MASS SPECTRA OF SUBSTITUTED PIPERIDINES*

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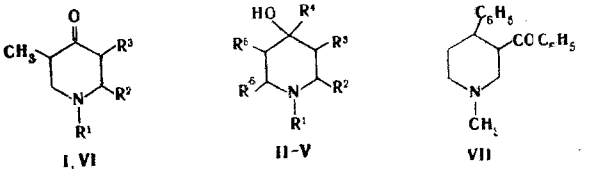
UDC 547.824:543.51

The mass spectra of piperidines and N-methylpiperidines with various functional groups attached to the heteroring carbon atoms were studied. The mechanisms of the formation and fragmentation of the amine fragments with various structures and specific hydrogen and skeletal rearrangements are discussed. It is shown that the sequence of cleavage of the heteroring bonds depends on the properties of the substituents and their positions in the ring.

In previous communications [1, 2] we examined the mass-spectrometric fragmentation of some of the simplest mono- and disubstituted piperidines. The fragmentation under the influence of electron impact of similar compounds with more complex substituents has not been previously studied. In the present research we studied the mass spectra of piperidines and N-methylpiperidines (I-VII) with various functional groups attached to the heteroring carbon atoms.



I, VI II-V VII

I $R^1=R^3=H$, $R^2=CH_3$; II $R^1=R^2=R^5=CH_3$, $R^3=R^6=H$, $R^4=CH_2C_6H_5$; III $R^1=R^4=R^6=H$, $R^2=R^5=CH_3$, $R^3=COOC_2H_5$; IV $R^1=R^2=R^6=CH_3$, $R^3=COOCH_3$, $R^4=H$; V $R^1=CH_3$, $R^2=R^6=C_6H_5$, $R^3=COOC_2H_5$, $R^4=R^5=H$; VI $R^1=CH_3$, $R^2=H$, $R^3=COOCH_3$

According to the NMR spectra, II-V are individual stereoisomers [3, 4], and we therefore used the principles previously found in a study of the fragmentation of the similar stereoisomeric pairs in series of 2,6-substituted 4-piperidols [2] in the discussion of the relative intensities of the peaks of the characteristic ions, which depend on their three-dimensional structures.

The behavior under the influence of electron impact of piperidines with methyl groups in the 2 and 5 (I-III) and 2 and 6 (IV) positions is determined primarily by the amine fragmentation (Table 1). The most intense peaks in their spectra at electron energies of 70 and 12 eV correspond to amine fragment a ($[M - CH_3]^+$) and ion b. Ion b is formed via Diels–Alder retrofragmentation of fragment a with synchronous cleavage of the C_3–C_4 and C_5–C_6 bonds (Scheme 1).

During a study of the mass spectra of analogous stereoisomeric 4-piperidols it was found [2] that the relative intensities of the peaks of the characteristic ions change as a function of the orientation of the substituent in the 2 position; the ratio of the intensities of the M^+ and $[M - CH_3]^+$ peaks also changes slightly in this case. However, regardless of the spatial orientation of the substituent attached to the C_2 atom, the peak of amine fragment a in the spectra of such compounds, as in the case of their analogs I-IV, retains its maximum intensity at ionizing electron energies of 70 and 12 eV.

The principal ions formed in the fragmentation of I-VII are amine fragments with an even number of electrons. In the spectra of the piperidines that we investigated, which contain one nitrogen atom, the peaks of such ions have even mass numbers. The mechanism of the

*Communication 9 in the series "Application of mass spectrometry in structural and stereochemical investigations." See [1] for Communication 8.

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 0009-3122/81/1701-0052$07.50

TABLE 1. Mass Spectra of I-VII at Electron Energies of 70 (a) and 12 eV (b)

Compound	m/e values (relative intensities of the ion peaks in percent relative to the maximum peak)
Ia	128 (6), 127 (56), 113 (2), 112 (36), 85 (8), 84 (22), 83 (2), 82 (3), 71 (2), 70 (6), 58 (4), 57 (23), 56 (100), 55 (8), 44 (22), 42 (26), 41 (18)
Ib	128 (6), 127 (100), 113 (4), 112 (73), 85 (10), 84 (20), 71 (2), 70 (14), 57 (12), 56 (64), 44 (4), 43 (2)
IIa	233 (4), 219 (6), 218 (28), 216 (6), 213 (8), 200 (5), 143 (3), 142 (16), 129 (4), 128 (3), 127 (3), 126 (8), 125 (2), 124 (8), 99 (2), 98 (8), 92 (13), 91 (100), 90 (4), 89 (7), 85 (3), 84 (8), 77 (8), 72 (4), 71 (14), 70 (38), 65 (33), 58 (14), 57 (12), 56 (28), 55 (10), 44 (15), 43 (18), 42 (45), 41 (12)
IIb	234 (4), 233 (22), 232 (2), 219 (14), 218 (100), 200 (2), 143 (3), 142 (19), 98 (2), 91 (2), 84 (3), 70 (16)
IIIa	202 (4), 201 (33), 186 (23), 184 (14), 172 (10), 168 (4), 156 (22), 155 (4), 154 (4), 140 (12), 139 (3), 138 (25), 129 (2), 128 (22), 127 (2), 110 (25), 109 (5), 98 (2), 97 (6), 96 (2), 87 (10), 86 (14), 85 (100), 84 (30), 83 (4), 82 (10), 71 (10), 70 (80), 69 (16), 58 (10), 57 (30), 56 (60), 55 (6), 45 (4), 44 (28), 43 (22), 42 (26), 41 (18)
IIIb	202 (4), 201 (56), 186 (31), 184 (19), 172 (16), 168 (2), 156 (12), 140 (6), 138 (12), 128 (14), 110 (20), 86 (12), 85 (100), 84 (18), 70 (30), 58 (6), 57 (10), 56 (10)
IVa	202 (8), 201 (14), 200 (4), 188 (4), 187 (34), 186 (100), 185 (3), 184 (6), 171 (6), 170 (14), 169 (5), 168 (43), 167 (3), 166 (2), 154 (4), 143 (3), 142 (23), 128 (4), 127 (8), 126 (3), 100 (4), 99 (8), 98 (12), 87 (2), 86 (8), 85 (10), 84 (24), 71 (10), 70 (6), 69 (10), 59 (10), 58 (28), 57 (72), 56 (24), 55 (6), 45 (4), 44 (8), 43 (10), 42 (40), 41 (14)
IVb	202 (7), 201 (56), 187 (10), 186 (100), 184 (5), 170 (6), 168 (8), 142 (3), 99 (4), 98 (3), 86 (3), 85 (3), 84 (8), 57 (6), 56 (4), 55 (3)
Va	340 (10), 339 (40), 338 (10), 324 (4), 322 (5), 310 (8), 294 (14), 266 (4), 262 (24), 261 (4), 248 (10), 234 (54), 222 (18), 206 (14), 188 (12), 163 (22), 162 (50), 161 (4), 160 (20), 146 (26), 131 (24), 130 (3), 129 (24), 120 (66), 119 (40), 118 (100), 105 (19), 104 (70), 103 (24), 91 (34), 77 (24), 71 (12), 57 (12), 56 (3), 55 (12)
Vb	340 (24), 339 (100), 324 (2), 322 (3), 310 (6), 234 (8), 263 (4), 262 (18), 248 (6), 235 (12), 234 (100), 222 (10), 206 (16), 205 (4), 188 (6), 163 (36), 162 (76), 161 (10), 120 (38), 119 (10), 118 (10), 105 (12), 104 (6)
VIa	186 (6), 185 (30), 184 (9), 171 (2), 170 (14), 168 (5), 154 (16), 153 (12), 152 (100), 143 (3), 142 (14), 127 (9), 126 (72), 111 (6), 110 (32), 109 (5), 108 (4), 100 (3), 99 (2), 98 (6), 84 (12), 83 (8), 82 (16), 70 (8), 69 (16), 58 (8), 57 (5), 56 (30), 55 (30), 54 (38), 44 (64), 43 (56), 42 (41), 41 (17)
VIb	186 (8), 185 (100), 184 (20), 171 (6), 170 (40), 152 (20), 128 (4), 127 (4), 126 (20), 142 (8), 127 (6), 126 (26), 111 (4), 110 (6), 45 (3), 44 (12)
VIIa	280 (4), 279 (26), 261 (2), 176 (8), 175 (68), 174 (6), 173 (2), 172 (6), 160 (6), 159 (12), 158 (100), 147 (6), 146 (5), 144 (2), 143 (3), 133 (7), 132 (6), 131 (4), 117 (4), 116 (2), 115 (6), 106 (2), 105 (20), 98 (10), 92 (2), 91 (12), 71 (10), 70 (22), 58 (5), 57 (6), 56 (5), 54 (6), 44 (12), 43 (30), 42 (22), 41 (2)
VIIb	280 (12), 279 (52), 176 (12), 175 (100), 159 (4), 158 (20)

formation of odd-electron fragment c is of interest, since genetically speaking it can be associated only with the molecular ion. Consequently, cleavages of the bonds in the molecular ion should competitively weaken amine fragmentation with splitting out of the α substituent. Ion c is formed by cleavage of the C_2—C_3 and C_4—C_5 bonds with ring contraction to a four-membered ring.

In the spectra of I-IV at an electron energy of 12 eV one's attention is directed to the high intensities of the peaks of the even-electron d and e fragments, which are also formed by ring contraction. A similar regularity was previously observed in the fragmentation of piperidines that are substituted only in the α position [5]. It should be noted that the peaks of ions similar to the c, d, and e ions formed in the cleavage of the ring bonds in the molecular ion do not depend on the three-dimensional structure of the molecule [2].

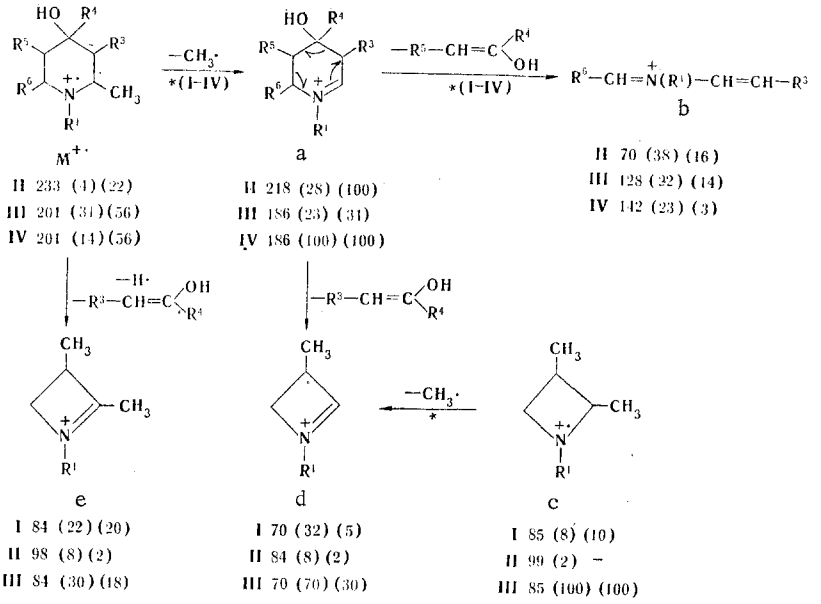
In the spectrum of N-methyl analog II the peak of the fragment with m/e 99 has very low intensity, since the $M_1^+ \rightarrow$ c process is suppressed by the formation of a tropylium ion with m/e 91, the peak of which has the maximum intensity in the spectrum at an electron energy of 70 eV.

The peak of principal intensity in the spectrum of analog III at high and low ionizing voltages corresponds to fragment c with m/e 85. The easier cleavage of the C_2—C_3 and C_4—C_5 bonds in the molecular ion of this compound as compared with derivatives I and II is evidently due to splitting out of a stable molecule of ethyl β-hydroxyacrylate. As expected, this process substantially suppresses the formation of an $[M - CH_3]^+$ fragment.

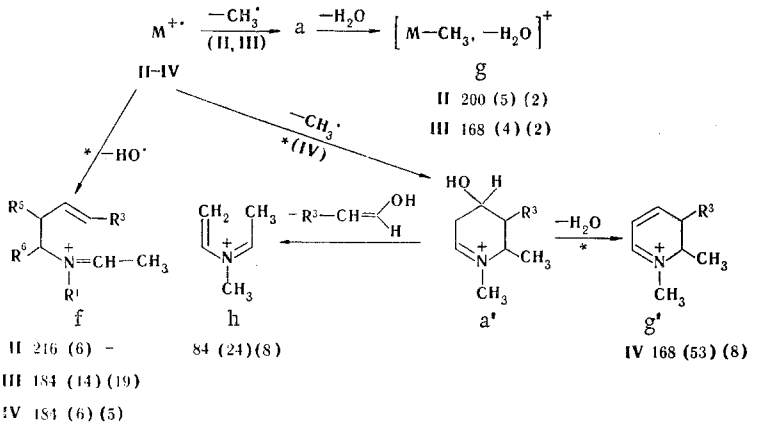
In contrast to analog III, virtually no c ion is formed in the fragmentation of IV; this is due to the presence of two methyl groups in the 2 and 6 positions and a hydroxy group in the 4 position, which increase the probability of the formation of cyclic amine fragments a and a' and characteristic ions f, g (g'), and h (Scheme 2).

In fact, in contrast to the fragmentation of analog III, in the fragmentation of IV the principal contribution to the overall ion current at ionizing-electron energies of 70 and 12 eV is due to cyclic fragments a and g' (Table 2).

Scheme 1



Scheme 2



The orientation of the hydroxy group in the 4 position has a substantial effect on the intensity of the peak of fragment g, which is formed by dehydration of ion a [2]. The large contribution of fragment g' to the total ion current in the case of IV (Table 2) and the magnitude of the ratio of the intensities of the peaks of g' and α' ions (J_g/J_a = 0.43 at 70 eV) constitutes evidence for an equatorial orientation of the hydroxy group; this is in agreement with the data from the NMR spectra [3]. The determination of the orientation of the OH group in the II and III molecules is difficult in view of the low intensity of the peak of the g ion in the spectra of these analogs. In the fragmentation of II this is associated with the predominant formation of a tropylium cation, whereas in the fragmentation of derivative III it is associated with the formation of a molecular ion with an open structure. This is confirmed by the data in Table 2, from which it follows that in the fragmentation of III the contributions to the overall ion current of cyclic ion α and fragment f with an open structure are comparable. Let us note that the geometrical isomers become identical in the formation of M^+ with an open structure [2]. A process similar to $\alpha' \rightarrow$ h (Scheme 2) occurs in the fragmentation of the amine fragment in the case of 2,6-dimethylpiperidine [6]; the relative intensities of the peaks of ions of the h type are close in the spectra of both compounds.

It also follows from a comparison of the mass spectra of III and IV that the presence of methyl groups in the piperidine ring has a substantial effect on the character of fragmenta-

*The relative intensities of the peaks at 70 and 12 eV are indicated in parentheses after the mass numbers of the fragments.

TABLE 2. Relative Intensities (in percent of the total ion current) of the Peaks of the Molecular Ions and the Characteristic Fragments in the Mass Spectra of II-IV

Compound	Ion							
	M^+		a		f		g	
	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV
II	0,8	12,0	5,6	53,0	1,2	—	1,0	1,1
III	4,9	14,8	3,5	8,2	2,1	5,0	0,6	0,5
IV	2,3	23,5	16,7	43,7	1,0	2,2	7,2	2,8

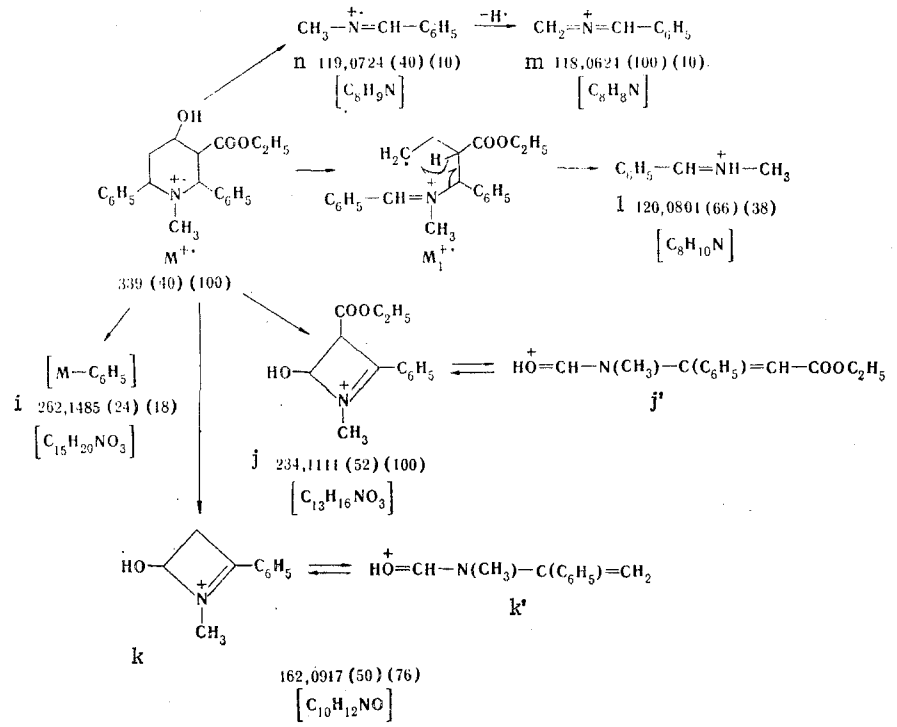
tion of the heteroring. Their positions in the ring can be determined by a study of the sequence of the cleavages of the ring bonds and a comparison of the relative intensities of the peaks of the amine fragments at high and low ionizing voltages. On the other hand, strong electron-acceptor substituents such as an oxo group in the 4 position and an ester group in the 3 position do not have a significant effect on the processes involved in the formation of fragments with a quaternary nitrogen atom.

A study of the peculiarities of the amine fragmentation of substituted piperidines that contain α substituents that are not inclined to undergo splitting out in the form of a free radical seems of interest from this point of view. The phenyl ring can be included among substituents of this sort [7]. It follows from the mass spectrum of V that the detachment of a phenyl group even from the α position of the molecular ion leads to ion i with m/e 262, the peak of which, even though it is observed in the spectra at ionizing-electron energies of 70 and 12 eV, is characterized by a considerably lower (by a factor of 4.5) intensity as compared with IV. The principal pathways of fragmentation of the molecular ion of V are due to cleavages of the C_5—C_6, C_2—N_1, and C_4—C_5, C_6—N_1 bonds. The intensities of the peaks of the principal ions formed in the fragmentation of this compound therefore are independent of the geometry of the molecule. Fragments i-n are formed as a result of rearrangements with the participation of the hydrogen atoms in the 2 or 6 position (Scheme 3).

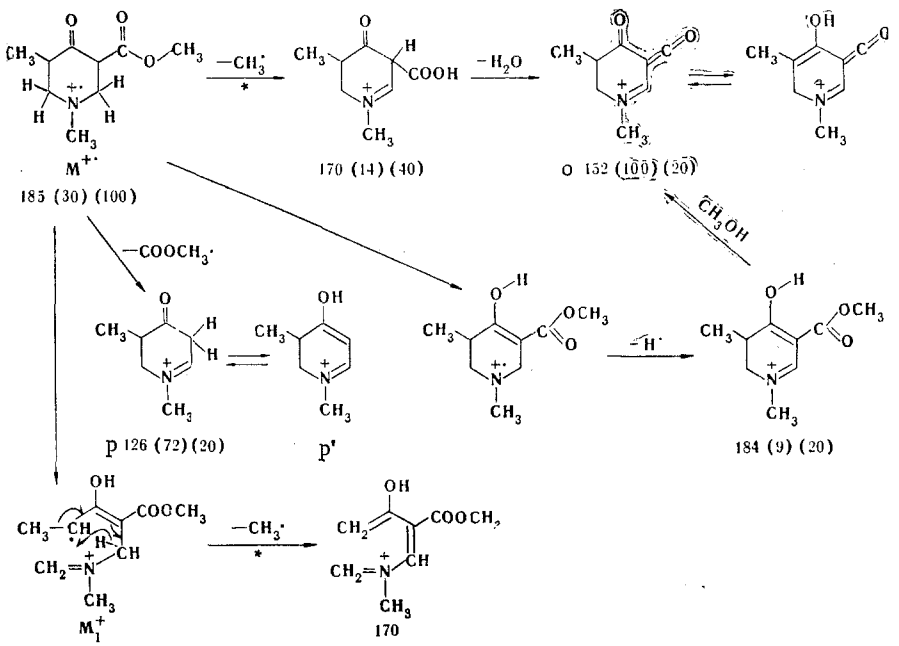
The fragmentation mechanisms proposed in Scheme 3 and the structures of the ions follow from the mass spectrum of hydroxy-labeled deutero analog V and the elementary composition of the fragments found from the high-resolution spectrum (see the scheme). The peaks of the i, j, and k ions in the spectrum of the deutero analog are shifted one unit toward the higher m/e side, while this sort of shift is absent for the peaks of l, m, and n fragments. In analogy with the fragmentation of I-IV and other similar analogs [5], the $M^+ \rightarrow j$ and $M^+ \rightarrow k$ processes are probably accompanied by ring contraction. However, it should be noted that even in the case of formation of noncyclic structures the charge in these ions is stabilized on the oxygen atom of the hydroxy group. The dependence of the intensity of the peaks of j, k, and n ions on the ionizing-electron energy is explained by the possibility of $j \rightleftarrows j'$ and $k \rightleftarrows k'$ isomerization. The maximum peak in the spectrum of V at an electron energy of 70 eV corresponds to the m ion. The intensity of the peak of this ion decreases substantially as the ionizing-electron energy is reduced to 12 eV, while the k ion peak retains its high intensity. The relative intensity of the peak of the j fragment increases markedly (from 52% to 100%). This sort of behavior is characteristic for cyclic ions in which the charge is localized on a quaternary nitrogen atom. Consequently, ions j and k should have cyclic structures at a low ionization energy. The considerable dependence of the i-n ion peaks on the ionizing-electron energy may also be due to both the substantial difference in the activation energies of the processes involved in their formation and the difference in the energies of the C_5—C_6, C_2—N_1 and C_4—C_5, C_6—N_1 bonds. Let us note that, as in the case of I, II, and IV, primarily even-electron fragments are formed in the fragmentation of derivative V.

Primarily hydrogen rearrangements occur in the fragmentation of piperidines in which substituents attached to the C_2 or C_6 atoms are absent. The maximum peak in the spectrum of VI corresponds to the $[M - CH_3 - H_2O]^+$ (o) or $[M - H - CH_3OH]^+$ ion with m/e 152. The peak of the $[M - COOCH_3]^+$ (p) ion with m/e 126 is the second most intense peak. It follows from an analysis of the mass spectrum that the o and p ions are not inclined to undergo further fragmentation and have stable structures. Their most probable formation is realized with the participation of one hydrogen atom from the 2 and 6 positions (Scheme 4).

Scheme 3



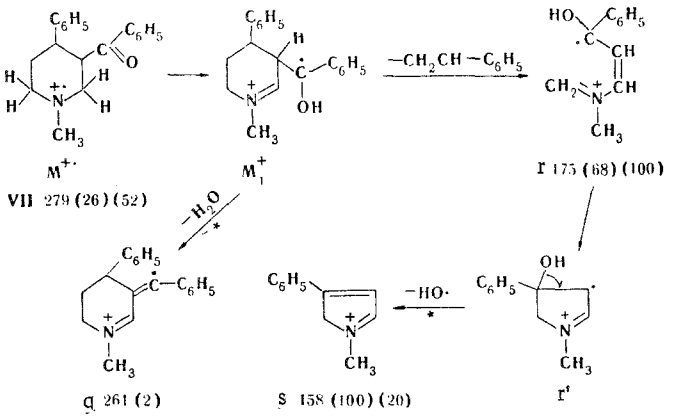
Scheme 4



In fact, the o and p fragments have cyclic structures with partially conjugated bonds that are stabilized by tautomeric forms; their fragmentation via a mechanism of the Diels–Alder retrocleavage type is therefore impossible.

The high lability of the hydrogen atoms in the 2 or 6 positions is manifested in the fragmentation of derivative VII. The splitting out of a phenylethylene molecule from the molecular ion with cleavage of the C_3–C_4 and C_5–C_6 bonds with the formation of odd-electron fragment r with m/e 175 can be explained only by isomerization of the molecular ion (M_1^+ with a quaternary nitrogen atom in the ring (Scheme 5).

Scheme 5



In this case Diels–Alder retrofragmentation is observed in the ion radical; this process is encountered extremely rarely for saturated six-membered nitrogen heterocycles. Nevertheless, this process is intensive in the fragmentation of M_1^+, since the radical center is outside the ring and does not affect synchronous cleavage of the C_3–C_4 and C_5–C_6 bonds. The peak of the r fragment is therefore the second most intense peak in the spectrum at an electron energy of 70 eV and is the maximum peak at low electron energies. Thus the odd-electron M_1^+ and r ions are essentially amine ions with respect to their behavior and the mechanisms of their formation. The splitting out of a water molecule from the M_1^+ ion, which is confirmed by the corresponding metastable transition, serves as a confirmation of the existence of the molecular ion in an isomerized form. Odd-electron fragment r is subsequently converted to ion s with m/e 158 by ejection of a hydroxyl radical.

Thus we have discovered previously unknown mechanisms for the formation and fragmentation of amine fragments, as well as specific hydrogen and skeletal rearrangements. We demonstrated that the sequence of cleavages of the heteroring bonds is determined by the character and position of the substituents in the ring.

EXPERIMENTAL

The investigated compounds I-VII were kindly supplied by E. S. Nikitskaya and B. V. Unkovskii. The synthesis of the compounds was described in [3, 4]. The mass spectra were investigated with an LKB-9000 mass spectrometer with direct introduction of the samples into the source. The ionizing voltages were 12 and 70 eV, the temperature of the ionization chamber was 250-290°C, and the emission current was 60 μA. The high-resolution mass spectrum was recorded with a JMS-01-SG-2 mass spectrometer.

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