11. V. P. Litvinov, V. K. Promonenkov, Yu. A. Sharanin, A. M. Shestopalov, L. A. Rodinovskaya, V. Yu. Mortikov, and V. S. Bogdanov, Izv. Akad. Nauk SSSR. Ser. Khim., No. 9, 2101 (1985).
12. B. Blank, N. W. Di Tullio, J. A. Krog, and J. H. Saunders, J. Med. Chem., 21, 489 (1978).
13. F. S. Babichev (ed.), Intramolecular Interaction of Nitrile and CH, OH, and SH Groups [in Russian], Naukova Dumka, Kiev (1985), p. 200.
14. V. I. Staninets and E. A. Shilov, Usp. Khim., 40, 491 (1971).
15. Yu. I. Gevaza and V. I. Staninets, Khim. Geterotsikl. Soedin., No. 4, 435 (1985).

MASS SPECTRA AND THREE-DIMENSIONAL STRUCTURES OF γ-N-ARYL(ALKYL)AMINOPIPERIDINES

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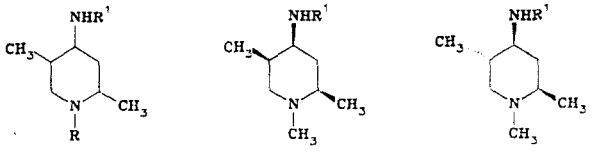
The fragmentation of the investigated compounds proceeds with both retention and cleavage of the piperidine ring and makes it possible to distinguish the spatial orientation of the methyl group in the $C_{(5)}$ position of the ring in the analysis of the geometrical isomers of this series.

Compounds with high specific physiological activity have been found among N-substituted γ-aminopiperidines. Some of them are used as medicinal preparations [1]. We have accomplished the mass-spectrometric analysis of I-XI, which were described in [2, 3]. Compounds I-VIII were studied in the form of mixtures of two geometrical isomers, while γ-aminopiperidines, cis-IX-cis-XI and trans-IX-trans-XI were the individual cis and trans isomers, the structures of which were previously established [4]. The 1,2e,5a-trimethyl-4e-arylaminopiperidines are the cis isomers, while the 1,2e-5e,-trimethyl-4e-arylaminopiperidines are the trans isomers.



I-VIII cis-IX-cis-XI trans-IX-trans-XI

I—VII R=CH_3, VIII R=$CH_2C_6H_5$; I R^1=CH_2CH_2OH, II R^1=$CH_2CH_2CH_2OH$, III R^1= =C_6H_{11}, IV R^1=$CH_2C_6H_5$, V R^1=$CH_2CH_2C_6H_5$, VI R^1=$C_6H_4OCH_3$-*o*, VII R^1=C_6H_4Br-*o*, VIII, IX R^1=C_6H_5, X R^1=$C_6H_4OCH_3$-*p*; XI R^1= α-pyridyl

It has been previously shown that the fragmentation of piperidine and its alkyl and acyl derivatives, as well as γ-piperidols, proceeds with localization of the positive charge primarily on the piperidine nitrogen atom [5-8]. The introduction of a carbonyl or amino group leads to the development of new pathways of dissociative ionization due to partial localization of the positive charge on these substituents [9-11]. Interest in a study of the effect of substituents attached to the endocyclic and exocyclic nitrogen atoms on the fragmentation of I-XI under the influence of electron impact and under chemical-ionization conditions was generated by these properties. It was also necessary to establish the possibilities of the mass-spectrometric method for determining the spatial orientation of the methyl group in the $C_{(5)}$ position of the cis-IX-cis-XI and trans-IX-trans-XI geometrical isomers. This problem cannot be solved in the 1,2,5-trimethyl-4-hydroxypiperidine series [8].

Molecular-ion peaks (M^+) of high and medium intensity are observed in the mass spectra of I-XI (Table 1). Their stabilities (W_M) (Table 2) are determined by the nature of substituent R^1 attached to the exocyclic nitrogen atom. In the case of the presence of an aromatic R^1 radical in the molecules of IV-XI the W_M value increases by a factor of two to seven as compared with the W_M values for I-V. According to the data from the mass spectra of I-XI,

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TABLE 1. Mass Spectra of Secondary γ-Aminopiperidines I-XI*

Compound	m/z (relative intensity, %)**
I	57 (40), 70 (72), 84 (28), 98 (23), 110 (100), 125 (81), 126 (32), 155 (17), 168 (10), 171 (10), 186 (M^+, 17)
I	*58 (11), 70 (28), 84 (11), 98 (8), 110 (45), 125 (42), 126 (20), 171 (5), 187 (100)*
II	57 (40), 58 (37), 70 (71), 84 (37), 98 (18), 110 (100), 125 (55), 126 (20), 169 (5), 185 (4), 200 (M^+, 11)
III	57 (40), 70 (64), 84 (37), 98 (26), 110 (100), 125 (60), 126 (25), 152 (14), 182 (7), 209 (6), 224 (M^+, 11)
III	*57 (14), 70 (25), 84 (16), 98 (13), 99 (5), 110 (68), 125 (80), 126 (20), 209 (4), 225 (100)*
IV	57 (40), 70 (60), 84 (26), 91 (100), 98 (20), 106 (20), 110 (54), 125 (30), 127 (28), 141 (37), 232 (M^+, 22)
IV	*70 (48), 84 (19), 91 (41), 98 (16), 110 (64), 112 (18), 125 (49), 127 (55), 141 (48), 218 (6), 233 (100)*
V	57 (32), 70 (49), 84 (34), 91 (23), 98 (25), 105 (13), 110 (66), 125 (68), 126 (42), 155 (100), 246 (M^+, 19)
VI	70 (90), 84 (23), 98 (21), 108 (36), 110 (81), 123 (43), 125 (63), 126 (35), 149 (27), 233 (10), 248 (M^+, 100)
VII	57 (57), 70 (100), 77 (13), 84 (32), 98 (19), 110 (67), 125 (45), 126 (32), **171 (9), 281 (5), 296 (M^+, 19)**
VIII	57 (23), 91 (100), 146 (37), 160 (12), 174 (11), 186 (21), 201 (15), 202 (36), 203 (11), 217 (24), 294 (M^+, 31)
cis-IX	58 (72), 70 (100), 84 (31), 110 (83), 119 (28), 125 (20), 126 (35), 133 (17), 146 (12), 203 (15), 218 (M^+, 73)
cis-IX	*84 (2), 98 (2), 110 (4), 125 (5), 126 (20), 203 (2), 218 (36), 219 (100), 261 (8), 275 (5)*
trans-IX	58 (37), 70 (100), 84 (24), 110 (70), 119 (9), 125 (48), 126 (20), 133 (13), 146 (9), 203 (10), 218 (M^+, 50)
trans-IX	*84 (2), 98 (1), 110 (6), 125 (35), 126 (14), 203 (1), 218 (36), 219 (100), 261 (8), 275 (4)*
cis-X	58 (49), 70 (100), 84 (34), 98 (23), 110 (97), 122 (23), 125 (20), 126 (44), 149 (29), 163 (23), 248 (M^+, 84)
trans-X	58 (30), 70 (100), 84 (22), 98 (7), 110 (60), 122 (10), 125 (31), 126 (15), 149 (20), 163 (9), 248 (M^+, 40)
cis-XI	57 (31), 70 (19), 72 (34), 84 (21), 110 (100), 120 (27), 125 (20), 126 (40), 134 (14), 147 (15), 219 (M^+, 40)
trans-XI	57 (25), 70 (15), 72 (24), 84 (24), 110 (100), 120 (19), 125 (35), 126 (19), 134 (10), 147 (10), 219 (M^+, 23)

*The molecular ion and the 10 most intense peaks are presented.
**The chemical-ionization spectra are denoted by italics; ammonia was the reactant gas for I, III, and IV, while isobutane was the reactant gas for cis-IX and trans-IX. The ions that contain the ^{79}Br isotope are denoted by boldface type.

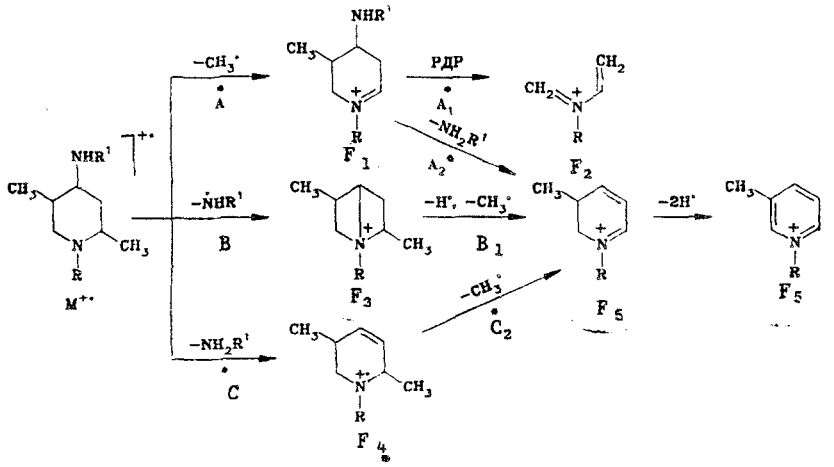
their fragmentation proceeds both from the cyclic form of the M^+ ion (Scheme 1) and from various open forms of ions $M_1^+ - M_4^+$ postulated in [6, 10, 12] (Scheme 2).

The molecular ions of I-XI readily lose an α-methyl radical with the formation of fragment F_1 (Scheme 1); this is characteristic for the fragmentation of all α-alkyl-substituted piperidines [6-12]. Pathway A_1 involves retrodiene cleavage of the ring [8, 12] and the appearance in the mass spectra of I-XI of fragment F_2, the peak of which is the maximum peak in the case of γ-aminopiperidines VII, IX, and X (Table 1). The indicated pathway is also realized in the fragmentation of 1,2,5-trimethyl-4-hydroxypiperidines [8] but is not characteristic for the dissociative ionization of $(M - CH_3)^+$ ions in series of γ-amino-substituted 2,2,6,6-tetramethylpiperidines [11].

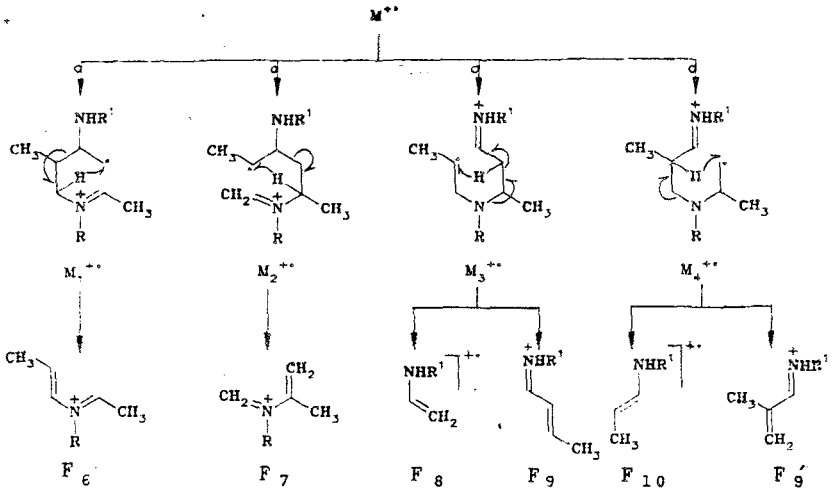
A second pathway of fragmentation of the F_1 ion (pathway A_2) is the formation of rearrangement fragment F_5 as a result of the elimination of a γ-amino radical and migration to it of a hydrogen atom from the piperidine ring [11]. The F_5 ion has the maximally intense peak in the mass spectra of I-III and XI. Its appearance is always accompanied by the development of aromatic fragment F_5' of low intensity (≤4%); this indirectly confirms retention of the cyclic structure in the F_1 and F_5 ions during their formation from molecular ion M^+.

In addition to the detachment of a methyl substituent from the M^+ ion, elimination of γ-amino radical NHR^1 with the formation of fragment F_3 (pathway B) and the appearance of rearrangement ion F_4, the development of which is due to migration of a hydrogen atom from the piperidine ring to the split-out amino substituent (pathway C), occur. Fragmentation pathways A, A_1, B, and C have structural-analytical value in that they make it possible to determine the nature of the radicals attached to the ring nitrogen atom and in the α position of the ring, as well as the character of substituent R^1 in the amino group.

Scheme 1



Scheme 2



The fragmentation of I-XI from the open forms of the molecular ions $M_1^+ - M_4^+$ is presented in Scheme 2. In addition to α elimination, cleavage of the $C_\alpha - C_\beta$ bond [6, 8], which in the case of the compounds under consideration leads to the development of M_1^+ and M_2^+ ions, is characteristic for the fragmentation of the piperidine derivatives. Their dissociative ionization is due to cleavage of the $C_{(4)}-C_{(5)}$ and $C_{(3)}-C_{(4)}$ bonds, respectively, and migration of a hydrogen atom to the radical center, which leads to the formation of characteristic F_6 and F_7 fragments. The fraction of the F_7 fragment is higher by a factor of 1.5-3 than that of the F_6 ion (Table 2); this is evidently due to primary migration of a tertiary hydrogen atom.

The presence of an amino group in the γ position leads to partial localization of positive charge on the exocyclic nitrogen atom [11], which is responsible for β cleavage of the bond relative to this atom. This sort of fragmentation is characteristic for cyclic amines [13]. Fragmentation of the M_3^+ and M_4^+ ions leads to the development of F_8-F_{10} fragments, the contribution of which to the total ion current increases when there is an aryl substituent attached to the nitrogen atom of the amino group. The genetic relationship of the ions presented in Schemes 1 and 2 is confirmed by metastable transitions and the shift of the corresponding fragments in the mass spectra of the deutero analogs of the investigated compounds.

Maximally intense peaks of protonated molecular ions $(M + H)^+$ are present in the mass spectra of I, III, IV, cis-IX, and trans-IX obtained under chemical-ionization conditions. Cluster ions $(M + C_4H_9)^+$ at 275* and $(M + C_3H_7)^+$ at 261 are formed in the fragmentation of geometrical isomers cis-IX and trans-IX (with isobutane as the reactant gas); the formation of

*Here and subsequently, the m/z values are presented.

TABLE 2. Intensities of the Peaks of the Characteristic Fragments in the Mass Spectra of I-XI in the Total Ion Current (Σ_{50})

Compound*	M	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9, F_9'	F_{10}
I	3,2	1,7	12,1	13,7	5,4	16,9	3,9	4,7	1,0	1,5	0,5
II	2,1	0,7	12,4	3,5	9,6	17,5	3,1	6,5	0,5	0,7	0,5
III	2,1	1,0	10,3	4,0	9,7	16,1	4,2	5,9	0,4	0,3	0,3
IV	3,8	1,5	8,7	2,8	4,4	7,9	2,9	3,8	1,5	1,2	1,4
V	3,4	1,5	7,5	6,5	10,5	10,2	3,8	5,2	0,4	0,9	0,6
VI	14,4	1,2	11,0	4,3	7,7	9,9	2,5	2,8	3,3	2,8	2,5
VII	6,4	1,5	14,7	4,7	6,6	9,8	2,8	4,7	1,2	0,8	0,8
VIII	6,8	1,6	4,4	6,4	2,7	3,7	1,9	2,1	1,7	2,2	1,6
cis-IX	9,0	1,6	10,8	3,8	2,1	8,9	1,2	3,3	3,0	1,3	1,8
trans-IX	7,7	1,3	13,3	2,7	6,4	9,3	1,2	3,2	1,2	1,2	1,7
cis-X	11,8	1,3	12,0	5,3	2,4	11,7	2,8	4,1	3,5	1,3	2,8
trans-X	7,2	1,1	15,3	2,3	4,8	9,2	1,1	3,4	3,1	1,2	1,4
cis-XI	7,7	1,2	3,2	6,7	3,3	16,7	1,7	3,5	4,5	2,5	2,3
trans-XI	5,1	0,8	2,9	3,6	6,7	19,2	1,3	4,6	3,6	1,9	1,9

*The following ion peaks are observed: $CH_2C_6H_5^+$ 91 (15.7%) for IV, $(M - CH_2C_6H_5)^+$ 155 (17.0%) for V, and $CH_2C_6H_5^+$ 91 (15.7%) for VIII.

TABLE 3. Ratios of the Intensities of the Peaks of the Characteristic Ions in the Electron-Impact Mass Spectra of the Geometrical Isomers of γ-Aminopiperidines IX-XI

Compound	$I_{(M-CH_3)^+}/I_{M^+}$	$I_{(M-NHR^1)^+}/I_{M^+}$	$I_{(M-NH_2R^1)^+}/I_{M^+}$	$I_{(M-NH_2R^1)^+}/I_{(M-CH_3)^+}$
cis-IX	0,20	0,43	0,26	1,29
trans-IX	0,20	0,31	0,89	4,33
cis-X	0,12	0,47	0,22	1,83
trans-X	0,12	0,28	0,72	5,67
cis-XI	0,17	0,91	0,48	2,75
trans-XI	0,17	0,69	1,46	8,44

the F_2 fragment, which has the maximum intensity in the electron-impact mass spectra, is not observed in this case. In the fragmentation of I, III, and IV (with ammonia as the reactant gas) the intensity of the rearrangement ions either decreases slightly or even increases as compared with the electron-impact mass spectra. Under chemical-ionization conditions F_8–F_{10} ions are not formed at all, and the intensity of the peaks of the F_6 and F_7 fragments depends on the reactant gas — it decreases sharply on passing from ammonia to isobutane (Table 1). Thus the fragmentation of the protonated molecular ions $(M + H)^+$ of piperidines I, III, IV, cis-IX, and trans-IX is due primarily to localization of the positive charge on the ring nitrogen atom.

The differences in the mass spectra of the stereoisomers of nitrogen-containing heterocycles are usually due to different probabilities of elimination of substituents with different spatial orientations in the ring [14, 15]. In the case of the cis-,trans-IX–cis-,trans-XI pairs of stereoisomers that we studied the $(M - CH_3)^+$ ion, according to the data in [6, 8, 12], is formed due to the ejection of a methyl group from the $C_{(2)}$ position rather than from the ring $C_{(5)}$ atom. Consequently, it is impossible to obtain information regarding the spatial orientation of the 5-CH_3 group on the basis of an analysis of the intensity of the $(M - CH_3)^+$ ion. This is confirmed by the identical $I_{(M-CH_3)}/I_{M^+}$ ratio for each pair of isomers (Table 3). However, its different orientation relative to the 4e-NHR^1 radical affects both the ease of splitting out of the radical and the formation of the $(M - NH_2R^1)^+$ rearrangement fragment. For the cis isomers the intensity of the peak of the $(M - NHR^1)^+$ ion at 126 is higher by a factor of two to three than in the mass spectra of the isomeric trans-IX–XI (Table 1). On the other hand, the intensity of the $(M - NH_2R^1)^+$ rearrangement fragment at 125 is higher by a factor of two to three in the mass spectra of the trans isomers. The noted peculiarity is readily explained if it is assumed that the hydrogen atoms that are cis-oriented to the split-out fragment migrate to it with the highest probability. In this case the presence of two such hydrogen atoms in the trans isomers rather than one, as in the fragmentation

of the cis isomers, leads to an increase in the intensity of the $(M - NH_2R^1)^+$ fragment. These differences, which are presented in Table 3, make it possible to readily distinguish one isomer from the other from the ratio of the intensities of the peaks of the characteristic ions.

The exposed principles of the fragmentation of secondary γ-aminopiperidines I-XI can be used for the reliable determination of the nature of the substituents and their position in the piperidine ring and in the γ-amino group. Stereoisomers with different orientations of the CH_3 group in the $C_{(5)}$ position of the ring can also be readily distinguished by means of them.

EXPERIMENTAL

The electron-impact and chemical-ionization mass spectra of I-XI were obtained with an LKB-2091 mass spectrometer (the ionizing-electron energy was 70 eV, the emission current was 50 μA, and the temperature of the ionization chamber was 250°C). Compounds I-XI were synthesized by the method in [2, 3]. The purity and individuality of the stereoisomers were monitored by TLC and IR, PMR, and mass spectrometry. The metastable ions and the mass spectra of the deutero analogs were obtained with an MKh-1303 spectrometer with a system for direct introduction of the samples into the ion source under conditions of deuterium exchange of vapors of the investigated compounds with CD_3OD vapors directly in the ionization chamber of the spectrometer at an ionizing voltage of 70 V and inlet temperatures of 50-80°C.

LITERATURE CITED

1. R. S. Vartanyan, Khim.-farm. Zh., No. 5, 540 (1983).
2. V. V. Kuznetsov, L. A. Gaivoronskaya, A. A. Fomichev, R. M. Romero, and N. S. Prostakov, Khim. Geterotsikl. Soedin., No. 7, 949 (1987).
3. V. V. Kuznetsov, E. E. Stashenko, L. A. Gaivoronskaya, and N. S. Prostakov, Patrice Lumumba International-Friendship University, Manuscript Deposited in the All-Union Institute of Scientific and Technical Information 29.05.86, No. 714-khp.
4. N. S. Prostakov, A. A. Fomichev, L. A. Gaivoronskaya, N. M. Golovtsov, and S. K. Das, Khim. Geterotsikl. Soedin., No. 11, 1512 (1982).
5. L. W. Daasch, J. Phys. Chem., 69, 3196 (1965).
6. A. M. Duffield, H. Budzikiewicz, D. H. Williams, and C. Djerassi, J. Am. Chem. Soc., 87, 810 (1965).
7. A. Morrison and A. P. Davies, Org. Mass Spectrom., 3, 353 (1970).
8. A. I. Ermakov, Yu. N. Sheinker, Zh. K. Torosyan, and V. A. Zamureenko, Khim. Geterotsikl. Soedin., No. 12, 1647 (1975).
9. A. I. Ermakov, Zh. K. Torosyan, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 4, 507 (1979).
10. A. I. Ermakov and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 1, 65 (1981).
11. A. I. Ermakov and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 1, 72 (1981).
12. P. B. Terent'ev, Mass Spectrometry in Organic Chemistry [in Russian], Vysshaya Shkola, Moscow (1979), p. 76.
13. N. S. Vul'fson, V. G. Zaikin, and A. I. Mikaya, Mass Spectrometry of Organic Compounds [in Russian], Khimiya, Moscow (1986), p. 130.
14. V. G. Zaikin and N. S. Vul'fson, Khim. Geterotsikl. Soedin., No. 11, 1443 (1978).
15. A. Mandelbaum, Mass Spectrom. Rev., 2, 223 (1983).