MASS SPECTRA OF PIPERIDINES WITH A SHIELDED NITROGEN ATOM*

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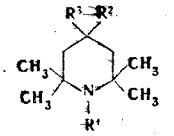
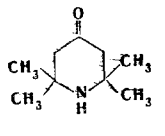
2,2,6,6-Tetramethylpiperidines with various substituents attached to the C_4 atom [R = H, OH, CN, CH_2COOH, C_6H_5, $N(CH_3)_2$, $N(COCH_3)CH_2C_6H_5$, $N(CH_2)_5$, and $N(CH_2CH_2)O$] were studied by means of mass spectrometry. The peculiarities of the fragmentation of the piperidine ring with a shielded electron pair at the heteroatom as a function of the type of substituent attached to the C_4 atom are discussed. The fragmentation was studied with the use of high-resolution mass spectrometry, low-voltage mass spectra, and deuterium labeling.

In the present communication we studied the behavior of piperidines I-XIII with a shielded nitrogen atom under electron impact.



I, II, IV–XIII



III

I R^1=H, R^2=R^3=H; II R^1=D, R^2=R^3=H; IV R^1=R^2=H, R^3=OH; V R^1=CH_3, R^2=H, R^3=OH; VI R^1=CH_3, R^2=H, R^3=CH_2COOH; VII R^1=H, R^2=CN, R^3=OH; VIII R^1=H, R^2=C_6H_5, R^3=OH; IX R^3=$N(CH_3)_2$; X R^3=$N(COCH_3)CH_2C_6H_5$; XI R^3=$N(CH_2)_4$; XII R^3=$N(CH_2)_5$; XIII R^3=$N(CH_2CH_2)_2O$; IX–XIII R^1=CH_3, R^2=H

In a continuation of our studies of the mass-spectral fragmentation of piperidines (see [2]) we will discuss the peculiarities of the fragmentation of a ring with a shielded electron pair of a heteroatom and various substituents attached to the C_4 atom.

The mass-spectral fragmentation of derivatives IV-XIII has not been previously studied. The mass spectra of I-III, which were presented in [3] as models and were examined from different points of view, were reinvestigated. The study of the fragmentation of I-XIII was carried out with the use of high-resolution mass spectrometry, the spectra at low ionizing-electron energies, and the metastable ions.

The fragmentation under electron impact of the molecular ions (M^+) of I and II and of the mono- and disubstituted analogs III-VIII (Table 1) is determined by the predominant localization of the charge on the nitrogen atom of the heteroring (Scheme 1).

The principal pathways of fragmentation of I-VIII entail α detachment of the substituent and α cleavage of the ring at the C_2–C_3 or C_5–C_6 bond, which leads to the formation of fragmentary cyclic ions a-c and rearranged fragment d. The maximally intense peak in the spectra at the ionizing-electron energy of 70 eV corresponds to amine fragment a ($[M-CH_3]^+$).

Thus the steric shielding of the unshared electron pair of the nitrogen atom and the substituents attached to the C_4 atom, which contain OH, CN, CH_2COOH, and C_6H_5 groups, do not suppress the characteristic pathway of fragmentation of the piperidine ring [2] in the case of I-VIII. It should be noted that the M_I^+ molecular ion with an open structure, which is an intermediate for the formation of fragment d, is also a typical amine ion radical. In the spectrum of the deutero analog of II the peak of ion d at 58 is shifted completely by one unit to the higher m/e side. The loss of isobutylene for unsubstituted I and II takes place

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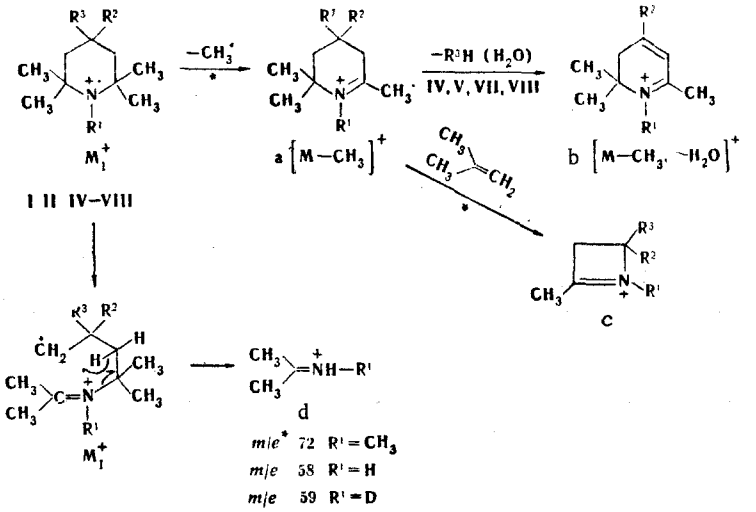
Scheme 1



*Here and subsequently in the test and in the schemes the numbers that characterize the ions are the mass-to-charge ratios.

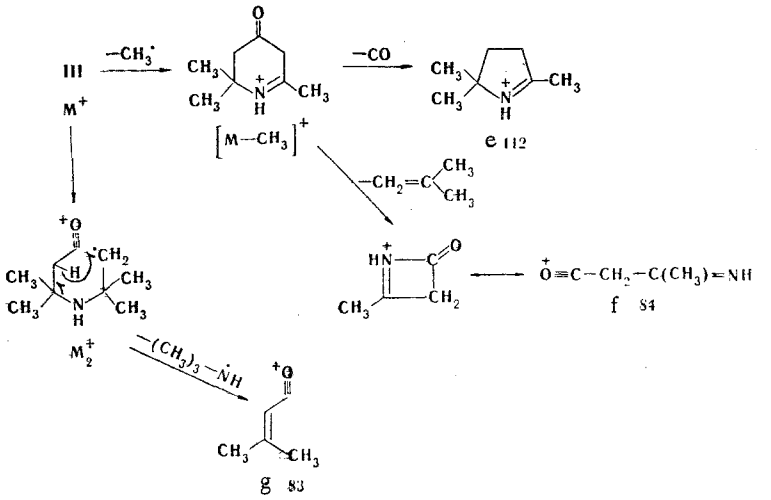
TABLE 1. Mass Spectra of I-X at Electron Energies of 70 (a) and 12 eV (b)

Compound	m/e values (relative intensities of the ion peaks in percent relative to the maximum)
I*a*	141 (2), 127 (30), 126 (100), 109 (8), 98 (4), 85 (2), 71 (8), 70 (43), 69 (40), 59 (38), 58 (63), 57 (5), 56 (6), 55 (3), 43 (6), 42 (8), 41 (14)
Ib	141 (2), 127 (40), 126 (100), 70 (2), 59 (6), 58 (5)
II*a*	142 (2), 128 (6), 127 (90), 126 (6), 109 (4), 98 (3), 71 (70), 70 (10), 69 (45), 59 (100), 58 (22), 56 (6), 55 (4), 43 (30), 42 (8), 41 (42)
IIb	142 (4), 127 (100), 126 (5), 71 (4), 59 (8)
III*a*	156 (4), 155 (20), 141 (21), 140 (100), 112 (15), 99 (8), 98 (38), 97 (4), 84 (50), 83 (100), 71 (6), 59 (15), 58 (92), 57 (15), 56 (23), 55 (34), 43 (28), 42 (68), 41 (17)
IIIb	156 (4), 155 (21), 141 (23), 140 (100), 112 (4), 98 (10), 84 (6), 83 (25), 71 (3), 58 (20), 42 (4)
IV*a*	157 (2), 142 (100), 124 (6), 107 (12), 106 (4), 98 (6), 86 (8), 85 (4), 79 (4), 78 (28), 77 (2), 58 (37)
V*a*	171 (12), 157 (12), 156 (100), 138 (8), 100 (16), 85 (8), 73 (3), 72 (56), 71 (4), 70 (4), 57 (6), 56 (34), 56 (6), 42 (6), 41 (12)
V*b*	171 (20), 157 (12), 156 (100), 138 (2), 100 (6), 72 (3)
VI*a*	213 (5), 199 (14), 198 (100), 196 (7), 142 (9), 139 (3), 127 (4), 109 (6), 85 (8), 72 (20), 56 (13), 55 (4)
VIb	213 (14), 199 (10), 198 (100), 196 (8), 142 (4)
VII*a*	182 (2), 168 (12), 167 (100), 155 (4), 149 (6), 141 (4), 140 (36), 112 (6), 111 (14), 110 (6), 99 (4), 98 (12), 84 (14), 85 (3), 71 (3), 70 (5), 58 (64), 57 (7), 56 (9), 55 (14), 43 (12), 42 (28), 41 (16)
VII*b*	182 (4), 168 (11), 167 (100), 141 (6), 140 (60), 98 (4), 85 (5), 58 (6)
VIII*a*	233 (0,4), 219 (22), 218 (100), 200 (21), 143 (4), 106 (4), 105 (72), 99 (14), 98 (56), 91 (6), 78 (5), 77 (16), 59 (4), 58 (43), 57 (4), 55 (3), 43 (4), 42 (17), 41 (6)
VIII*b*	233 (0,1), 219 (16), 218 (100), 200 (4), 105 (2), 99 (7), 98 (7), 58 (2)
IX*a*	199 (2), 198 (12), 183 (10), 138 (5), 127 (10), 126 (2), 113 (8), 112 (100), 85 (4), 73 (2), 72 (40), 71 (5), 70 (6), 57 (2), 56 (34), 55 (5), 42 (7), 41 (6)
IXb	199 (10), 198 (62), 184 (10), 183 (66), 138 (4), 128 (10), 127 (100), 113 (6), 112 (82), 85 (10), 72 (46)
X*a*	302 (7), 287 (5), 231 (5), 212 (3), 211 (22), 167 (6), 113 (7), 112 (100), 92 (4), 91 (48), 85 (7), 84 (4), 73 (3), 72 (74), 71 (4), 57 (3), 56 (42), 55 (7)
X*b*	303 (14), 302 (62), 278 (6), 287 (18), 271 (6), 232 (6), 231 (37), 212 (16), 211 (100), 113 (7), 112 (80), 73 (3), 72 (45)

both from M^+ and from the $[M-CH_3]^+$ ion, whereas for the III-VIII analogs the formation of ion c is due to fragmentation of only amine fragment a. As in the case of the previously investigated 4-hydroxypiperidines [2], fragmentation in the direction a → b is also typical for the IV, V, VII, and VIII derivatives.

We must note an interesting peculiarity that is manifested in the fact that in the spectra of I-VIII the relative intensities of the M^+ and $[M-CH_3]^+$ ion peaks, like the $[M]^+/[M-CH_3]^+$ intensity ratios, remain virtually constant or change only slightly over the range of ionizing-electron energies (12-70 eV). This fact contradicts the quasiequilibrium theory

Scheme 2



of mass spectra and can be explained by the existence of isolated electronic states of the molecular ion [4]. Ionization of the I-VIII molecules primarily at the nitrogen atom with surplus electron density probably promotes this.

In contrast to the I, II, and IV-VIII derivatives, the fragmentation of III has a number of peculiarities. Peaks of 112, 98, and 84 fragments, the analogs of which are absent in the spectra of the I, II, and IV-VIII derivatives, are observed in the spectrum. According to our data and the literature data [3, 5], the mechanisms of the formation of these ions can be represented by Scheme 2.

It follows from Scheme 2 that the fragmentation of III with the formation of fragments e, f, and g is explained by competitive distribution of charge in the M^+ and $[M-CH_3]^+$ ions between the nitrogen atom and the oxygen atom of the oxo group. Both hydrogen and skeletal rearrangements with cleavage of the C_5-C_6, N_1-C_2, and C_3-C_4 bonds are intensive processes in this case. The maximum peak in the specturm at 30 eV corresponds to a rearranged fragment of the oxonium type (g), which, in addition to the peak of the $[M-CH_3]^+$ amine fragment, retains an extremely high relative intensity when the ionizing-electron energy is lowered to 12 eV. The competitive distribution of the charge between the heteroatoms is in agreement with the fact that the ionization potential of III, which is 8.3 eV [4], is extremely high for an amine (≈7.4 eV), since this value is close to the ionization potential of oxygen-containing compounds. Consequently, ionization of the molecule at the oxygen and nitrogen atoms is unlikely.

One should expect that the competition in the distribution of the charge between the heteroatoms and, consequently, the rearrangement fragmentation processes should have even more pronounced character when substituents that contain ordinary amine nitrogen are introduced. In fact, the change in the relative intensities of the M^+ and $[M-CH_3]^+$ ion peaks in the spectra of IX-XIII when the ionizing-electron energy is varied from 70 to 12 eV does not follow the principles that are characteristic for the I-VIII derivatives. The peak of the $[M-CH_3]^+$ fragment in the spectra of IX-XIII may have a low intensity at both 70 and 12 eV (Fig. 1). Furthermore, regardless of the character of the amine nitrogen atom in the substituent attached to the C_4 atom, characteristic peaks of $[M-71]^+$, 112, and 72, the appearance of which can be explained only by rearrangement processes, are observed in the spectra

TABLE 2. Elementary Compositions of the Principal Ions of XI-XIII According to Data from High-Resolution Mass Spectra

XI, *m/e*	209	153	138	112	110	96	72
Ion compos.	$C_{13}H_{25}N_2$	$C_{10}H_{19}N$	$C_9H_{16}N$	$C_7H_{14}N$	$C_7H_{12}N$	$C_6H_{10}N$	$C_4H_{10}N$
XII, *m/e*	223	167	152	138	124	112	72
Ion compos.	$C_{14}H_{27}N_2$	$C_{11}H_{21}N$	$C_{10}H_{18}N$	$C_9H_{16}N$	$C_8H_{14}N$	$C_7H_{14}N$	$C_4H_{10}N$
XIII, *m/e*	225	169	154	138	126	112	72
Ion compos.	$C_{13}H_{25}N_2O$	$C_{10}H_{19}NO$	$C_9H_{16}NO$	$C_9H_{16}N$	$C_7H_{12}NO$	$\frac{C_6H_{10}NO}{C_7H_{14}N}$	$C_4H_{10}N$

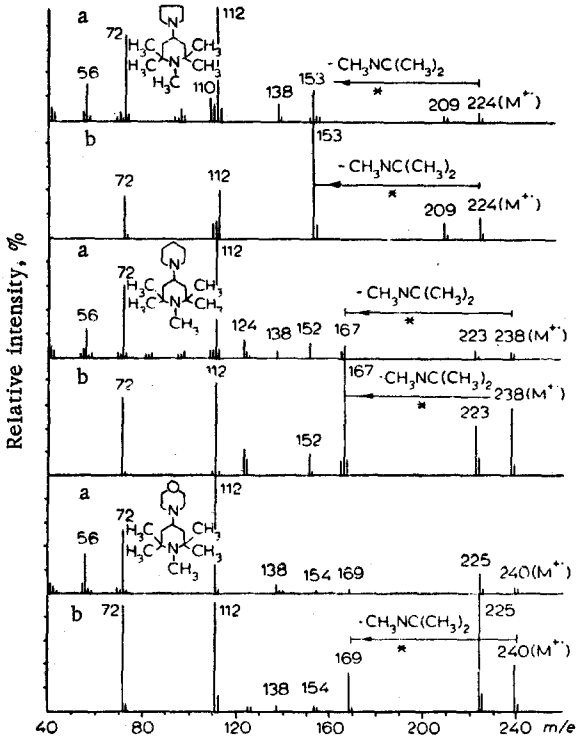
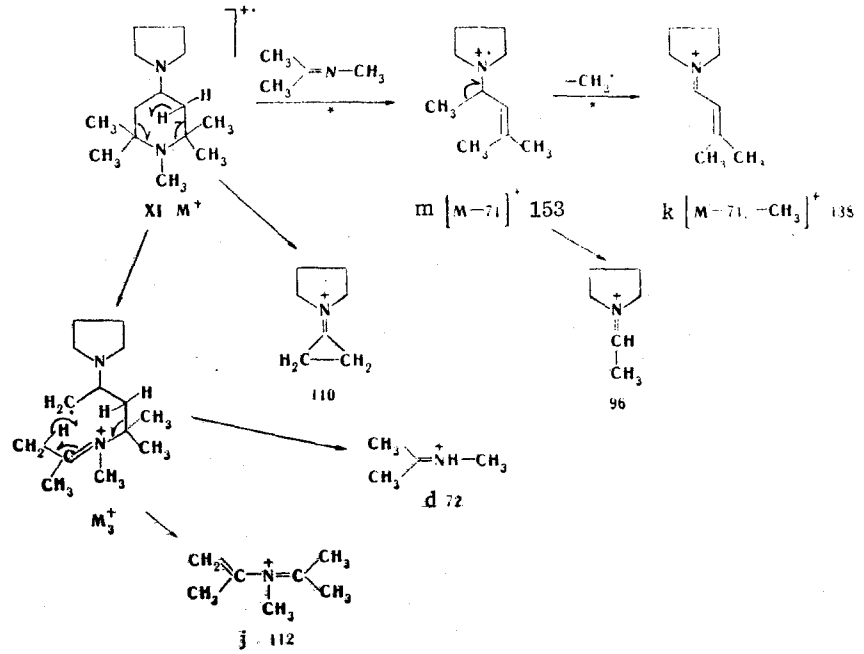


Fig. 1. Mass spectra of XI-XIII at electron energies of 70 (a) and 12 eV (b).

Scheme 3



of the IX-XIII analogs. According to the data from the high-resolution mass spectra, these fragments in all cases have identical elementary compositions (Table 2) and their formation, for example, for XI, with allowance for the observed metastable transitions, can be represented by Scheme 3.

It follows from Scheme 3 that in the fragmentation of the IX-XIII derivatives one observes the unusual (for α-substituted piperidines [2]) process $M^+ \rightarrow i$ with detachment of a neutral particle, which, according to the data from high-resolution spectroscopy (Table 2), contains nitrogen and corresponds to the $CH_3NC(CH_3)_2$ molecule. It follows from this that cleavage of the C_5—C_6 and N_1—C_2 bonds is realized in the molecular ion with splitting out of a fragment containing a piperidine nitrogen atom.

The molecular ion with an open structure explains both the appearance of fragment i, in which the charge is localized on the nitrogen atom of the substituent, and fragments d and j with the charge on the sterically hindered piperidine nitrogen atom. The $[M-CH_3NC(CH_3)_2]^+$(i) ion peak in the spectra at an ionizing-electron energy of 70 eV is usually of low intensity, but its relative intensity increases sharply (up to the maximum value) in the low-voltage mass spectra. It may be assumed that the probability of localization of the charge on the amine nitrogen atom of the substituent increases at low ionizing-electron energies.

The reason for this behavior is probably determined by the fact that two nitrogen atoms in IX-XIII are para-oriented to one another. The formation of M_3^+ as a result of α cleavage in the ionization of the molecule at the N_1 atom is therefore favorable for stabilization of the charge on the sterically hindered nitrogen atom. In the case of localization of the charge on the nitrogen atom of the substituent the process $M^+ \rightarrow$ i with cleavage of the C_5—C_6 bond should be regarded as β cleavage. In the case of fragmentation of branched aliphatic amines [5] β cleavage with respect to the charge localized on the nitrogen atom is accompanied by a hydrogen rearrangement.

It should be assumed that the pathways of fragmentation of IX-XIII via routes involving α and β cleavages that are accompanied by a hydrogen rearrangement are energically favorable, since extremely stable i, j, and k ions are formed. It is interesting to note that fragment j is an even-electron fragment, which is also probably responsible for the high intensity of the peak corresponding to it in the spectra at electron energies of 70 and 12 eV. The sharp increase in the peak of the odd-electron fragment i in the low-voltage spectrum is evidently determined by the rearrangement process $M^+ \rightarrow$ i, which should have a low activation energy or a low frequency factor [7].

The high-resolution mass spectra make it possible to interpret a number of other interesting mechanisms of fragmentation of XI-XIII, which have specific character as a function of the substituent attached to the C_4 atom. Such processes are presented in Scheme 3 for the XI analog.

Thus as a result of our study we have established the basic principles and mechanisms of the fragmentation of mono- and disubstituted (in the 4 position) piperidines with a shielded nitrogen atom. It was found that amine fragmentation of the piperidine ring is weakened when substituents that contain oxygen and nitrogen atoms are present. It was also shown that β cleavage with respect to the charge localized on the nitrogen atom of the substituent occurs along with β cleavage in the case of a sterically hindered ring with nitrogen-containing substituents in the 4 position.

The observed fragmentation principles can be used to establish the structures of nitrogen-containing saturated compounds.

EXPERIMENTAL

The investigated compounds III-XIII were synthesized, purified, and kindly placed at our disposal by E. S. Nikit-skaya and co-workers. The synthesis of the compounds was published in [8].

The mass spectra were investigaged with MKh-1303 and LKB-9000 mass spectrometers with direct introduction of the samples into the ion source. The ionizing voltages were 12, 14, 30, and 70 eV, the ionization chamber temperatures were 100-150°C (MKh-1303) and 250-290°C (LKB-9000), and the emission currents were 1.5 mA (MKh-1303) and 60 μA (LKB-9000). The high-resolution mass spectra were recorded with a JMS-0.1-SF-2 mass spectrometer.

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CONVERSION OF THE QUINOLINE RING TO AN INDOLE RING

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4-Nitro-3-hydroxyquinoline is readily converted to indole derivatives in aqueous alkaline and acetic acid media. The contraction of the quinoline ring to an indole ring under the conditions of mild methylation of 4-nitro-3-hydroxyquinoline in an aqueous alkaline medium proceeds through the formation of the N-methyl derivative of 4-nitro-3-hydroxyquinoline and N-methyl-2-formyl-3-nitroindole. 3-Nitroindole is formed when 4-nitro-3-hydroxyquinoline is heated in aqueous alkali, whereas isatin is formed in acetic acid. The methylation of 4-nitro-3-hydroxyquinoline in refluxing acetic acid leads to N-methylisatin.

We have previously reported that contraction of the pyridine ring to give N-methyl-3-nitroindole (II) in ∿60% yield occurs when 4-nitro-3-hydroxyquinoline (I) is treated with dimethyl sulfate in an aqueous alkaline medium [1].

The formation of indole II from quinoline I under the conditions presented above is a consequence of two chemical transformations: contraction of the pyridine ring and methylation. We were able to ascertain the interrelationship and sequence of the indicated processes. It was found that when dimethyl sulfate is absent, I remains unchanged in an aqueous alkali medium at room temperature, whereas the N-methyl-4-nitro-3-hydroxyquinolinium salt (III) forms indole II smoothly. This indicates the primacy of and the necessity for methylation in ring contraction under mild conditions.

In addition to II, a small amount of a substance that is insoluble in acidic media and was identified as N-methyl-4-nitro-1,2-(or 1,4-)dihydro-2,3-dihydroxyquinoline (IV) is formed both in the case of methylation of quinoline I in alkaline media and in the case of treatment of quaternary compound III with alkali. The carbon atom that is split out during ring contraction was detected in the volatile reaction products in the form of formic acid.

The ring contraction can evidently proceed via two pathways: either with the formation of a C_2—C_4 bond or an N_1—C_3 bond. In the first case the 2-formyl derivative (V) will be formed as an intermediate, while in the second case one might have expected the formation of a nitro derivative of oxindole. The first pathway seemed most likely to us, since it was easy to imagine the possible deformylation of the 2-formyl derivative under the reaction conditions to give II and sodium formate.

In fact, N-methyl-3-nitro-2-formylindole (V) and the known pseudobase IV were isolated when quinoline I was treated with dimethyl sulfate in an aqueous solution of sodium carbonate. Compound III behaves similarly in an aqueous solution of sodium acetate. As expected, V is readily deformylated in an aqueous alkali solution to give II.

Thus, the methylation of quinoline I in an alkaline medium proceeds through the formation of N-methyl derivative III, which undergoes structural conversion to formylindole V with the probable formation of a new C_2—C_4 bond.

Further studies showed that contraction of the quinoline ring may also occur without methylation but under more severe conditions. Thus, 3-nitroindole (IV) is formed in ∿55% yield when I is refluxed for a long time in a 2 N aqueous solution of sodium hydroxide.

We were able to observe ring contraction in media other than alkaline media. When quinoline I is methylated with dimethyl sulfate in acetic acid, N-methylisatin (VII) is formed in ∿7% yield along with a preponderant amount of III. Isatin VIII is formed in 33% yield when I is refluxed in glacial acetic acid. The lack of conformity with the preceding logical

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