class compounds are employed as important synthetic intermediates, ligands, optically active substances [4]. In this connection a considerable attention is directed to the development of new convenient synthetic procedures, to the extension of their number, and to detailed study of their characteristics, including spectral ones.

We recently discovered a fundamentally new approach to designing azacycloheptadienes (dihydroazepines) and azacycloheptatrienes (azepines) from available allenes or alkynes, isothiocyanates and alkylating agents. The procedure includes two preparative stages: the synthesis [5] and deprotonation (by treatment with *t*-BuOK) [6] of conjugated 2-aza-1,3,5-trienes **I** (Scheme 1). "Precise" (excluding or minimizing the concurrent formation of structural isomers: pyrroles and 2,3-dihydropyridines) thermally induced [1,5]-sigmatropic rearrangement of the primary reaction products formed in the reaction of allene carbanions with isothiocycnates, 1-aza-1,3,4-trienes, afforded the target 2-aza-1,3,5-trienes **I** that under the action of *t*-BuOK easily transformed into formerly unknown and hardly available by other procedures 2-(methylsulfanyl)-4,5-dihydro-3*H*-azepines **II–VII** [6].

In the previous communication [1] we studied for the first time and described the mass spectra of the first representative of the new family of 2-(methylsulfanyl)-4,5-dihydro-3*H*-azepines, 7-methyl-2-(methylsulfanyl)-3-methoxy-4,5-dihydro-3*H*-azepine (**IIIa**) and its structural isomers, formerly unknown 1-isopropyl-2-(methylsulfanyl)-3-methoxypyrrole and 2,2-dimethyl-6-(methylsulfanyl)-5-methoxy-2,3-dihydropyridine obtained from the α-lithiated methoxyallene, isopropyl isothiocycnate, and methyl iodide. As should be expected, the most stable molecular ion formed from the substituted pyrrole (relative intensity of the peak 100%). The intensity of the

*For Communication VI, see [1].

Scheme 1.



molecular ions of 2,3-dihydropyridine and 4,5-dihydro-3*H*-azepine (**IIIa**) are comparable: 50 and 58% respectively. It was established that the primary fragmentation act under the electronic ionization (70 eV) was the same in all the heterocyclic isomers and consists in the rupture of a methyl radical. Therewith the ion $[M-\text{Me}]^+$, *m/z* 170 (42%) formed by the fragmentation of the molecular ion of 4,5-dihydro-3*H*-azepine (**IIIa**) was less stable than its five-membered and six-membered analogs. Further fragmentation of the ion $[M-\text{Me}]^+$ alongside the elimination of NCS radical leading to the diagnostic ion with m/z 112 (100%) consists in the contraction of the seven-membered heterocycle into a five-membered ring forming an ion $[M-\text{Me}-C_2H_4]^+$, *m/z* 142 (9%).

We have not found other publications on the purposeful and detailed studies of mass spectra of dihydroazepines including 4,5-dihydro-3*H*-azepines. Mass spectra of three penta- and hexa-substituted 4,5-dihydro-1*H*-azepines containing as substituents Me, MeO, $MeCO_2$, CN, and 2,5-pyrrolidin-1-yldione group were published in Mass Spectral Database (NIST/EPA/NIH). But they are unsuitable for comparison with the spectra of the objects of this study.

In this study in continuation of the systematic investigation of the mass spectra of new heterocycles generated from lithiated allenes or alkynes and isothiocyanates [1, 7–10] in order to reveal whether the rules found for the fragmentation of the molecular ion of 4,5-dihydro-3*H*-azepine (**IIIa**) [1] were general we applied GC–MS method to a wider set (nine compounds) of previously unknown 3-alkoxy-, 3-phenyl-, and 3-(1-pyrrolyl)-substituted 2-(methylsulfanyl)-4,5-dihydro-3*H*-azepines (Scheme 1) for elucidation of their behavior under electronic ionization (70 eV).

The analysis of mass spectra showed that all studied 4,5-dihydro-3*H*-azepines **II–VII** under electronic ionization formed in registered amount molecular ions $[M]^{+\cdot}$ whose stability unexpectedly strongly depended on the structure and the nature of substituents in the positions *3* and *7*. For 3-alkoxy-4,5-dihydro-3*H*-azepines **II–V** the intensity of peaks $[M]^{+\cdot}$ varied from 13 (for compound **IIId**) to 90% (for compound **V**). The presence in the structure of 4,5-dihydro-3*H*-azepines **II–V** of two heteroatomic substituents (alkoxy and alkylsulfanyl groups) makes it possible to consider them not only like azacycloheptadienes but also like ethers and sulfides. Consequently, same as in the case of their five-membered and six-memebered heterocyclic structural isomers (pyrroles and 2,3-dihydropyridines [1]) containing similar heteroatomic substituents, the fragmentation of the molecular ions of compounds **II–V** should fit not only to the rules characteristic of azaheterocycles (with the localization of the ion-radical site on the nitrogen) but those governing the fragmentation of ethers and/or

sulfides (with the localization of the charge on oxygen or sulfur respectively). For instance, the primary fragmentation of molecular ions of 2-(alkylsulfanyl)pyrroles lacking substituents in the position *3* occurred by the sulfide mechanism (with the rupture of C–S bonds) [8]. In contrast, the rupture of C–N bonds in the nitrogen-containing substituent, namely, the amine fragmentation, occurred at the electronic ionization in the isomeric to 2-(alkylsulfanyl)pyrroleas *N*-alkyl- and *N,N*-dialkyl-2-thiophenylamines [9]. Especially strong effect of a heteroatomic substituent (and of the character of the heteroatom therein: N, S) on the direction and the character of molecular ions fragmentation we observed investigating the mass spectra of 2-(*N*-alkyl-*N*-methylamino)-3-phenylthiophenes and their structural isomers, 3-alkyl-4-methylene-2-(*N*-methylimino)-3-phenylthietanes and 3-(alkylsulfanyl)-1-(*N*-methylimino)-2-phenyl-2-cyclobutenes [10] synthesized from 1,3-dilithiopropargylbenzene, methyl isothiocyanate, and alkyl halides [11]. Inasmuch as the objects of the present study belong simultaneously to three chemical classes of compounds (compounds **II–V** to dihydroazepines, ethers, and sulfides; compound **VI** to dihydroazepins, sulfides, and benzenes; compound **VII** to dihydroazepines,sulfides, and pyrroles) the fragmenta-tion of their molecular ions might follow beside the already mentioned directions also quite unpredicted routes.

The study of molecular ions fragmentation of 3-methoxy-substituted 4,5-dihydro-3*H*-azepines **II, IIIa, IV**, and **V** differing by the structure of substituents in the positions *6* and *7* of the heterocycle showed that for all studied structures, both for 6,7-unsubstituted [$R^2 = R^4 =$ H (**II**)], for 7-alkyl-substituted [R^4 = H: R^2 = Me (**IIIa**), Et (**IV**)], and for 6,7-fused system [R^2,$R^4 = (CH_2)_3$ (**V**)] the fragmentation of molecular ions occurred by common channels forming diagnostic ions (Scheme 2, Table 1) [1].

The main fragmentation channel of molecular ions of 3-methoxydihydroazepines was apparently the decomposition of the heterocycle with ejection of methyl thiocycnate

Scheme 2.

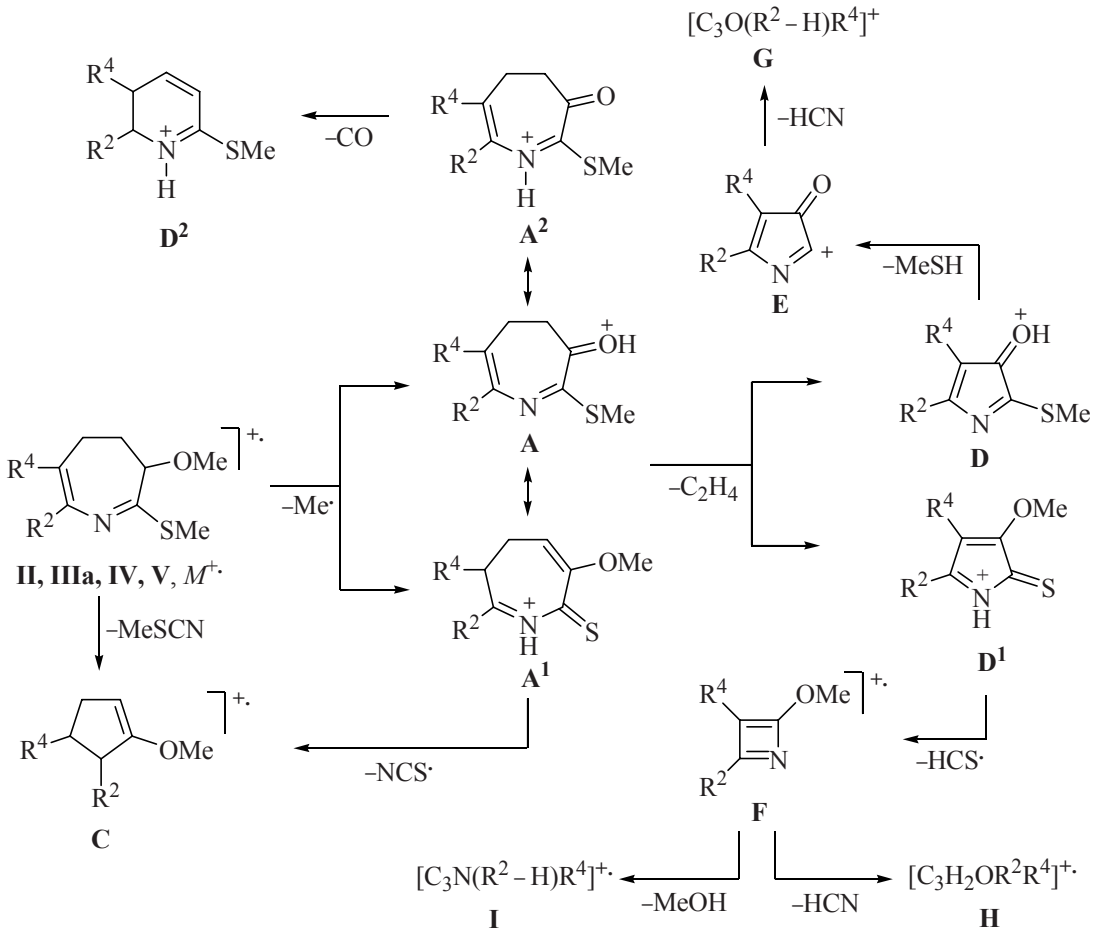


Table 1. Principal characteristic ions in the mass spectra of 4,5-dihydro-3*H*-azepines **II, IIIa, IV**, and **V**

Ions		*m/z* (I_{rel}, %)			
		II	**IIIa** [1]	**IV**	**V**
	$[M]^{+\cdot}$	171 (32)	185 (59)	199 (88)	211 (90)
A, **A^1**, **A^2**	$[M - Me]^+$	156 (30)	170 (42)	184 (57)	196 (48)
B	$[M - MeS]^+$	124 (24)	138 (10)	152 (20)	164 (38)
C	$[M - MeSCN]^{+\cdot}$ or $[\mathbf{A} - NCS]^{+\cdot}$	98 (100)	112 (100)	126 (100)	138 (25)
D, **D^1**, **D^2**	$[\mathbf{A} - C_2H_4]^+$ or $[\mathbf{D^2} - CO]^+$	128 (6)	142 (9)	156 (10)	168 (0)
E	$[\mathbf{D} - MeSH]^+$	80 (21)	94 (11)	108 (16)	120 (11)
F	$[\mathbf{D^1} - HCS]^{+\cdot}$	83 (6)	97 (12)	111 (18)	123 (4)
G	$[\mathbf{E} - HCN]^+$	53 (22)	67 (11)	81 (14)	93 (6)
H	$[\mathbf{F} - HCN]^{+\cdot}$	56 (9)	70 (60)	84 (10)	96 (2)
I	$[\mathbf{E} - MeOH]^{+\cdot}$	51 (7)	65 (9)	79 (22)	91 (15)
J	$[\mathbf{B} - H_2O]^+$	106 (11)	120 (10)	134 (18)	146 (23)
K	$[\mathbf{B} - R^2CN]^+$, *m/z* 97	(23)	(12)	(7)	
L	$[\mathbf{K} - C_2H_2]^+$, *m/z* 71	(20)	(17)	(26)	(100)[a]
M	$[\mathbf{K} - C_2H_4O]^+$, *m/z* 53	(22)	(56)	(39)	

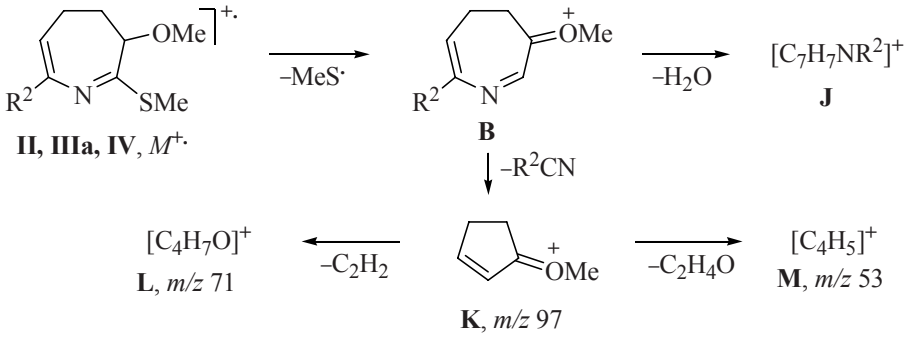
[a] This ion might form due to the fragmentation of the open-chain form of molecular ion $[M_2]^{+\cdot}$ with the charge localized on the oxygen atom (Scheme 5).

(or methyl isothiocyanate) molecule resulting in an odd-electron ion $[M - MeSCN]^{+\cdot}$ (**C**). In the spectra of compounds **II**, **IIIa**, and **IV** this peak has the maximum abundance. The relatively abundant ions $[M - Me]^+$ (**A**, **A^1**, **A^2**) formed after elimination of the methyl radical (with the rupture of O–Me and S–Me bonds) eject an ethylene molecule giving ions $[M - Me - C_2H_4]^+$ (**D**, **D^1**) or C=O species giving ion $[M - Me - CO]^+$ (**D^2**) The further fragmentation of these ions can occur in two directions, either with the loss of a methanethiol molecule (**E**) or of HCS radical (**F**). The elimination of NCS radical from ions **A** also leads to diagnostic ion **C**.

One more channel of sulfide fragmentation of the molecular ion of 3-methoxy-4,5-dihydro-3*H*-azepines consists in the rupture of the heterocycle–S bond and ejection of methylsulfanyl radical (Scheme 3). The arising ion $[M - MeS]^+$ (**B**) and the products of its further decomposition (ions **J**–**M**) significantly contribute to the total ion current (Table 1).

The fusion of 4,5-dihydro-3*H*-azepines increased the stability of the molecular ion whose peak is second in abundance (90%) in the spectrum of compound **V**. Besides this spectrum was characterized by the presence of intense ion peaks corresponding to the fragmentation of

Scheme 3.



ion **B** with *m/z* 164 that were not observed in the other spectra (Scheme 4).

In the spectrum of compound **V** the peak of maximum abundance belonged to ion **L** with m/z 71 whose intensity in the mass spectra of the other methoxy-substituted 4,5-dihydro-3*H*-azepines **II, IIIa**, and **IV** is essentially lower, from 17 to 26% (Table 1). Presumably at ionization and before the fragmentation the molecular ion of 4,5-dihydro-3*H*-azepine **V** suffered the isomerization into open-chain structures with the opening of the heterocycle at the C^2–C^3 bond and the separation of the cationic and the radical sites. The charge may localize either on the nitrogen (ion $[M_1]^{+\cdot}$) or on the oxygen (ion $[M_2]^{+\cdot}$) (Scheme 5). In the first instance the fragmentation of the molecular ion $[M_1]^{+\cdot}$ involved the rupture of the C^7–N bond and the formation of the diagnostic odd-electron ion $[M - MeSCN]^{+\cdot}$ (**C**) occurred whose peak as already mentioned was the most strong in the spectra of compounds **II**, **IIIa**, and **IV**.

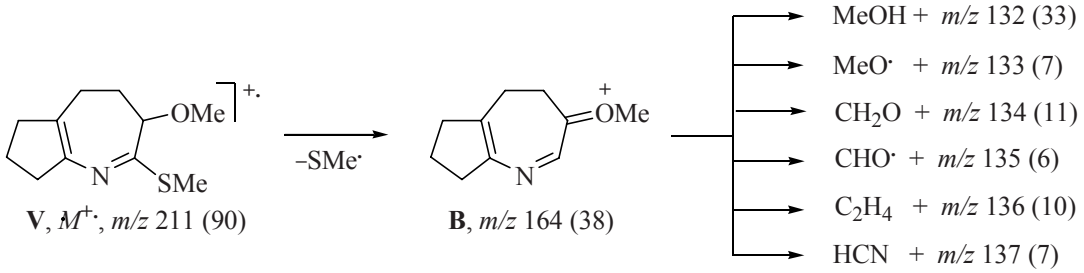
The fusion of 4,5-dihydro-3*H*-azepines shifted the equilibrium to the formation of ion $[M_2]^{+\cdot}$ with the charge localized on the oxygen atom. The rupture of C^5–C^6 bond resulted in ion with m/z 71 (100%) in keeping with the Stevenson– Audier rule [12].

The influence of the structure of the alkoxy substituent on the fragmentation character of 7-methyl-2-(methylsulfanyl)-4,5-dihydro-3*H*-azepines was investigated by examples of compounds **IIIa–IIId** (Schemes 2, 6, and 7). It turned out that in going from 3-methoxy- (**IIIa**) to 3-*tert*-butoxy-dihydroazepine (**IIId**), i.e., at increasing the length and the bulk of the alkyl part of the alkoxy substituent the character of the molecular ion fragmentation essentially changed (Table 2, Scheme 6).

For instance, unlike methoxy derivatives, the fragmentation of whose molecular ion involved all three heteroatoms, the fragmentation of molecular ion of compounds **IIIb–IIId** occurred through the channels governed by the prevailing localization of the charge and the lone electron on the ether oxygen. This statement is confirmed, firstly, by the absence in the mass spectra of 3-alkoxy-dihydroazepines **IIIb–IIId** of peak of the ion $[M - MeSCN]^{+\cdot}$ which is the strongest in the spectra of 3-methoxy-4,5-dihydro-3*H*-azepines **II, IIIa**, and **IV**, and also of ions $\mathbf{A^1}$ and **B** (sulfide fragmentation at Me–S and heterocycle–S bonds respectively). Inasmuch as in contrast to compounds **II, IIIa**, **IV**, and **V** the *m/z* values of ions $[M - MeSCN]^{+\cdot}$ and $[M - Alk - NCS]^{+\cdot}$ (**C**) are different for dihydroazepines **IIIb–IIId** (since Alk ≠ Me) it is possible to determine unambiguously which of the two possible channels provides ion **C** and in particular to exclude the channel related to the ion $[M - MeSCN]^{+\cdot}$.

Secondly, the ether fragmentation type of the molecular ions of alkoxy-substituted dihydroazepines **IIIb–IIId** is confirmed by the fact that the primary reactions initiated

Scheme 4.



V, $M^{+\cdot}$, *m/z* 211 (90) **B**, *m/z* 164 (38)

Scheme 5.

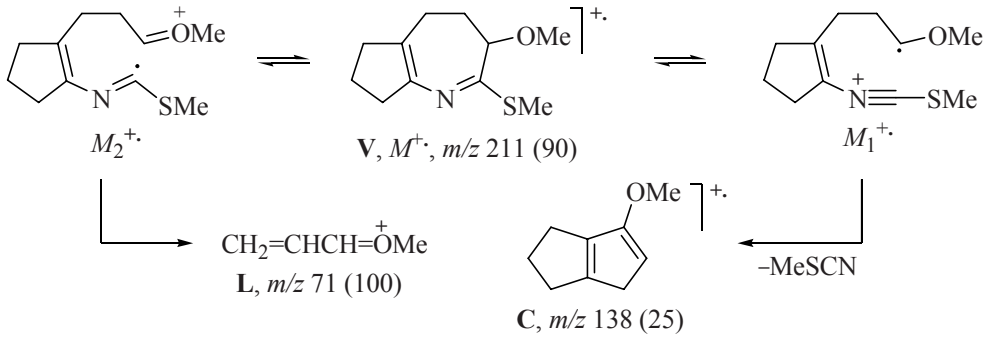


Table 2. Principal characteristic ions in the mass spectra of 3-alkoxy-7-methyl-(2-methylsulfanyl)-4,5-dihydro-3*H*-azepines **IIIb–IIId**

Ions		*m/z* (I_{rel}, %)		
		IIIb	**IIIc**	**IIId**
	$[M]^{+\cdot}$	199 (31)	213 (44)	227 (13)
A, **A**^{2}	$[M - Alk]^+$, *m/z* 170	(55)	(80)	(57)
C	$[\mathbf{A}^{5} - NCS]^{+\cdot}$, *m/z* 112	(100)	(92)	(22)
D, **D**^{2}	$[\mathbf{A} - C_2H_4]^+$ or $[\mathbf{A}^{2} - CO]^+$, *m/z* 142	(13)	(23)	(15)
E	$[\mathbf{D} - MeSH]^+$, *m/z* 94	(17)	(31)	(19)
G	$[\mathbf{E} - HCN]^+$, *m/z* 67	(19)	(31)	(17)
	$[M - AlkOH]^+$, *m/z* 153	(5)	(18)	(11)
$[M_3]^{+\cdot}$, $[M_4]^{+\cdot}$	$[M - C_nH_{2n}]^+$, *m/z* 171	–	(28)	(12)
A^{3}	$[M_3 - Me]^+$, *m/z* 156	–	(11)	(7)
B^{1}	$[M_3 - MeS]^+$, *m/z* 124	–	(16)	(8)
N	$[M_4 - MeCS]^+$ or $[\mathbf{A}^{3} - CS]^+$, *m/z* 112	–	(92)[a]	(22)[a]
	$[\mathbf{A}^{3} - H_2O]^+$, *m/z* 138	–	(21)	(8)
	$[\mathbf{B}^{1} - H_2O]^+$, *m/z* 120	–	(31)	(12)
	$[C_6H_9O]^+$, *m/z* 97	(12)	(41)	(38)
	$[C_6H_{11}]^+$, *m/z* 83	(7)	(11)	(3)
	$[C_4H_7O]^+$, *m/z* 71	(11)	(15)	(5)
	$[C_4H_7]^+$, *m/z* 55	(21)	(34)	(23)
	$[C_4H_5]^+$, *m/z* 53	(58)	(70)	(36)
	$[Alk]^+$	[b]	43 (94)	57 (100)
	$[C_3H_6]^{+\cdot}$, $[C_2H_2O]^{+\cdot}$, $[C_2H_4N]^+$, *m/z* 42	(19)	(35)	(18)
	$[C_3H_5]^+$, $[C_2H_3N]^{+\cdot}$, *m/z* 41	(97)	(100)	(100)

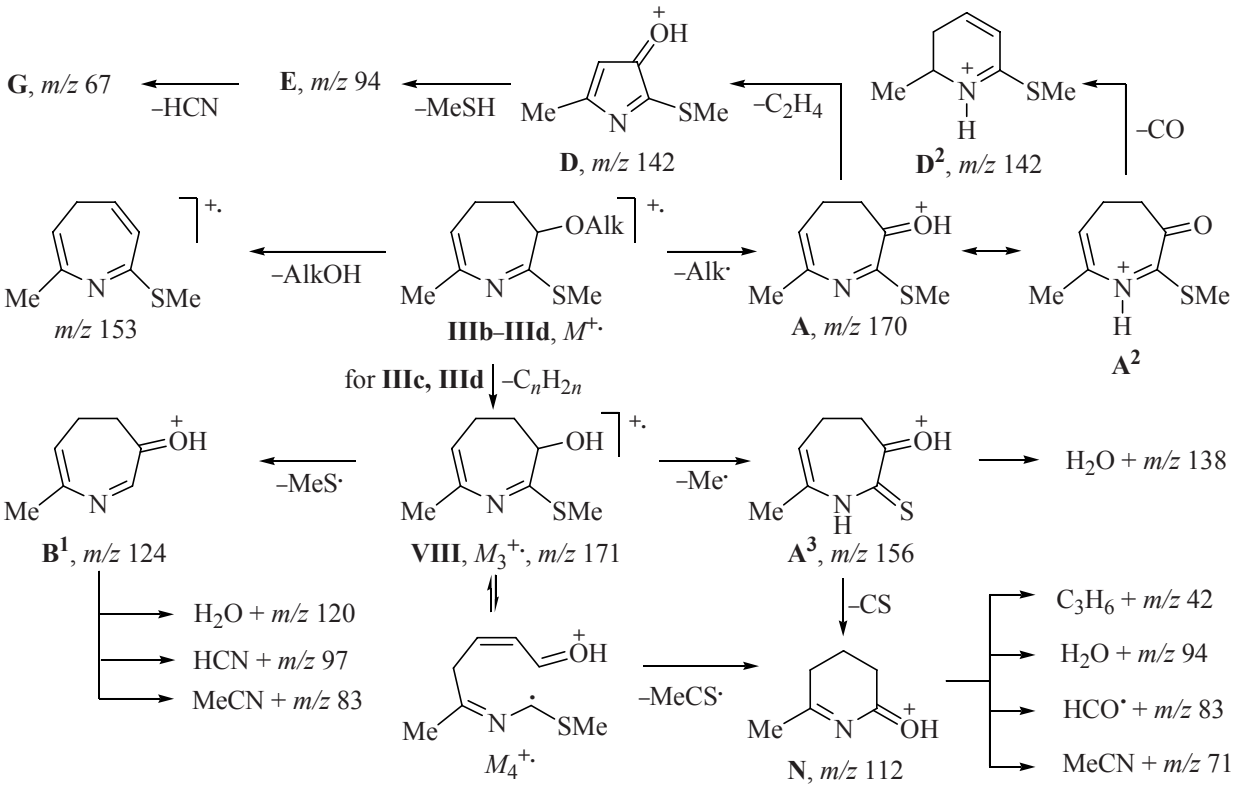
[a] Overlapped with the peak of ion-radical **C**. [b]Masses below *m/z* 35 were not registered.

by the radical center lead through the rupture of C–O bond to ions $[M - Alk]^+$ with m/z 170 (**A** and/or **A**^{2}) whose peaks are sufficiently intense (Table 2). Further fragmentation of ion **A** occurs by channels described for the methoxy analogs (cf. Schemes 2 and 6).

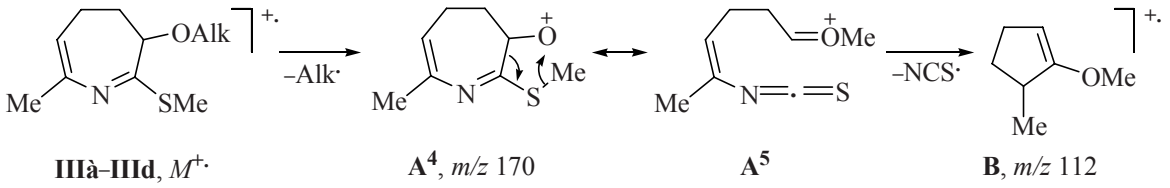
Besides for alkoxy-substituted dihydroazepines **IIIc** and **IIId** the formation of ions $[Alk]^+$ was characteristic, since owing to their branching these ions possessed a considerable thermodynamic stability. Especially feasible became the bond ruptures giving tertiary cation [13]. For instance, peaks of ion $[C(Me)_3]^+$ with *m/z* 57 and products of its fragmentation prevail in the spectrum of compound **IIId**.

Mass spectra of alkyl ethers with large alkyls are commonly characterized by abundant peaks of odd-electron fragments [14]. The growing alkyl group in alkoxydihydroazepines **IIIb–IIId** leads to the appearance of two new channels of $[M]^{+\cdot}$ fragmentation involving the elimination of (C_nH_{2n}, $n > 2$) or alkanol molecules (Scheme 6). The odd-electron ion $[M - C_nH_{2n}]^{+\cdot}$ with *m/z* 171 ($[M_3]^{+\cdot}$) most probably has the structure of 7-methyl-2-(methylsulfanyl)-4,5-dihydro-3*H*-azepin-3-ol (**VIII**). The main directions of fragmentation of this cation-radical consist in the rupture of the C–S bond and the formation of ions $[M_3 - Me]^+$ with m/z 156 (**A**^{3}), $[M_3 - MeS]^+$ with m/z 124 (**B**^{1}), and also of ion $[M_4 - MeCS]^+$ with m/z 112 (**N**) originating apparently from the open-chain form of the molecular ion $[M_4]^{+\cdot}$ (Scheme 6). Hence in contrast to methoxy- (**II, IIIa, IV, V**) and alkoxy- (**IIIb–IIId**) dihydroazepines the fragmentation of the molecular ion of 4,5-dihydro-3*H*-azepin-3-ol (**VIII**) is more like the sulfide type of fragmentation. The spectrum of compound **IIIb** lacks the peak of ion $[M - C_nH_{2n}]^{+\cdot}$ with m/z 171,

Scheme 6.



Scheme 7.



and the peak of ion with m/z 112 is the most abundant. Consequently, it is not ion **N** (Scheme 6), and its formation occurs along another mechanism. Presumably, ion with m/z 112 has the structure of ion **C** (Scheme 7), and its appearance is due to the skeletal rearrangement of ion $[M-\mathrm{Alk}]^+$ with *m/z* 170 (**A**^{4}) consisting in a migration of a group of atoms to the cationic site [15], in this event of a methyl group to the O-centered cation providing an open-chain ion **A**^{5} that further ejects radical NCS [16]. Obviously this process may occur in the fragmentation of $[M]^{+\cdot}$ of all studied 3-alkoxydihydroazepines and therefore to make certain or prevailing contribution into the intensity of peaks of ions $[M - \mathrm{MeSCN}]^{+\cdot}$ (for methoxy analogs **II, IIIa, IV**, and **V**) and **N** (for compounds **IIIc** and **IIId**) (Tables 1 and 2).

The fragmentation of the cation-radical $[M-\mathrm{AlkOH}]^{+\cdot}$ with m/z 153 will be discussed in detail further (Scheme 11).

In general, the mass spectra of 3-alkoxy-4,5-dihydro-3*H*-azepines **IIIb–IIId** (Alk > Me) contain three series of ions corresponding to ether fragmentation type of the proper compounds **IIIb–IIId** and to sulfide fragmentation type of the odd-electron ions formed therefrom with *m/z* 171 and 153, namely, of the molecular ions of 4,5-dihydro-3*H*-azepin-3-ol (**VIII**) (Scheme 6) and 2-methyl-7-(methylsulfanyl)-3*H*-azepine (**XII**) (Scheme 11).

Introducing into the position *3* of 4,5-dihydro-3*H*-azepine of a phenyl and a pyrrole ring changes the character of the molecular ion fragmentation. The peak of ion $[M-\mathrm{MeSCN}]^{+\cdot}$ and/or of $[\mathbf{A}^{1}-\mathrm{NCS}]^{+\cdot}$ (**C**), the diagnostic

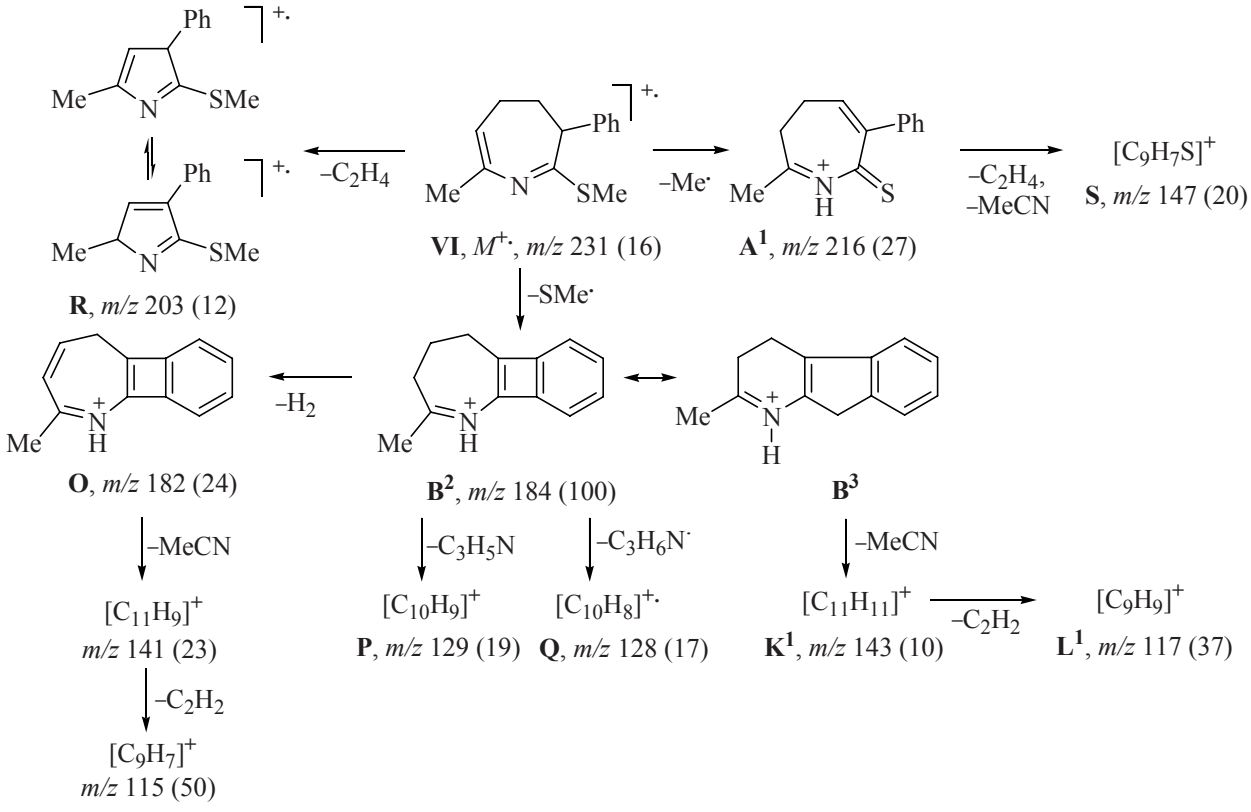
ion for the fragmentation of 3-methoxy-substituted 4,5-dihydro-3*H*-azepines, and also peaks of a number of other ions characteristic of the fragmentation $[M]^{+\cdot}$ of compounds **II–V** are lacking in the spectra of 3-phenyl-4,5-dihydro-3*H*-azepine (**VI**) and 3-(pyrrol-1-yl)-4,5-dihydro-3*H*-azepine (**VII**). The probable routes of formation, *m/z* values, relative intensities, and the structures of the main fragment ions of compounds **VI** and **VII** are presented in Schemes 8 and 9.

For compound **VI**, unlike compounds **II–V**, the prevailing channel is the rupture of C^2–S bond to form a stable ion $[M - MeS]^+$ with m/z 184 (100%) (**B²** or **B³**). Its further fragmentation occurs both along channels characteristic of compounds **II, IIIa, IV**, and **V** (formation of ions **K¹** [**B²** – MeCN]$^+$ and **L¹** [**K¹** – C_2H_2]$^+$) and via new fragmentation channels (Scheme 8). The channels belonging to the latter are the ejection by ion **B²** of hydrogen and 2,3-dihydroazete molecules, and also of 2,3-dihydroazetium cation leading to the formation of ions **O**, **P**, and **Q** with m/z 182, 129, and 128 respectively. The successive ejection by ion **O** of molecules MeCN and C_2H_2 results in ions with m/z 141 (23%) and 115 (50%).

Alongside the main ion $[M - MeS]^+$ in the spectrum of dihydroazepine **VI** two more ions are present corresponding to the primary fragmentation of $[M]^{+\cdot}$. These are ions $[M - Me]^+$ (**A¹**) and $[M - C_2H_4]^{+\cdot}$ (**R**). The latter fragmentation channel of the molecular ion involving synchronous or successive rupture of C^3–C^4 and C^5–C^6 bonds and the formation of a molecule of 2*H*- or 3*H*-pyrrole was not previously observed in the series of the studied 4,5-dihydro-3*H*-azepines. Evidently the phenyl substituent destabilized the dihydroazepine ring. The same is confirmed by the relatively low intensity of the molecular ion of dihydroazepine **VI** and, on the contrary, the maximum intensity of the ion peak with m/z 184 formed by the elimination of MeS radical followed by the rearrangement of the primary ion involving the phenyl group. The likely driving force of this rearrangement of ion $[M - MeS]^+$ is the formation of a stable tricyclic fused system: ions of 2-methyl-4,4-dihydro-3*H*-benzo[3,4]cyclobuta[1,2-*b*]azepinium **B²** or 2-methyl-4,9-dihydro-3*H*-indeno[2,1-*b*]pyridinium **B³**.

Unlike 3-phenyl-4,5-dihydro-3*H*-azepine (**VI**) 3-(pyrrol-1-yl)-4,5-dihydro-3*H*-azepine (**VII**) formed a maximum stable molecular ion (peak intensity 100%). In the

Scheme 8.



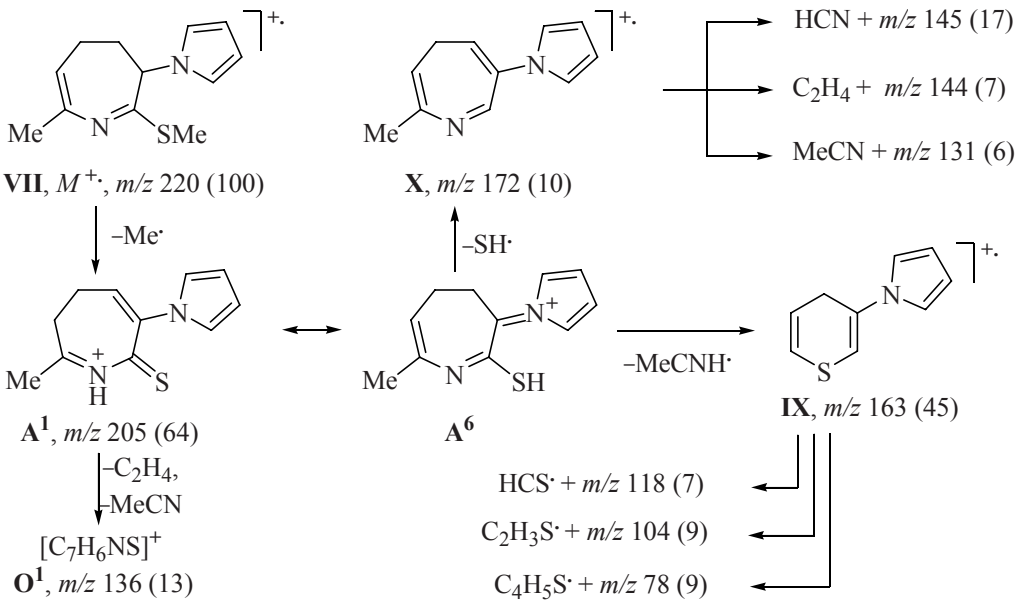
hetaryl-substituted 4,5-dihydro-3*H*-azepine **VII** no fragmentation occurs leading to the formation of ions $[M - MeS]^+$ and $[M - C_2H_4]^{+\cdot}$. The only channel of the primary fragmentation of the molecular ion is here the ejection of a methyl radical. Besides the possibility to stabilize the primary fragment ion $[M - Me]^+$ with m/z 205 by localization of the positive charge on the nitrogen of the pyrrole ring (**A**^{6}) completely changes the character of its fragmentation (Scheme 9).

Further fragmentation of ion $[M - Me]^+$ takes two new, previously unknown routes (with the elimination of MeCNH and SH radicals) and results in odd-electron ions with m/z 163 (45%) and 172 (10%) that presumably has structures respectively of 1-(4*H*-thiopyran-3-yl)-1*H*-pyrrole (**IX**) and 2-methyl-6-(1*H*-pyrrol-1-yl)-4*H*-azepine (**X**) (or its isomers). Structure **IX** is confirmed by its subsequent fragmentation with the loss of sulfur-containing radicals HCS, C_2H_3S, and C_4H_5S. The fragmentation of ion with *m/z* 172 (azepine **X**), on the contrary, involves the ejection of neutral species HCN, MeCN, and C_2H_4.

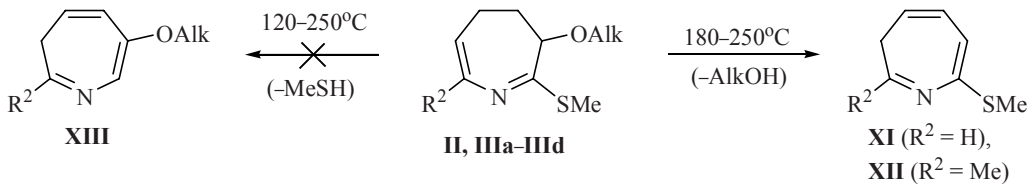
In the course of spectral monitoring of 4,5-dihydro-3*H*-azepines **II** and **IIIa–IIId** using a system of chromatographically introducing samples into the ion source we discovered a new thermally induced reaction of alkanol elimination leading to the formation of previously unknown 7-(methylsulfanyl)-3*H*-azepines **XI** and **XII** (Scheme 10).

It turned out that at the chromatographical introduction of samples (vaporizer and ion source temperature 120–180°C, pressure 100–150 kPa) on the chromatograms alongside the peak of the analyzed compound **II** or **IIIa** were registered peaks of its structural isomer and of one more substance whose mass spectrum corresponded to 7-(methylsulfanyl)-3*H*-azepine (**XI** or **XII** respectively) or its isomers (Schemes 10 and 11). At 250°C and the pressure 150 kPa the samples **IIIb–IIId** also suffered thermal decomposition with alkanol elimination and the formation of 3*H*-azepine **XII**. In the chemical experiment we failed to observe this reaction route (although did not exclude it). The thermal elimination of methanethiol with the formation of 6-alkoxy-3*H*-azepines **XIII** did not occur

Scheme 9.



Scheme 10.



under these or even more rigid conditions (250°C, 100–280 kPa). The analysis of chromatograms suggests that the alkanol elimination occurs not from the initial 4,5-dihydro-3*H*-azepines, but from their structural isomers forming only under the chromatographic conditions and having indentical mass spectra.

It was established that at electronic ionization 3*H*-azepines **XI** and **XII** formed stable molecular ions whose primary fragmentation in both compounds involved the elimination of methylsulfanyl group or its fragments to give ions $[M - MeS]^+$, $[M - CH_2S]^{+\cdot}$, $[M - SH]^+$, and $[M - Me]^+$ (Scheme 11). Further fragmentation of the latter involves the elimination of R^2CN, C_2H_2, and CS species.

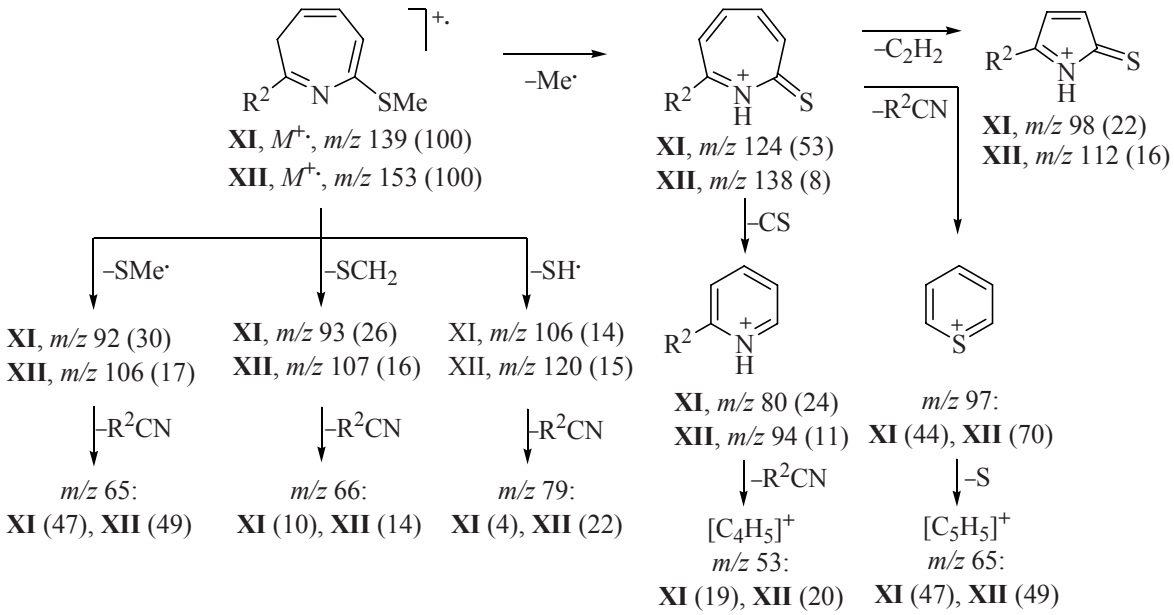
By the same channels occurs the fragmentation of the odd-electron ion $[M - AlkOH]^{+\cdot}$, *m/z* 153, formed at the fragmentation of molecular ions of alkoxydihydroazepines **IIIb–IIId**.

Hence it was established that the molecular ion fragmentation of all 3-methoxy-4,5-dihydro-3*H*-azepines **II, IIIa, IV**, and **V** proceeded by the same three competing channels with the localization of the cation-radical center on nitrogen, oxygen, or sulfur atoms giving diagnostic ions $[M - MeSCN]^{+\cdot}$ or $[M - Me - NCS]^{+\cdot}$. Namely, the rules we had previously found for the fragmentation of 7-methyl-2-(methylsulfanyl)-3-methoxy-4,5-dihydro-3*H*-azepine (**IIIa**) under electronic ionization [1] were general for all studied 3-methoxy-substituted dihydroazepines.

In 3-alkoxy-4,5-dihydro-3*H*-azepines **IIIb–IIId** where Alk > Me the fragmentation of the molecular ion follows the rules characteristic of alkyl ethers. Beside the simple rupture of C–O bond to obtain ions $[Alk]^+$ and $[M - Alk]^+$ here also cleavage occurs of carbon–oxygen bonds with simultaneous hydrogen transfer, in particular, the ejection from $[M]^{+\cdot}$ of alkene molecule (from the alkoxy substituent), and also of alkanol with the formation of odd-electron ions $[M - C_nH_{2n}]^{+\cdot}$ and $[M - AlkOH]^{+\cdot}$ corresponding to the structures of 7-methyl-2-(methylsulfanyl)-4,5-dihydro-3*H*-azepin-3-ol (**VIII**) and 2-methyl-7-(methylsulfanyl)-3*H*-azepine (**XII**) respectively. Further fragmentation of the arising cation-radicals might contribute certain "distortions" into the overall pattern of fragmentation of the molecular ions of compounds **IIIb–IIId**. 7-(Methyl-sulfanyl)-3*H*-azepines **XI** and **XII** formed also by thermal decomposition of compounds **II** and **IIIa–IIId** respectively during the registering of mass spectra. It should be noted that the products of simple elimination of hydrogen or alkyl radicals from the α-position (α-cleavage is usually the prevailing process in ethers decomposition) were not identified in the spectra of 3-alkoxy-4,5-dihydro-3*H*-azepines **IIIb–IIId**.

Molecular ions of aryl- and hetaryl-substituted 4,5-dihydro-3*H*-azepines **VI** and **VII** undergo fragmentation mainly by the sulfide type. However here the similarity between them ends. From 3-phenyl-4,5-dihydro-3*H*-azepine (**VI**) form both possible ions of the sulfide frag-

Scheme 11.



mentation, $[M - Me]^+$ and $[M - MeS]^+$, and the latter prevails. This ion has a maximum intensity (100%) and a probable structure of 2-methyl-4,4-dihydro-3*H*-benzo-[3,4]cyclobuta[1,2-*b*]azepinium or 2-methyl-4,9-dihydro-3*H*-indeno[2,1-*b*]pyridinium. Besides in this case operates a quite new third fragmentation channel of the molecular ion: ejection of the ethylene molecule to form an odd-electron ion corresponding to the structure of 2*H*- or 3*H*-pyrrole.

3-(Pyrrol-1-yl)-4,5-dihydro-3*H*-azepine (**VII**), on the contrary, is characterized by a single way of primary fragmentation of $[M]^{+\cdot}$: the cleavage of S–Me bond and the formation of ion $[M - Me]^+$ whose specific feature is the localization of the charge on the nitrogen atom of the pyrrole ring. This phenomenon not only stabilizes the arising ion (its peak intensity is 64%), but also fundamentally affects the directions of its further fragmentation. Stable 1-methylene-1*H*-pyrrolium ions of approximately similar peak intensity (62–63%) formed at the α-fragmentation of molecular ions of 1-alkylpyrroles [17]. The significant contribution of the "pyrrole" component into the general pattern of the fragmentation of compound **VII** at electronic ionization is apparently also seen from the highest (of all the studied) stability of the formed molecular ion (100%) characteristic of some pyrrol structures [1, 8].

It is clear from the above, that the key role in the fragmentation of molecular ions of the studied 4,5-dihydro-3*H*-azepines **II–VII** belongs to the nature of the substituents in the position *3* of the heterocycle.

EXPERIMENTAL

2-(Methylsulfanyl)-4,5-dihydro-3*H*-azepines **II–VII** were prepared by procedures from [6].

Mass spectra of electronic ionization (70 eV) of compounds **II–VII, XI**, and **XII** were obtained on an instrument Shimadzu GCMS-QP5050A (quadrupole mass-analyzer, the range of detected masses 34–650 Da). The chromatographic separation of compounds under study was carried out on a capillary column SPB-5 (60 m × 0.25 mm × 0.25 μm), carrier gas helium, flow rate 0.7 ml/min. The measurements were performed in two modes: temperature of vaporizer and ion source 250°C, pressure 150 kPa, ramp from 70 to 250°C at a rate 10 deg/min; temperature of vaporizer and ion source 150°C, pressure 300 kPa, ramp from 60 to 150°C at a rate 10 deg/min.

The study was carried out under a financial support of the Russian Foundation for Basic Research (grant no. 05-03-32578a).

REFERENCES

1. Klyba, L.V., Nedolya, N.A., and Zhanchipova, E.R., *Zh. Org. Khim*., 2008, vol. 44, p. 135.
2. Proctor, G.R. and Redpath, J., *Monocyclic Azepines*. Chichester: Wiley, 1996; Sterner, O., Steffan, B., and Steglich, W., *Tetrahedron*, 1987, vol. 43, p. 1075; Smith, A.B. III, Cho, Y.S., Zawacki, L.E., Hirschmann, R., and Pettit, G.R., *Org. Lett*., 2001, vol. 3, p. 4063; Kaltenegger, E., Brem, B., Mereiter, K., Kalchhauser, H., Kahlig, H., Hofer, O., Vajrodaya, S., and Greger, H., *Phytochem*., 2003, vol. 63, p. 803; O'Hagan, D., *Nat. Prod. Rep*., 1997, p. 637; Gill, M., *Nat. Prod. Rep*., 2003, vol. 20, p. 615.
3. Acques, E., and di Chiara, G., *Eur. J. Pharmacol*., 1999, vol. 383, p. 275; Rosowsky, A., Cody, V., Galitsky, N., Fu, H.N., Papoulis, A.T., and Quenner, S.F., *J. Med. Chem*., 1999, vol. 42, p. 4853; Albright, J.D., Santos, E.G.D., Dusza, J.P., Chan, P.S., Coupet, J., Ru, X., and Mazandarani, H., *Bioorg. Med. Chem. Lett*., 2000, vol. 10, p. 695; Levy, O., Erez, M., Varon, D., and Keinan, E., *Bioorg. Med. Chem. Lett*., 2001, vol. 11, p. 2921; Inghilleri, M., Conte, A., Frasca, V., Curra'A., Gilio, F., Manfredi, M., and Berardelli, A., *Exp. Brain, Res*., 2004, vol. 154, p. 488; Knapp, R.J., Goldenberg, R., Shuck, C., Cecil, A., Watkins, J., Miller, C., Crites, G., and Malatynska, E., *Eur. J. Pharmacol*., 2002, vol. 440, p. 27; Andres, J.I., Alcazar, J., Alonso, J.M., Diaz, A., Fernandez, J., Gil, P., Iturrino, L., Matesanz, E., and Meert, T.F., *Bioorg. Med. Chem. Lett*., 2002, vol. 12, p. 249.
4. Smalley, R.K., *Comprehensive Heterocyclic Chem. I,* Katritzky, A.R. and Rees, C.W., Eds., Oxford: Elsevier, 1986, vol. 7, p. 491; Le Count, D.J., *Comprehensive Heterocyclic Chem. II,* Katritzky, A.R., Rees, C.W., and Scriven, E.F.V., Oxford: Elsevier, 1996, vol. 9, p. 1; Smolli, R.K., *Comprehensive Organic Chemistry, B*arton, D. and Ollis, W.D., Eds., Oxford: Pergamon, 1979, vol. p. 8; Satake, K., Takaoka, K., Hashimoto, M., Okamoto, H., Kimura, M., and Morosawa, S., *Chem. Lett*., 1996, p. 1129; Brass, S., Chan, N.-S., Gerlach, C., Luksch, T., Bottcher, J., and Diederich, W.E., *J. Organometal. Chem*., 2006, vol. 691, p. 5406; Glennon, R.A. and Dukat, M., *Pharm. Acta Helv*., 2000, vol. 74, p. 103.
5. Nedolya, N.A., *Ph.D. Thesis of Utrecht University. Utrecht*, 1999; Brandsma, L., *Eur. J. Org. Chem*., 2001, p. 4569; Brandsma, L. and Nedolya, N.A., *Synthesis*, 2004, p. 735.

6. Nedolya, N.A., Dmitrieva, L.L., Albanov, A.I., Klyba, L.V., Tarasova, O.A., and Ushakov, I.A., *Zh. Org. Khim*., 2006, vol. 42, p. 477.
7. Klyba, L.V., Nedolya, N.A., Brandsma, L., and Schlyakhtina, N.I., *Arkivoc*, 2001, vol. IX, p. 117; Klyba, L.V., Nedolya, N.A., Shlyakhtina, N.I., and Zhanchipova, E.R., *Zh. Org. Khim*., 2005, vol. 41, p. 1576.
8. Klyba, L.V., Bochkarev, V.N., Brandsma, L., Nedolya, N.A., and Trofimov, B.A., *Zh. Obshch. Khim*., 1999, vol. 69, p. 1885; Klyba, L.V., Bochkarev, V.N., Brandsma, L., Nedolya, N.A., and Trofimov, B.A., *Izv. Akad. Nauk, Ser. Khim*., 2001, p. 2282.
9. Klyba, L.V., Bochkarev, V.N., Brandsma, L., Tarasova, O.A., Vvedenskii, V.Yu., Nedolya, N.A., and Trofimov, B.A., *Zh. Obshch. Khim*., 1999, vol. 69, p. 1881; Klyba, L.V., Bochkarev, V.N., Brandsma, L., Tarasova, O.A., Nedolya, N.A., and Trofimov, B.A., *Izv. Akad. Nauk, Ser. Khim*., 2000, p. 1560.
10. Klyba, L.V., Tarasova, O.A., Brandsma, L., Nedolya, N.A., and Petrushenko, K.B., *Zh. Org. Khim*., 2006, vol. 42, p. 1023.
11. Brandsma, L., Spek, A.L., Trofimov, B.A., Tarasova, O.A., Nedolya, N.A., Afonin, A.V., and Zinchenko, S.V., *Tetrahedron Lett*., 2001, vol. 42, p. 4687; Tarasova, O.A., Brandsma, L., Nedolya, N.A., Afonin, A.V., Ushakov, I.A., Klyba, L.V., and Trofimov, B.A., *Zh. Org. Khim*., 2003, vol. 39, p. 1521; Tarasova, O.A., Nedolya, N.A., Brandsma, L., and Albanov, A.I., *Tetrahedron Lett*., 2004, vol. 45, p. 5881.
12. Stevenson, D.P., *Discuss. Faraday Soc*., 1951, p. 35; Audier, H.E., *Org. Mass Spectrom*., 1969, p. 289.
13. Jonstone, R., *Mass-Spectrometry for Organic Chemists*, Cambridge University Press, 1992.
14. Vul'fson, N.S., Zaikin, V.G., and Mikaya, A.I., *Mass-spektrometriya organicheskikh soedinenii* (Mass Spectrometry of Orgaic Compounds), Moscow: Khimiya, 1986, p. 185; Zaikin, V.G., Varlamov, A.V., Mikaya, A.I., and Prostakov, N.S., *Osnovy mass-spektrometrii organicheskikh soedinenii* (Bases of Mass Spectrometry of Organic Compounds), Moscow: MAIK, "Nauka/Interperiodika", 2001, p. 141.
15. Takhistov, V.V. and Ponomarev, D.A., *Organicheskaya mass-spektrometriya* (Organic Mass-Spectrometry), St. Petersburg: VVM, 2005, p. 53.
16. Hamed, A.R., Abdel-Shafeek, K.A., Abdel-Azim, N.S., Ismail, S.I., and Hammouda, F.M., *eCAM*., 2007, vol. 4, p. 25.
17. Duffield, A.M., Beugelmans, R., Budzikiewicz, H., Lightner, D.A., Williams, D.H., and Djerassi, C., *J. Am. Chem. Soc*., 1965, vol. 87, p. 805.