MASS SPECTRA AND PECULIARITIES OF THE FRAGMENTATION OF SOME SUBSTITUTED PIPERIDINES*

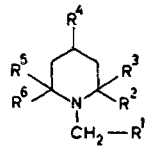
A. I. Ermakov and Yu. N. Sheinker

UDC 547.822.3:543.51

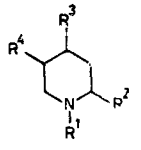
N-Substituted piperidines with R = CH_2OCH_3, $(CH_2)_4COCH_3$, $CH_2COOC_2H_5$, $(CH_2)_2N(CH_3)_2$, $(CH_2)_2N(C_2H_5)_2$, N=O, CH_3, H, $COOC_2H_5$, and OH were investigated by mass spectrometry. The ratios of the intensities of the peaks and the behavior of the amine fragments with exocyclic double bonds attached to the quaternary nitrogen atom that are formed from the molecular ion by detachment of a radical from the C_2 atom and from the substituent attached to the nitrogen atom were studied. It is shown that the ratios of the intensities of the peaks of the amine fragments are determined both by the type of substituent and the energy of the ionizing electrons.

The available data [2, 3] on the stabilities with respect to electron impact of piperidine derivatives were obtained on the basis of a study of the mass spectra of their simplest alkyl and acyl derivatives. Investigations of this type have not been carried out for most other functionally substituted piperidines. A quantitative evaluation of the contribution to the total ion current of the characteristic amine fragments with the original cyclic structure and of the ions formed with cleavage of the bonds in the heteroring [1] seems of interest for the study of the stability with respect to electron impact of a piperidine ring with various substituents. Such mass-spectrometric characteristics of substituted piperidines have not been previously investigated.

The aim of the present research was to study the stabilities with respect to electron impact of piperidine derivatives I-VIII and to obtain quantitative changes in the ratios of the intensities of the peaks of the characteristic fragments as a function of the properties of the substituents, their position in the ring, and the energy of the ionizing electrons.



I–IV



V–VIII

I $R^1=OCH_3$, R^2-R^6=H; II $R^1=(CH_2)_3COCH_3$, R^2-R^6=H; III $R^1=CH_2COOC_2H_5$, $R^2=R^3=R^5=R^6=H$, $R^4=COOC_2H_5$; IV $R^1=COOC_2H_5$, $R^2=R^3=R^5=R^6=CH_3$, $R^4=COOC_2H_5$; V $R^1=R^4=H$, $R^2=CH_3$, $R^3=COOC_2H_5$; VI $R^1=NO$, $R^2=CH_3$, $R^3=COOC_2H_5$, $R^4=H$; VII $R^1=CH_2CH_2N(CH_3)_2$, $R^2=R^4=CH_3$, $R^3=OH$; VIII $R^1=CH_2CH_2N(C_2H_5)_2$, $R^2=R^4=CH_3$, $R^3=OH$

Ethyl N-methylpiperidine-2-carboxylate (IX) and unsubstituted piperidine (X), the mass spectra of which have been published [4, 5], were used as model compounds in the study of the fragmentation of derivatives I-VIII.

The maximum peaks in the spectra of derivatives I-IV at ionizing-electron energies of 70 and 12 eV correspond to $[M-R^1]^+$ ions; the $[M-CH_3]^+$ ion peak is also very intense in the

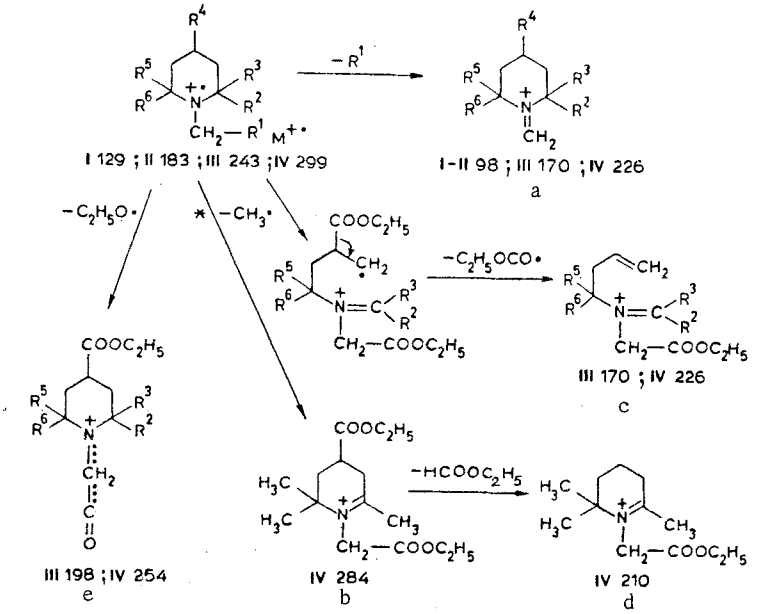
*Communication 11 from the series "Application of mass spectrometry in structural and stereochemical studies." See [1] for Communication 10.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 221-228, February, 1981. Original article submitted December 18, 1979; revision submitted July 28, 1980.

 0009-3122/81/1702-0160$07.50

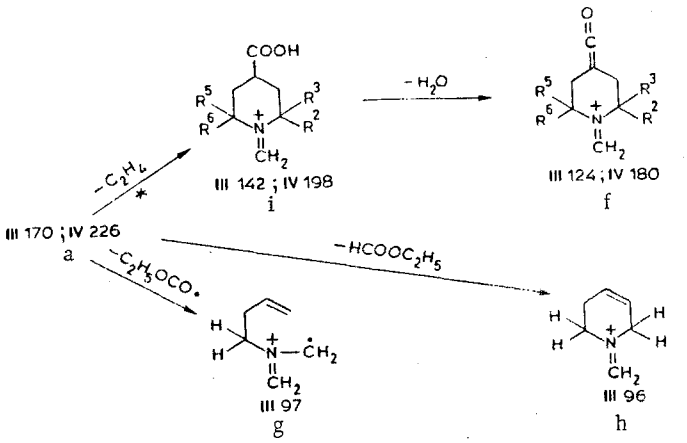
spectrum of IV. High stability is typical for amine fragments formed by splitting out of substituents from the α position relative to the ion-radical center. Cyclic structures a and b with endo- and exocyclic double bonds should be assigned to the $[M-R^1]^+$ and $[M-CH_3]^+$ ions formed in the fragmentation of I-IV (Scheme 1).

Scheme 1



The subsequent fragmentation of ion a for III-IV takes place with the formation of fragments f, g, h, and i (Scheme 2):

Scheme 2



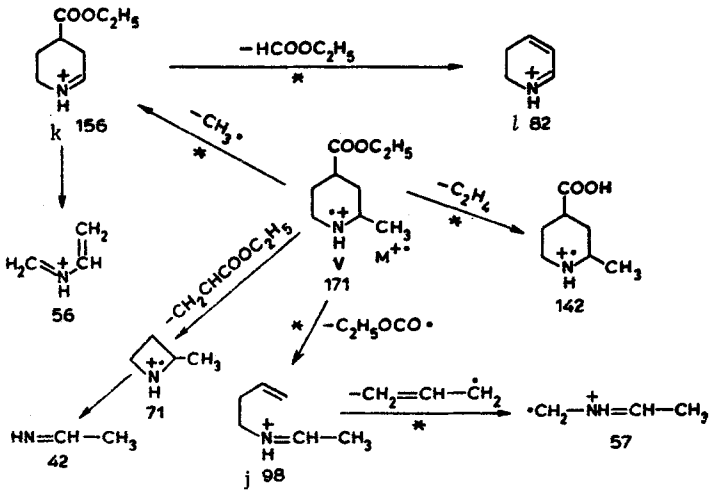
The elimination of the ester group attached to the C_4 atom that is observed in the mass spectrum of V† and confirmed by the corresponding metastable peak (Scheme 3) indicates that, in addition to the formation of a ($[M-COOC_2H_5]^+$, 170 and 226) ions, c ions with the same m/e values but with an open structure should be formed in the case of III and IV (Scheme 1).

It is interesting to note that in the fragmentation of derivative VI the ester group is split out from the $[M-NO]^+$ ion only in the form of a neutral ethyl formate molecule by capture of a hydrogen atom from the 4 position (Scheme 4).

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

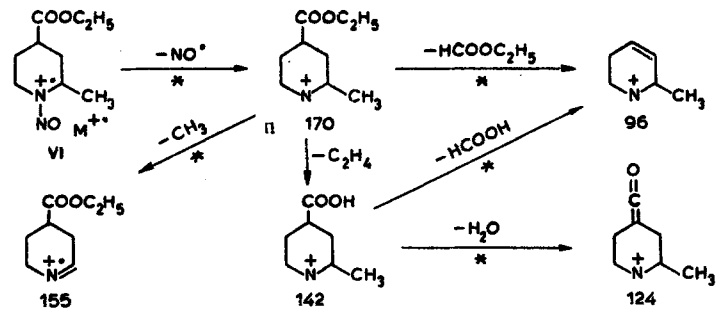
†Compounds V and VI are mixtures of two epimers with respect to the C_2 atom. In [1] it is shown that the intensities of the characteristic ions in the spectra of such compounds are virtually independent of the orientation of the substituent in the 2 position.

Scheme 3



The fragmentation of VI is of interest, since the peculiarities of the fragmentation of N-nitroso-substituted amines have not been previously investigated, except for [6], in which the mass spectra of nitrosomethoxymethylamine, nitrosodimethylamine, and N-nitrosoazetidine are presented. As in the case of derivative VI, the $[M-NO]^+$ ion peak in the spectra of such compounds is characteristic, and its intensity increases as the ionizing voltage is lowered to 12 eV. This is particularly characteristic when the splitting out of a nitroso group is a rearrangement process, as, for example, in the fragmentation of nitrosomethoxymethylamine

Scheme 4



[6]. It follows from Scheme 4 that the peculiarities in the fragmentation of VI as compared with the fragmentation of derivatives I-V can be explained by the primary formation of ion n ($[M-NO]^+$, 170). Processes involving detachment of ester or methyl radicals from even-numbered fragment n are energetically unfavorable, and the $[M-NO-COOC_2H_5]^+$ ion peak is therefore not observed in the spectrum of VI, while the $[M-NO-CH_3]^+$ ion peak has a very low intensity. The fragmentation of I-VI presented in Schemes 1-4 is in agreement with the fragmentation of similar esters in series of saturated and aromatic amines [4, 5].

Let us introduce the following parameters for the quantitative characterization of the processes involved in the fragmentation of I-VI: W_M is the stability of a molecule with respect to electron impact,* I_O is the overall intensity of the peaks of the fragments formed as a result of opening of the piperidine ring, and I_C is the overall intensity of the peaks of the ions in which the heteroring is retained. The W_M, I_O and I_C parameters, as well as the relative intensities of the peaks of the characteristic ions in percent of the total ion current, are presented in Table 2. The same parameters were calculated for model analogs IX and X.

Fragments with cyclic structures, the peaks of which are characterized by high intensities, are presented in Schemes 1-4. The peaks of fragments that have mass numbers below m/e 80, as well as of the ions with open structures presented in Schemes 1-4, enter into the overall intensity of the peaks of ions formed by ring cleavage.

*$W_M = I_M^+/\Sigma_{40}$, where I_M is the intensity of the molecular-ion peak (including the monoisotopic ion), and Σ_{40} is the total ion current.

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

Compound	m/e values (relative intensities of the ion peaks in % relative to the maximum peak)
I	a) 129 (12), 128 (17), 99 (10), 98 (100), 97 (5), 96 (7), 85 (2), 84 (5), 83 (1), 82 (3), 70 (3), 69 (6), 68 (3), 57 (3), 56 (6), 55 (15), 45 (42), 44 (6), 43 (6), 42 (19), 41 (15)
I	b) 130 (1,5), 129 (33), 128 (8), 99 (13), 98 (100), 97 (25), 85 (2), 84 (2), 82 (2), 45 (1,5).
II	a) 183 (10), 182 (10), 138 (6), 124 (6), 110 (3), 99 (8), 98 (100), 97 (3), 96 (3), 86 (16), 85 (26), 84 (32), 60 (3), 59 (3), 58 (2), 57 (4), 56 (5), 55 (14), 45(6), 44 (6), 43 (18), 42 (10), 41 (14)
II	b) 184 (16), 183 (100), 182 (3), 98 (22), 86 (22), 85 (40), 84 (6)
III	a) 244 (3), 243 (22), 242 (2), 199 (6), 198 (48), 172 (6), 171 (56), 170 (100); 156 (7), 143 (3), 142 (22), 124 (22), 99 (22), 98 (5), 97 (5), 96 (12), 95 (5), 83 (4), 82 (8), 81 (4), 70 (4), 69 (8), 68 (3), 59 (3), 57 (6), 56 (4), 55 (10), 44 (6), 43 (3), 42 (10), 41 (5).
III	b) 244 (8), 243 (42), 171 (12), 170 (100), 154 (4).
IV	a) 300 (3), 299 (10), 285 (17), 284 (100), 270 (2), 254 (10), 227 (16), 226 (88), 224 (10), 210 (5), 199 (5), 198 (26), 197 (5), 196 (22), 124 (5), 123 (14), 122 (3), 99 (5), 98 (8), 71 (3), 70 (8), 59 (8), 58 (8), 57 (6), 45 (3), 44 (5), 43 (6), 42 (3), 41 (3).
IV	b) 300 (16), 299 (97), 285 (22), 284 (100), 254 (3), 227 (8), 226 (52), 244 (8), 199 (3), 198 (30), 196 (28)
V	a) 172 (4), 171 (16), 170 (6), 157 (12), 156 (100), 143 (6), 142 (34), 129 (2), 128 (4), 127 (5), 126 (5), 100 (5), 99 (6), 98 (70), 97 (6), 96 (20), 84 (7), 83 (15), 82 (90), 81 (30), 72 (5), 71 (46), 70 (78), 69 (16), 58 (6), 57 (40), 56 (36), 55 (16), 43 (14), 42 (20), 41 (5)
V	b) 172 (20), 171 (100), 157 (10), 156 (82), 143 (10), 142 (22), 98 (20), 82 (6), 70 (36), 57 (20)
VI	a) 200 (8), 170 (40), 156 (5), 155 (12), 143 (2), 142 (18), 128 (4), 127 (5), 126 (3), 109 (3), 98 (6), 97 (18), 96 (100), 95 (4), 83 (6), 82 (40), 81 (6), 81 (6),71 (10), 70 (10), 69 (24), 68 (6), 67 (5), 57 (12), 56 (38), 55 (22), 54 (5), 45(6),44 (6), 43 (12), 42 (16), 41 (16)
VI	b) 201 (3), 200 (24), 171 (20), 170 (100), 156 (6), 155 (10), 142 (8), 127 (2), 98 (5), 97 (4), 96 (28), 82 (5), 69 (6), 56 (4)
VII	a) 200 (0,5), 143 (12), 142 (100), 124 (2), 98 (3), 72 (8), 71 (3), 70 (6), 58 (36), 57 (2), 56 (5), 43 (16), 42 (6), 41 (12).
VII	b) 200 (1), 143 (12), 142 (100), 58 (10)
VIII	a) 228 (1,2), 143 (10), 142 (100), 87 (4), 86 (64), 70 (5), 58 (6), 57 (2), 43 (4), 42 (6),41(4).
VIII	b) 228 (3,8), 143 (10), 142 (100), 86 (30)

TABLE 2. W_M, I_o, and I_c Parameters* and Intensities of the Peaks of the Characteristic Fragments from the Data from the Spectra of I-X

Cpd.	W_M		I_o		I_c		I_a		I_b		$I_{[M-COOC_2H_5]^+}$	
	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV
I	4,2	18	36	16	35	53	33	53	—	—	—	—
II	3,2	47	30	10	64	42	32	10	—	—	—	—
III	5,0	25	33	2	59	72	23	60	—	—	23	60
IV	2,2	26	25	—	55	73	19	14	22	27	19	14
V	2,2	31	68	62	31	37	—	—	14	31	9	6
VI	1,7	11	54	8	44	80	—	—	—	—	—	—
IX	4,5	6	41	2	54	91	—	—	—	—	45	79
X	11	16	68	43	32	10	—	—	21	—	—	—

*The intensity of the M^+ peak does not enter into either the I_c or I_o parameter.

The following conclusions can be drawn from the data presented in Table 1. As compared with piperidine X and its alkyl derivatives [2], the stabilities with respect to electron impact of derivatives I-VI are considerably lower. The principal contribution to the overall current of I-IV is due to the overall intensity of the peaks of ions with cyclic structures; the I_c parameters for II-IV are more than twice the I_o parameters. The I_c parameters for I, III, and IV-VI increase at a low ionizing voltage, while the overall intensity of the

peaks of ions formed with cleavage of the ring bonds decreases markedly. In the case of V the I_o parameters are high at ionization energies of 70 and 12 eV.

It follows from Table 2 that the principal contribution to the I_c parameters is due to ions a and b. The intensity of the peak of the $[M-H]^+$ amine fragment (of the b type) with a cyclic structure* in the spectrum of piperidine does not exceed 21% of the total ion current. The overall intensity of the peaks of ions formed with cleavage of the bonds of the unsubstituted heteroring is higher by a factor of more than three. When the ionizing voltage is reduced to 12 eV, the intensity of this peak is sharply reduced in the spectrum of piperidine. On the other hand, the intensity of the peak of the analogous $[M-COOC_2H_5]^+$ amine fragment in the spectrum of analog IX is approximately half the total ion current at an ionizing electron energy of 70 eV and increases to 79% at a low ionizing voltage. It should be noted that the detachment of a bulky substituent from the α position with respect to the charge on the nitrogen atom suppresses the mechanisms of formation of ions with cleavage of the ring bonds even at a high ionizing voltage, and in contrast to the spectrum of unsubstituted piperidine, the spectra of I-IV and IX therefore do not contain intense peaks of nitrogen-containing fragments with m/e 41, 42, 43, and 56.

Similar principles are characteristic for the formation of amine fragment a with an exocyclic double bond attached to the nitrogen atom. In the spectra of I, III, and IV the peak of this fragment also retains its maximum intensity even when the ionizing voltage is lowered to 10 eV. In the fragmentation of derivative II the $M^+ \rightarrow$ a process is suppressed by competitive hydrogen rearrangements with the participation of hydrogen atoms from the hydrocarbon side chain. The fact that the I_c parameter for this compound is somewhat lower at an electron energy of 12 eV than at the high ionizing voltage can probably be explained by this.

The principles of the behavior of the I_c parameter and the relative intensities of the peaks of ions a and b as a function of the electron energy that were found in this research are at present difficult to explain unambiguously. It should evidently be assumed that the increase in the I_c, I_a, and I_b values† as the ionizing voltage is decreased is a diagnostic sign of the formation of cyclic amine fragments with detachment of substituents from the α position relative to the ion-radical center.

In the fragmentation of IV fragments a and b are formed directly from the molecular ion, and it therefore seems of interest to trace the change in the relative intensities of the peaks of these fragments as a function of the ionizing electron energy. In the mass spectrum at an electron energy of 70 eV the ratio of the intensities of the peaks of ions a and b corresponds to $I_b/I_a = 1.1$. When the electron energy is lowered to 12 eV, this ratio increases to favor fragment b with an endocyclic double bond ($I_b/I_a = 1.9$). One should evidently assume that in the fragmentation of IV the formation of an exocyclic double bond at the sterically shielded nitrogen atom is impaired because of steric hindrance. In the mass spectrum of derivative IV the intensity of the peak of ion a expressed in percent of the maximum peak or of the total ion current is lower than in the case of I and III (Tables 1 and 2).

In the mass spectrum of V the intensity of the peak of ion j ($[M-COOC_2H_5]^+$, 98, Scheme 3), which has an open structure, does not exceed 9% at the high ionizing voltage and 6% at the low ionizing voltage (Table 2). For this compound the I_o parameter at ionizing electron energies of 70 and 12 eV remains virtually constant and very high. Hence, it may be assumed that detachment of the ester group from the 4 position promotes fragmentation of V with cleavage of the heteroring bonds and with the primary formation of ions with low mass numbers (71, 70, 57, 56, 55, 43, and 42). It should be noted that the contribution to the total ion content of the $[M-COOC_2H_5]^+$ ion is insignificant as compared with the overall intensity of the peaks of fragments with low mass numbers.

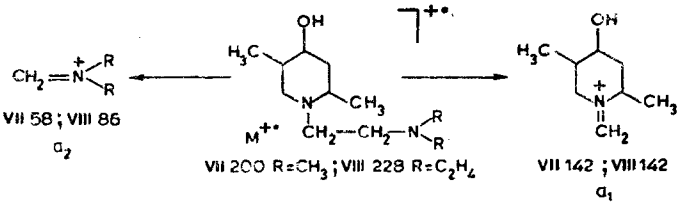
Starting from the assumption that detachment of the ester group from the 4 position in the case of III-V takes place via a single mechanism and by comparing the relative intensities of the peaks of the $[M-COOC_2H_5]^+$ ions in the spectra of derivatives III-V, we arrived at the conclusion that at both high and low ionization energies the principal contribution to the intensities of the peaks of the ions with m/e 170 and 226 (III and IV) is due to

*Detachment of a hydrogen atom exclusively from the α position of the piperidine ring with the formation of an ion with this structure was proved in [7].
†The I_a and I_b values are the relative intensities of the corresponding ions.

amine fragment a (Scheme 1). It may be assumed that in the fragmentation of these compounds the formation of ions with ring opening is suppressed by $M^+ \rightarrow a$ or $M^+ \rightarrow b$ processes, which probably have lower activation energies than the $M^+ \rightarrow c$ or $M^+ \rightarrow j$ reaction (Schemes 1 and 3).

From this point of view, VII and VIII, in the fragmentation of which an ion of the a type and amine fragment a_2, which is known to be energetically favorable, are formed by cleavage of the same carbon–carbon bond, are of interest (Scheme 5).

Scheme 5



The peak of fragment a_2 in the spectra of all of the aliphatic amines is the principal peak at high and low ionizing voltages [8]. However, the maximum peak in the spectra of VII and VIII at electron energies of 70 and 12 eV corresponds to fragment a_1; the ratios of the intensities of the peaks of ions a_1 and a_2 [I_{a_1}/I_{a_2} = 3.0 (70 eV) and 1.6 (12 eV) for VII and, respectively, 10.0 (70 eV) and 3.0 (12 eV) for analog VII] constitute evidence for the formation of fragment a_1. Thus in the fragmentation of VII and VIII localization of the charge on the nitrogen atom in the ring is more likely on the aliphatic substituent than on the nitrogen atom. Localization of the charge primarily on two nitrogen atoms that are symmetrically situated relative to the C–C bond also explains the fact that one virtually does not observe the formation of fragment ions other than a_1 and a_2 in the fragmentation of VII and VIII. It is known [9] that, according to Stevenson's rule, in bond cleavage in an ion the charge is retained primarily in the particle with the lower ionization potential (IP). The IP for the $(CH_3)_2NCH_2$ radical (6.8 eV [10]) is the lowest value of those observed for all of the nitrogen-containing radicals and neutral molecules for which this parameter has been measured [11]. Hence, it may be assumed that the primary formation of a cyclic amine fragment of the a_1 type in the fragmentation of I-III, VII, and VIII is due to the even lower IP (<6.8 eV) of the corresponding radical.

Thus, as a result of this research, we have studied the stabilities of piperidine derivatives with respect to electron impact as a function of the type of substituent and its position in the ring. The peculiarities of the behavior of amine fragments with various structures and their contribution to the total ion current as a function of the ionizing electron energy and the character and position of the substituents were demonstrated.

EXPERIMENTAL

Compounds I-VIII were synthesized and kindly placed at our disposal by R. G. Kostyanovskii (I), V. G. Plekhanov (II), and L. N. Yakhontov, E. S. Nikit-skaya, and co-workers (III-VIII). The mass spectra were investigated with MKh-1303 and LKB-9000 mass spectrometers with direct introduction of the samples into the ion source; the ionizing voltages were 12 and 70 eV, the temperatures of the ionization chamber 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).

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MASS-SPECTROMETRIC STUDY OF 3,9-DIAZABICYCLO- AND 3,9-OXAAZABICYLO[3.3.1]NONANES*

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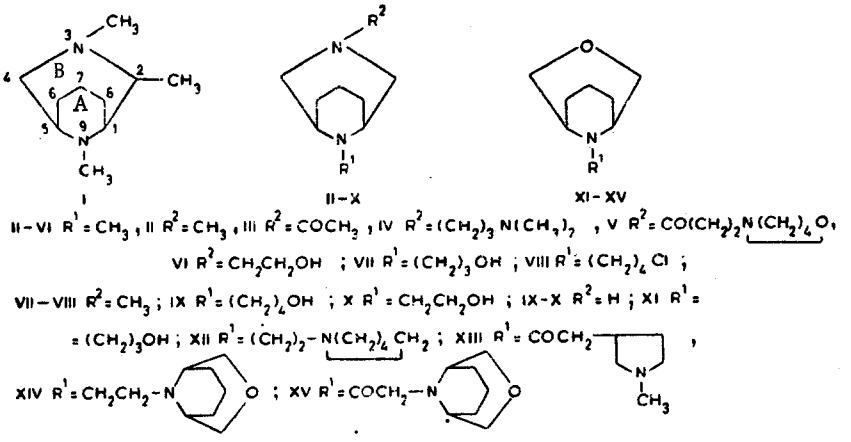
UDC 547.834.3'867:543.51

The mass spectra of substituted 3,9-diazabicyclo- and 3,9-oxaazabicyclo[3.3.1]-nonanes were studied as a function of competitive distribution of the charge between the N_3 and N_9 and O_3 and N_9 atoms and the properties of the substituents attached to the heteroatoms. It is shown that a characteristic peculiarity of the fragmentation of 3,9-diazabicyclo[3.3.1]nonanes is fragmentation of the molecular ion with an open structure that is formed by cleavage of the C_1—C_2 bond. The formation of an amine fragment with retention of the bicyclic structure with an exocyclic double bond attached to the quaternary N_9 atom is characteristic for 3,9-oxaazabicyclo[3.3.1]nonanes. It is shown that this sort of behavior of the investigated compounds is determined by their structures and the properties of the heteroatoms in the saturated bicyclic systems.

In a continuation of our research on the mass-spectrometric fragmentation of saturated bicyclic amines [2] we have studied the mass spectra of 3,9-diazabicyclo[3.3.1] nonanes I-X and 3,9-oxaazabicyclo[3.3.1]nonanes XI-XV.



According to the results of chemical investigations [3] and data from the PMR spectra [4], the piperazine ring in I-X exists primarily in the chair conformation. We expected that both heteroatoms in derivatives I-X and their oxygen analogs XI-XV would have a specific effect on the character of the fragmentation of the bicyclic system as a function of the competitive distribution of the charge between them and on the properties of the substituents attached to these atoms. The present research was therefore undertaken to study the fragmentation of I-XV under electron impact.

*Communication 12 from the series "Application of mass spectrometry in structural and stereochemical studies." See [1] for Communication 11.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 229-235, February, 1981. Original article submitted January 3, 1980.

 0009-3122/81/1702-0166$07.50