MASS SPECTRA AND THREE-DIMENSIONAL STRUCTURE OF 4-HYDROXYPIPERIDINE DERIVATIVES*

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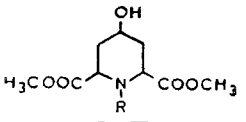
The mass spectra of stereoisomeric derivatives of 4-hydroxypiperidines obtained at various ionizing-electron energies with the application of isotopic substitution and high-resolution mass spectrometry are examined. The character of the fragmentation of the piperidine ring as a function of the position and spatial orientation of the substituent is discussed.

The available data on the fragmentation of piperidines are limited and pertain mainly to alkyl derivatives (for example, see [2-4]). In a study of the fragmentation of an N-acylpiperidine it was found [5] that the observed 80% detachment of a CH_3 group from the molecular ions is associated with ring cleavage. A comparison of the mass spectra of 1-, 2-, 3-, and 4-methylpiperidines and other analogs [2-6] shows that the intensity of fragmentation processes with ring cleavage depends on the mutual orientation of the ring nitrogen atom and the substituent.

A systematic study of the mass spectrometric fragmentation of piperidine derivatives from this point of view has not been made. In addition, there has been no research devoted to the study of the effect of the spatial orientation of the substituents on the character of cleavage of the piperidine ring. Studies of this type have been made only in the perhydroquinolol series (for example, see [7, 8]). In the present communication we have studied the fragmentation of functional derivatives of 4-hydroxypiperidine as a function of the position and orientation of the substituents with the application of low-energy electrons, the spectra of the deutero analogs, and high-resolution mass spectrometry.

We first studied the stereoisomers of 2,6-dicarbomethoxy-4-hydroxypiperidines (I-III) and of their N-CH_3 analogs (IV-VII). The spatial orientation of the substituents in these compounds presented below was determined from the PMR spectra [9, 10].



I – VII

I—III R=H; IV—VII R=CH_3; substituent orientation: I 2*e*, 4*e*, 6*e*; II 2*e*, 4*a*, 6*e*; III 2*a*, 4*a*, 6*e*; IV 2*e*, 4*a*, 6*e*; V 2*e*, 4*e*-OD, 6*e*; VI 2*e*, 4*a*, 6*e*; VII 2*a*, 4*a*, 6*e*

According to the PMR data, the isomers of I-VII are conformationally homogeneous and do not undergo conversion. The mass spectra of piperidines IV-VII are presented in Fig. 1. The principles of the fragmentation of IV, VI, and VII are adhered to completely in the case of their analogs (I-III), in the spectra of which the peaks of the characteristic fragments are shifted by 14 m/e units to the lower-mass side with respect to the corresponding ions of piperidines IV, VI, and VII.

We examined the fragmentation of the investigated compounds in comparison with the fragmentation of some α-alkylpiperidines as the closest model analogs of I-VII. The relative intensities of the $M^{+\cdot}$ peaks of

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TABLE 1. Composition of Some Ions from High-Resolution Mass-Spectrometry Data

I—III	m/e 217	158	140	126	82	80
Ion composition	$C_9H_{15}NO_5$	$C_7H_{12}NO_3$	$C_7H_{10}NO_2$	$C_6H_8NO_2$	C_4H_4NO	C_6H_8N
IV—VII	m/e 231	172	154	140	96	94
Ion composition	$C_{10}H_{17}NO_5$	$C_8H_{14}NO_3$	$C_8H_{12}NO_2$	$C_7H_{10}NO_2$	C_6H_6NO	C_6H_8N

TABLE 2. Relative Intensities of the Ion Peaks at m/e 140 and 154

Spectrometer	Relative intensity, %*			
	m/e 140(I)	m/e 154(IV)	m/e 140(II)	m/e 154(VI)
MKh-1303 (30 eV)	75	66	28	30
LKB-9000 (70 eV)	70	70	30	20
JMS-01-SG-2 (75 eV)	70	80	30	20

*The relative intensities are the average values of the results of three measurements.

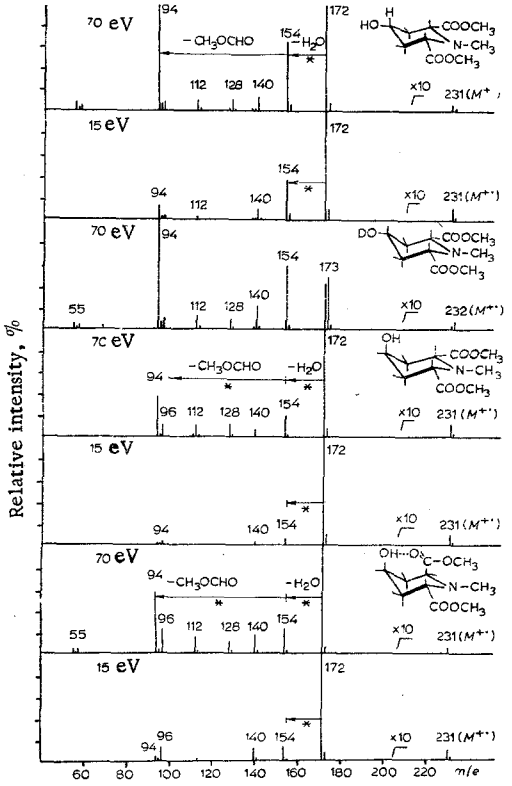


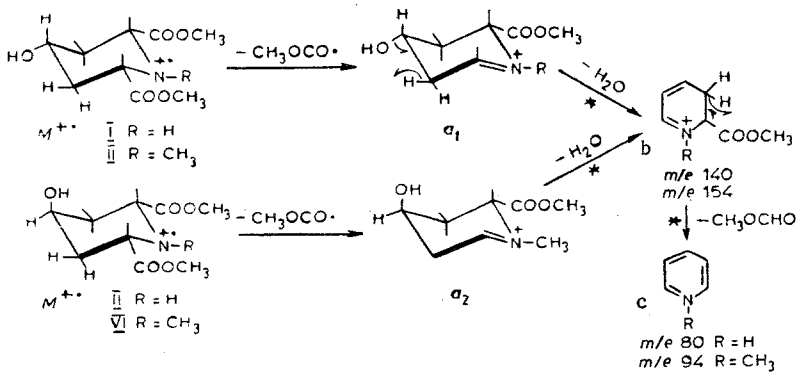
Fig. 1. Mass spectra of IV-VII.

I-VII are extremely low (< 1%). The lowest stability with respect to electron impact among the alkyl piperidines is observed for 1,2,6-trimethylpiperidine (the relative intensity of the $M^{+\cdot}$ peak is ~6%). As in the case of all α-alkylpiperidines [2, 3, 6], the first step in the fragmentation of I-VII is detachment of the substituent from the 2 or 6 position. The peaks of $(M-COOCH_3)^+$ amine fragments with m/e 158 (I-III) and m/e 172 (IV, VI, and VII) in the spectra of 70 eV (Fig. 1) have the maximum intensities. The primary $(M-CH_3)^+$ ion in the case of 1,2,6-trimethylpiperidine [3] undergoes subsequent fragmentation with ring opening and elimination of a C_2H_4 molecule. The presence of a hydroxyl group in the 4 position of I-VII radically changes the direction of fragmentation of the amine fragment. According to data from the high-resolution mass spectra (Table 1), the spectrum of deutero analog V (Fig. 1), and the observed metastable transitions, the ions with m/e 140 (I-III) and m/e 154 (IV-VII) (Fig. 1) are formed from the $(M-COOCH_3)^+$ amine fragment by splitting out of H_2O molecules.

The relative intensities of the ion peaks at m/e 140 and m/e 154 (Fig. 1) differ in the spectra of each of the isomers and their magnitude depends only slightly on the type of spectrometer and the experimental conditions. The relative intensities of the dehydration fragments with m/e 140 and 154 for epimers I, II and IV, VI are presented in Table 2. The difference in the three-dimensional structures of I and II and of IV and VI consists only in the orientation of the hydroxyl group.

The ratio of the peaks at m/e 140 (I, II) and 154 (IV, VI) (Table 2) remains practically constant at an ionization chamber temperature of 125-300° and as the ionizing voltage varies from 30 to 100 eV. It follows from Table 2 that the intensities of the peaks at m/e 140 and 154 in the spectra of I and IV with an equatorial orientation of the OH group is higher by a factor of more than two than the intensity of the peak of the analogous ion in the case of epimers II and VI with an axial hydroxyl group. This ratio will be observed only if the precursors of the dehydration fragments in the fragmentation of I, II and IV, VI have the same configuration as the I, II and IV, VI molecules prior to ionization. In other words, ring cleavage and ring conversion should be excluded in the fragmentation of the epimers. Thus the fragmentation of piperidines I, II and IV, VI can be represented by the scheme

Scheme 1

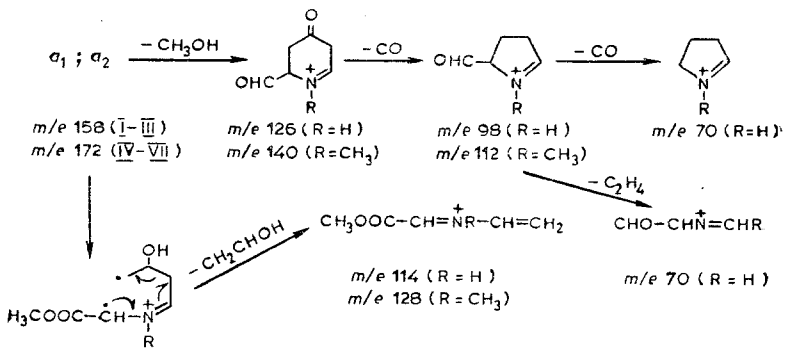


These conditions can be satisfied for α-substituted piperidines, for which intense amine stabilization with ring retention is characteristic. In fact, the α substituent is split out for $t \ll 10^{-6}$ sec, while ring conversion, if it does occur during excitation by electron impact, is a considerably slower process. In this case one should take into account the fact that the double bond at the nitrogen atom, which rigidly fixes the skeleton of the fragment, hinders ring conversion in the amine fragment. Under these conditions, greater effectiveness of the interaction of the OH group and H atoms (in the 3 or 5 positions) can be assumed for process $a_1 - H_2O$ (scheme 1) as compared with $a_2 - H_2O$. It should be noted that the detachment of H_2O characteristic for I-VII is characterized by a low intensity in the case of α-substituted perhydro-4-quinolols [7, 8].

In the light of the above statements, the identical character of the mass spectra of some epimers of quinuclidine (for example, see [11]) and bicyclo[3.3.1]nonanols [12] is explained by the fact that stereospecificity is lost in the first step of the fragmentation of these compounds as a result of the formation of an open molecular ion.

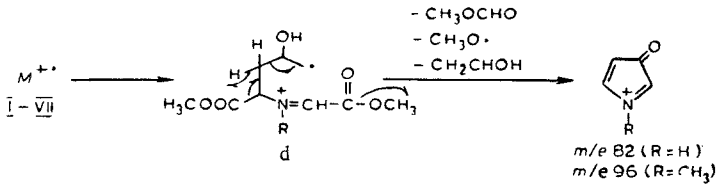
The energically favorable formation of cyclic aromatic fragment c should evidently be considered to be the driving force for subsequent fragmentation of ions a_1 and a_2. The formation of fragments with m/e 126, 114, 98, and 82 (I-III) and 140, 128, 112, and 96 (IV-VII), the peaks of which are characterized by low intensities, can, in conformity with data from high-resolution mass spectrometry, be represented by scheme 2:

Scheme 2



Fragments with m/e 82 and 96 are formed from the open form of the molecular ion as a result of specific rearrangement:

Scheme 3



In the case of an axial orientation of one of the ester groups (III and VII) only a small increase in the intensities of the peaks with m/e 82 and 96 is observed in the spectra as compared with the same peaks in the

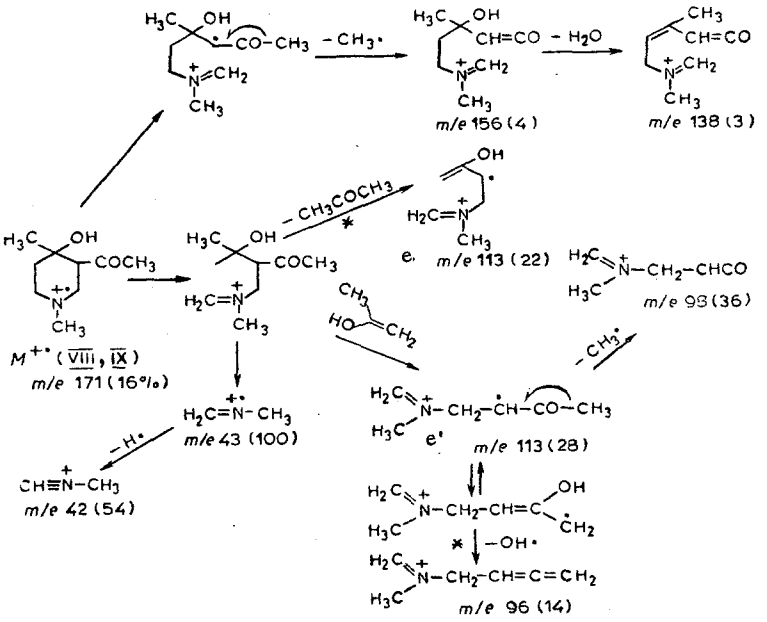
spectra of piperidines I, II, IV, and VI. The relative intensities of the peaks of fragments with m/e 140 and 154 in the spectra of III and VII and, respectively, II and V are practically identical. Thus a change in the orientation of the ester group and the development of a hydrogen bond in III and VII (Fig. 1) do not affect the dehydration process in the fragmentation of the investigated epimers. In a study of the stereochemistry of 1,2-dimethylperhydro-4-quinolols it was shown [7] that the $(M-CH_3)/M$ value depends on the orientation of the $2\text{-}CH_3$ group. Reliable values of parameters of this sort cannot be obtained for piperidines I-VII, inasmuch as the intensity of the $M^{+\cdot}$ peak in the spectra of the epimers is practically at the level of the background.

Open molecular ion d (scheme 3) is by nature a typical amine fragment, and α cleavage of the piperidine ring is therefore just as typical as detachment of the α substituent. However, I-VII constitute exceptions to this rule. A distinguishing feature of 2- and 6-substituted 4-hydroxypiperidines shows up in the fact that opening of the molecular ions during their fragmentation is competitively suppressed by the formation of aromatic fragments. From an examination of the fragmentation of piperidines I-VII one should assume that the hydroxyl group in the 4 position of α-substituted piperidines promotes fragmentation with ring retention.

When an α-substituent is absent, the fragmentation of the piperidine derivatives is realized primarily with α cleavage of the ring. For example, this sort of process is characteristic for 1,3-dimethylpiperidine [3].

We studied the peculiarities of the fragmentation of 3-substituted 4-hydroxypiperidines in the case of epimers of 1,4-dimethyl-3-acetyl-4-hydroxypiperidines [VIII (mp 126°) and IX (mp 84°)]. Identical mass spectra are observed for these epimers,* and this can be explained only by fragmentation of the open molecular ion:

Scheme 4



The fragmentation of VIII and IX is confirmed by the spectrum of the deutero analog of X with respect to the hydroxyl group. The structure of the ion with m/e 113 (e, e') follows from the distribution of the deuterium label during the fragmentation of X, in the spectrum of which the peak at m/e 113 is only partially shifted by one mass unit to the higher-mass side. The fragment with m/e 96 does not contain a deuterium label, and its formation is confirmed by metastable ions.

Thus it does not seem possible to distinguish the epimers in the 4-hydroxypiperidine series by means of the mass spectra when there is no α substituent.

Inasmuch as splitting out of the α substituent stabilizes the ring, whereas, on the other hand, a substituent in the 3 or 5 position promotes fragmentation of the open form of the molecular ion, competition between these processes should be expected in the fragmentation of 2- and 3- (or 5-)substituted piperidines. We studied the mass spectra of the stereoisomers of 1,2,5-trimethyl-4-hydroxypiperidines (XI-XIX), the orientation of the substituents in which is presented below:

*If the mass spectrum is not presented in Fig. 1, the relative intensity at 70 eV is indicated in parentheses after the mass number of the fragment in the fragmentation schemes.

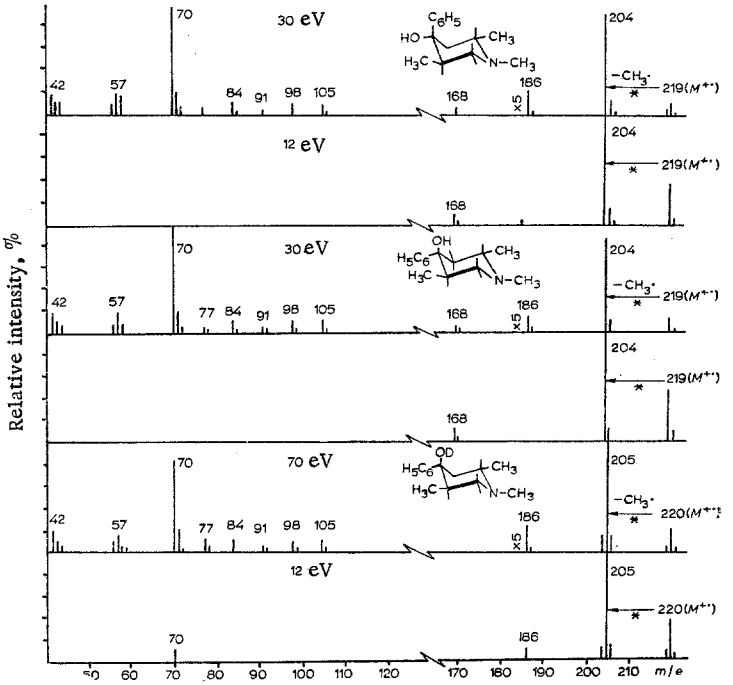
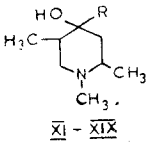


Fig. 2. Mass spectra of XIV-XIX.

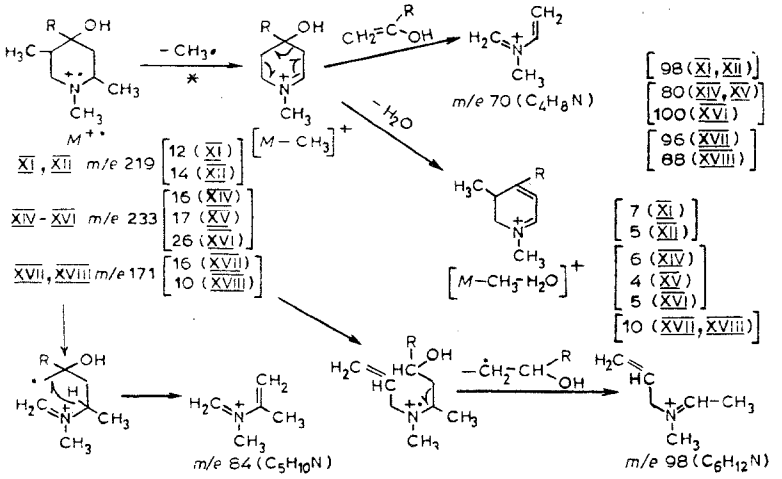


XI - XIX

XI—XIII R=C_6H_5; XIV—XVI R=$C_6H_4CH_3$-*m*; XVII—XIX* R=C_2H_5; substituent orientation
XI 2*e*, 4*e*-OH, 5*e*; XII 2*e*, 4*a*-OH, 5*e*; XIII 2*e*, 4*a*-OD, 5*e*; XIV 2*e*, 4*e*-OH, 5*e*;
XV 2*a*, 4*a*-OH, 5*e*; XVI 2*e*, 4*a*-OH, 5*e*; XVII 4*a*-OH; XVIII 4*e*-OH; XIX 4*e*-OD

The configuration of XI-XIX was determined from the IR and NMR spectra in [13, 14]. The fragmentations of piperidines XI-XIX adhere to identical principles and are characterized by the formation of common ions. The principal peaks in the spectra of XI-XVI (Fig. 2) and, similarly, XIV-XIX at 70 eV correspond to $(M-CH_3)^+$ amine fragments and ions with m/e 70. The low mass number of the fragment with m/e 70 constitutes evidence that it is formed by ring cleavage. In conformity with the high-resolution mass spectrum of XIV and the spectra of the deutero analogs of XVI and XIX, the general scheme of the fragmentation of piperidines XI-XIX can be represented as follows:

Scheme 5



* The orientation of the 2-CH_3 group was not determined in [14].

Fragments $(M-CH_3)^+$ and $(M-CH_3-H_2O)^+$ with m/e 98, 84, and 70 (scheme 5) are characteristic for XI-XIX. These ions do not contain a deuterium label in the case of the fragmentation of the deutero analogs of XVI-XIX.

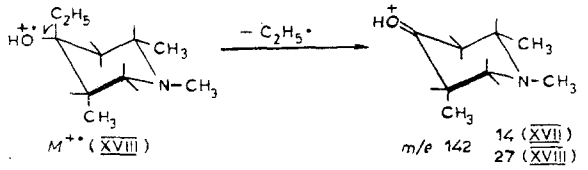
In contrast to piperidines I-VII, the peak of the $(M-CH_3-H_2O)^+$ dehydration fragment is very small in the spectra of XI-XIX. This fragmentation capacity is due to the fact that the $(M-CH_3)^+$ amine fragment in the case of XI-XIX undergoes intensive fragmentation via a synchronous mechanism with ring cleavage and formation of an ion with m/e 70. A similar but less intensive process is observed for the $(M-CH_3)^+$ ion in the case of 1,2,6-trimethylpiperidine [3]. The peaks of the amine fragment and the ion with m/e 70 are the most intense peaks in the spectra of XI-XIX at 70 eV. However, the intensive character of the process involving ring cleavage decreases sharply when the ionizing voltage is reduced to 15 eV, while the $(M-CH_3)^+$ ion peak remains the principal peak in the spectrum.

Thus, as we assumed, splitting out of a H_2O molecule from $(M-CH_3)^+$ in compounds of the XI-XVIII type is competitively suppressed by synchronous ring cleavage in the amine fragment.

The low intensity of the $(M-CH_3-H_2O)^+$ peak is an obstacle to the mass-spectrometric determination of the orientation of the hydroxyl group in piperidine derivatives similar to XI-XVIII. However, despite this, the $I_1 = (M-CH_3-H_2O)/M$ ratio in the spectra of XI and XIV is higher than for isomers XII-XVI with an axial orientation of the OH group ($I_1 = 0.92$ for XI, $I_1 = 0.3$ for XII).

Fragments corresponding to detachment of phenyl and m-tolyl substituents from $M^{+\cdot}$ are absent in the fragmentation of XI-XVI. In contrast to piperidines XI-XVI, the peaks of $(M-C_2H_5)^+$ fragments are extremely high in the spectra of XVII-XIX, and detachment of a radical is realized more intensively in the case of axial orientation of the ethyl group. It should be assumed that the charge is localized on the oxygen atom in this case:

Scheme 6



In the case of epimers XVII and XVIII the $I_2 = (M-C_2H_5)/M$ ratio may be a criterion for the determination of the orientation of the substituent in the 4 position. As has been established for the stereomers of perhydro-4-quinolols, which are similar to XVII and XVIII, a large R_2 ratio corresponds to an axial orientation of the ethyl substituent. A similar principle is also observed for the epimers of 1,3,5-trimethyl-4-ethyl-4-hydroxypiperidines ($I_2 = 0.37$ for XVII, and $I_2 = 2.62$ for XVIII). It should be noted that the application of a parameter of the I_2 type is not possible for compounds with substituents of the C_6H_5, $C_6H_4CH_3$, $C\equiv CH$, $C\equiv N$, and $C=CH_2$ types in the 4 position, inasmuch as elimination of these particles as radicals is observed extremely rarely.

The orientation of the hydroxyl group in epimers XVII and XVIII can be determined from the $(M-CH_3-H_2O)/M$ ratio, inasmuch as the I_1 ratio for isomer XVIII with an equatorial OH group is somewhat higher than for the compound with an axially oriented hydroxyl group ($I_1 = 0.82$ and $I_1 = 0.67$).

Thus the orientation of the substituents in the 4 position in XVII and XVIII can be determined both from the OH groups and from the C_2H_5 groups. The mass-spectrometric data on the configuration of the 4 center are in agreement with the results in [13].

Inasmuch as the fragmentation of α-substituted piperidines is realized with primary formation of a cyclic amine fragment, this process should depend on the spatial orientation of the substituent in the 2 position. According to the principles set forth in [7] for 2-methylperhydro-4-quinolols, an axial orientation of the methyl group corresponds to a higher value of the $I_3 = (M-CH_3)/M$ ratio. This tendency is also retained in the fragmentation of epimers of 4-hydroxypiperidine (XIV-XIX) (Fig. 2), in the spectra of which $I_3 = 4.54$ (XIV) and $I_3 = 4.16$ (XVI), whereas $I_3 = 6.25$ (XV) for an axial orientation.

On the basis of measurements of the I_3 parameter for epimers XVII and XVIII and the data in [14], one should evidently assume that the $2\text{-}CH_3$ group for XVII is oriented equatorially ($I_3 = 5.87$), whereas it is axially oriented in the case of XVIII ($I_3 = 9.11$).

A study of the peculiarities of the fragmentation of piperidines I-XIX shows that the orientation of the substituents in the 3 or 5 position of the piperidine ring is not determined by mass spectrometry.

Thus as a result of the present study we established the mechanisms of fragmentation of various epimers of 4-hydroxypiperidines. On the basis of our results, we propose a mass spectrometric method for the determination of the orientation of the substituents in the 2 and 4 positions. The method is applicable only when a minimum of two epimers is available for each of the compounds.

EXPERIMENTAL

The investigated compounds were synthesized and graciously placed at our disposal by E. S. Nikit-skaya and co-workers (I-VII), N. S. Prostakov and co-workers (XI-XVI), and B. V. Unkovskii and co-workers (VIII, IX, and XVII-XIX), for which we extend our thanks. The synthesis of the investigated compounds was published in [9, 13, 14]. The mass spectra were investigated with MKh-1303 and LKB-9000 spectrometers with direct introduction of the samples into the ion source. The ionizing voltages were 12, 15, 30, and 70 eV, and the ionization chamber temperatures were 100-250° (MKh-1303) and 250-290° (LKB-9000). The emission currents were 1.5 mA (MKh-1303) and 60 mA (LKB-9000). The high-resolution mass spectra were recorded with a JMS-0.1-SG-2 spectrometer.

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