MASS SPECTRA OF SOME 3-SUBSTITUTED BENZO[b]QUINUCLIDINES

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The mass spectra of 3-methoxycarbonyl-, 3-ethoxycarbonyl-, 3-(2-dimethylaminoethoxy)-carbonyl-, 3-amino-, 3-hydroxymethyl-, 3-chloro-3-methoxycarbonyl-, 3-chloro-3-ethoxycarbonyl-, and 3-chloro-3-cyano-substituted benzo[b]quinuclidines were investigated. The fragmentation of these compounds under electron impact through the open form of the molecular ion is discussed.

In [1,2] it was established that the fragmentation of substituted β-quinuclidines, 3-acyloxyquinuclidines, and their benzo analogs proceeds through the open form of the molecular ion. In the present communication we examine the mass spectra of some 3-substituted benzoquinuclidines, the disintegration of which follows the principles that are general for such compounds. It was demonstrated that the fragmentation of the investigated compounds is also realized through the open form of the molecular ion, which is formed primarily during cleavage of the bridge bond containing a substituent.

The mass spectra of 3-methoxycarbonyl- and 3-ethoxycarbonylbenzo[b]quinuclidines (I and II) (Fig. 1) are first of all characterized by intense peaks (70% of the maximum) of molecular ions $M^{+\cdot}$ with m/e 217 and 231. The cleavage of the bond between the carbon atom in the 3 position and the substituent, which leads to formation in both cases of the same fragment with m/e 158 (m* = 115 for I, m* = 108 for II), is most clearly expressed in the fragmentation of $M^{+\cdot}$ of I and II. Practically completely identical character of the mass spectra of I and II is therefore observed in the region of mass numbers with m/e 158 and below. The frag-

*See [1] for communication II.

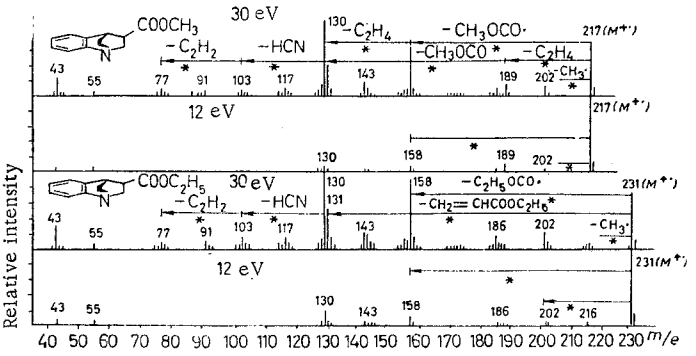

Fig. 1. Mass spectra of 3-methoxycarbonyl- and 3-ethoxycarbonylbenzo[b]quinuclidines.

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ment with m/e 130, the peak of which is of maximum intensity in the spectra, is formed during the elimination of 28 mass units from the ion with m/e 158 (m* = 107 for I). In addition, the disintegration of $M^{+\cdot}$ in the reverse order with initial detachment of 28 mass units to form ions with m/e 189 (m* = 164 for I and 203 for II) and subsequent ejection of alkoxycarbonyl groups (m* = 89.5 for I) from them similarly leads to the formation of fragments with m/e 130.

The appearance of ion peaks with m/e 186 and 202 in the spectra of I and II is due to cleavage of the bonds in the methoxycarbonyl and ethoxycarbonyl groups and elimination of methyl, and ethyl, and, respectively, methoxy and ethoxy radicals from $M^{+\cdot}$.

It has been demonstrated [1-5] that the ionization of various substituted quinuclidines and benzoquinuclidines proceeds at the unshared electron pair of the nitrogen atom. If, therefore, elimination of alkoxycarbonyl groups directly from $M^{+\cdot}$ is assumed, one should expect the formation of an ion with m/e 158 with two radical centers. Correspondingly, the fragment with m/e 130, the formation of which from the ion with m/e 158 can be represented as the result of elimination of an unsubstituted bridge bond (C_7-C_8) as a neutral C_2H_4 molecule, will prove to be a diradical ion in this case. A similar pattern with the formation of diradical structures will occur for the disintegration of I and II in the sequence

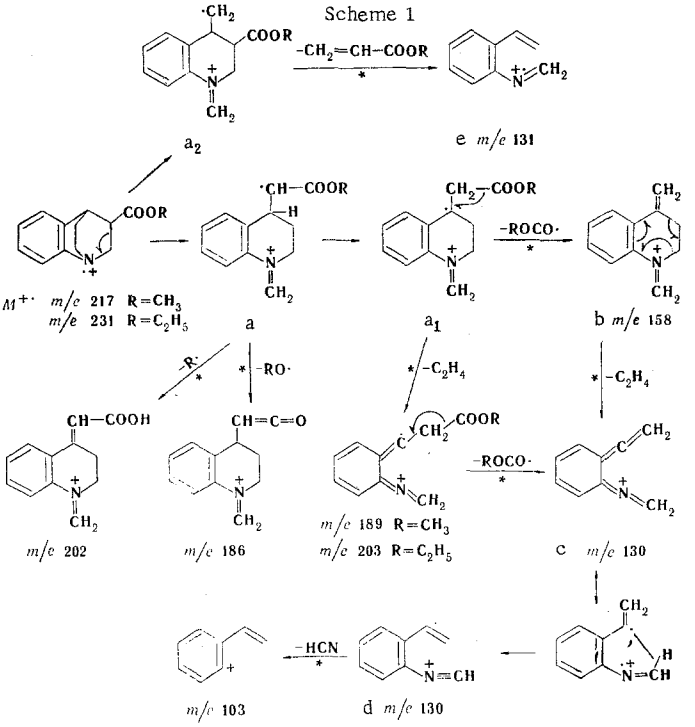
$$M^{+\cdot} \xrightarrow[*]{-C_2H_4} m/e\ 189\ (I),\ m/e\ 203\ (II) \xrightarrow[*]{-ROCO} m/e\ 130.$$

However, these sorts of processes cannot be coordinated with the high intensity of the peaks of the ions in the mass spectra of the investigated compounds.

α-Cleavage is one of the most preferred directions of disintegration in the fragmentation of aliphatic and monocyclic (five-membered, six-membered, etc) amines [6-8]. The fragments formed in this case are characterized by high peak intensities for both normal ionizing voltages and when the latter are reduced to 12 eV. The disintegration of I and II therefore finds a simple explanation when their fragmentation from the open forms of the molecular ions (a and a_1, scheme 1) is considered. The formation of the a form occurs during simple α cleavage of the C_2-C_3 bridge bond in $M^{+\cdot}$, which contains a substituent, while ion a_1 is a rearranged ion that is also formed in the cleavage of the C_2-C_3 bond but with simultaneous migration of the hydrogen atom from the 4 position to the 3 position.

In fact, fragmentation from the open form of the molecular ion (a and a_1) provides an explanation for the processes $a_1 \rightarrow$ m/e 158, $a_1 \rightarrow$ m/e 189, a $\rightarrow$ m/e 186, and a $\rightarrow$ m/e 202, the driving force of which is stabilization of the radical centers attached to the carbon atoms in the 4 and 3 positions to form stable structures.

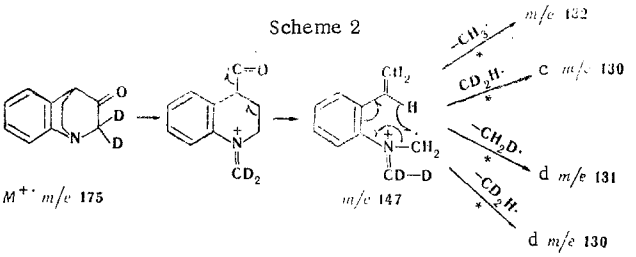
Scheme 1



At the same time, the formation of fragment c with m/e 130 is now considered to be a coordinated shift of the electrons in ion b with m/e 158 with elimination of C_2H_4. Consequently, as may be expected, the peak of fragment c in the spectrum in this case should be one of the maximum intensity peaks.

The detachment of HCN from the fragment with m/e 130 (m* = 81.8) to form an ion with m/e 103 occurs in accordance with the process c → d → m/e 103. It has been demonstrated [1] that the formation of an ion with m/e 130 is also a characteristic process in the fragmentation of benzo[b]-3-quinuclidone and its derivatives. However, in view of the peculiarities of their disintegration, it was assumed that this fragment can have only structure d. Two peaks with m/e 131 and 132, respectively, were observed in addition to the ion peak with m/e 130 in the mass spectrum of deuterium-labeled (in the α position) benzo[b]-3-quinuclidone. We were unable to explain the appearance of the peaks with m/e 131 and 132. All three peaks were characterized by about the same intensities. If the peaks of the fragments with m/e 130 and 131 were explained by structure d, then, as now becomes clear, the appearance of a peak with m/e 132 was caused by structure c, the formation of which from the fragment with m/e 147 occurred during the elimination of $CH_3^{\cdot}$ through a six-membered transition state with splitting out of a hydrogen atom from the 4 position (scheme 2).

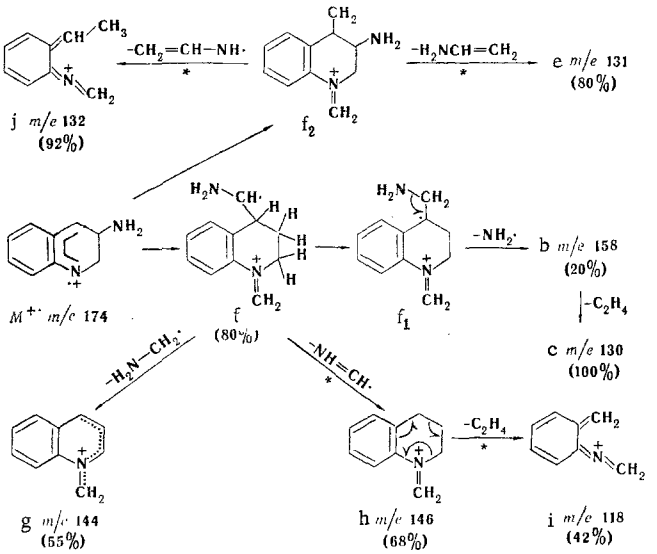
Scheme 2



Thus it follows from a joint examination of the fragmentations of I, II, and similar functional derivatives that the peak of the fragment with m/e 130 in the spectra of I and II is due to structures c and d, and, as in the fragmentation of benzo-3-quinuclidone, their contributions are apparently about the same. The transition from one structure to the other is evidently due to the energetic favorability of rearrangement through a six-membered transition state. We note that the peaks of fragments with m/e 103 in the spectra of I and II and benzo[b]-3-quinuclidone are characterized by an extremely insignificant intensity, which again attests to the high stability of structures c and d.

In contrast to the previously investigated quinuclidine and benzo[b]quinuclidine derivatives [1,2], the opening of the molecular ions of which occurred as a result of cleavage of only one bridge bond containing a functional group,† the open molecular ion a_2, which formed on cleavage of the unsubstituted methylene bridge, is observed in the disintegration of I and II. In fact, the appearance of peaks of fragments with m/e 131 in the spectra of I and II is due to ion radical e, which is formed from a_2 on elimination of methyl acrylate (for I) or ethyl acrylate (for II). For I, this process is confirmed by a mestastable ion (m* = 74).

Scheme 3



†This process was intensive even when the ionizing voltage was reduced to 12 eV.

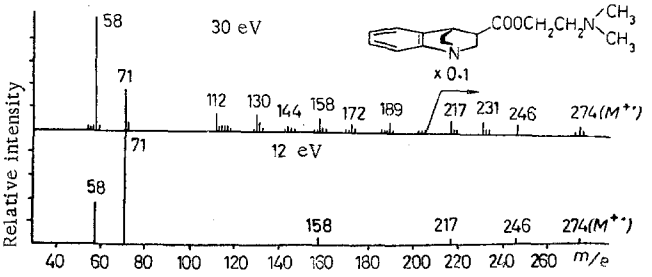


Fig. 2. Mass spectra of β-dimethylaminoethyl benzo-[b]quinuclidine-3-carboxylate.

The formation of the fragments characteristic for 3-substituted benzo[b]quinuclidines also occurs in the disintegration of 3-aminobenzo[b]quinuclidine (III) (scheme 3).†

Ions with m/e 158, 131 (m* = 98.5), and 130 are formed from the open form of the molecular ions (f, f_1 and f_2) and have the same structures as fragments b, e, and c, respectively, in the disintegration of I (scheme 1).

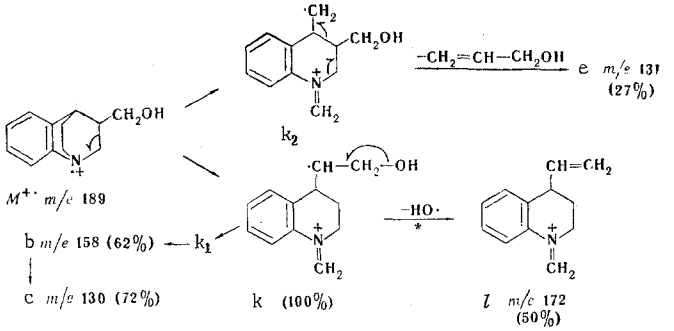
Structure g with partially conjugated bonds apparently corresponds to the fragment with m/e 144. The splitting out of an HN = CH· radical from f with migration of one of the hydrogen atoms of the amino group in the 4 position‡ leads to the formation of fragment h with m/e 146 (m* = 122.5), which subsequently eliminates C_2H_4 to give ion i with m/e 118 (m* = 95.5).

The formation of ion j with m/e 132 (m* = 100), the peak of which is one of the maximum-intensity peaks in the spectrum, proceeds from the open molecular ion f_2 and, because of migration of one of the hydrogen atoms of the amino group to the radical center in the 8 position, also with detachment of an HN = CH − CH_2· radical.

The proposed disintegration of 3-aminobenzo[b]quinuclidine is in complete conformity with the mass spectrum of the deuterium analog (deuterated amino group), in which a shift of the peaks with m/e 118, 132, and 146 by one unit toward the higher-mass side is observed.

The fragmentation of 3-hydroxymethylbenzo[b]quinuclidine (IV) (scheme 4) is similar in many respects to that of I, II, and III. The spectrum of IV contains characteristic peaks of fragments with m/e 158 (m* = 132), 131, and 130, which have the same structures as the ions with the same mass numbers in the disintegration of I, II, and III. However, in contrast to I, II, and III, yet another possibility for the stabilization of the radical center in the 3 position – detachment of a hydroxyl radical (m* = 156) leading to ion *l* with m/e 172, the peak of which has considerable intensity in the spectrum – is realized in open molecular ion k. The indicated fragmentation processes are confirmed by the disintegration of deuterium analog IV (deuterated in the hydroxyl group), in the spectrum of which the mass numbers of peaks with m/e 130, 131, 158, and 172 remained unchanged.

Scheme 4



Thus a distinctive peculiarity of the fragmentation of I-IV is the high intensity of the peaks of the molecular ions, the open form of which is generated not only by cleavage of the $C_2 - C_3$ bond but also by cleavage of the $C_7 - C_8$ bond, which does not contain a substituent. This sort of behavior of these compounds under

†When the mass spectrum is not presented, the relative intensity of the peaks of the ions under consideration are indicated in parentheses.

‡ This process is characteristic for 3-hydroxybenzo[b]quinuclidines, the mass spectra of which will be published separately.

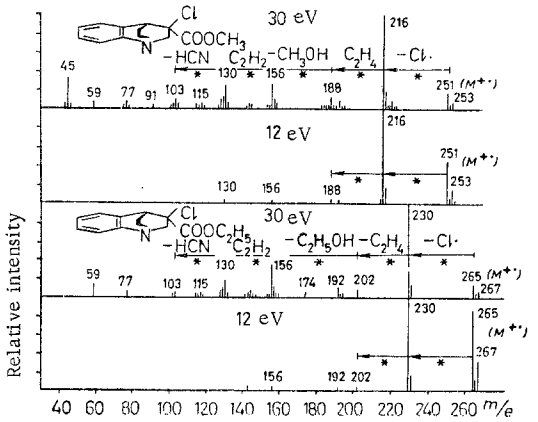
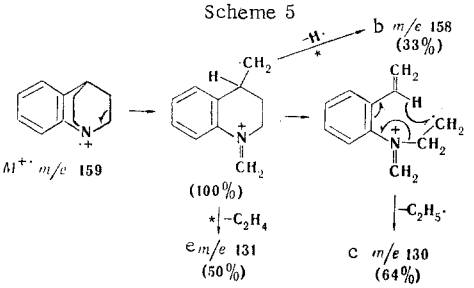


Fig. 3. Mass spectra of 3-chloro-3-methoxycarbonyl- and 3-chloro-3-ethoxycarbonylbenzo[b]quinuclidines.

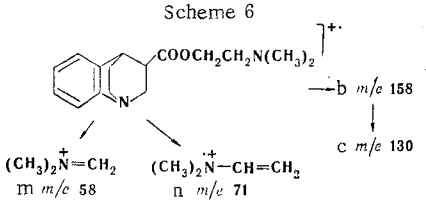
electron impact can be explained only by the fact that considerably less weakening of the C_2-C_3 bridge bond is observed for 3-monosubstituted derivatives than for 3,3-disubstituted derivatives [2] or for compounds that contain a functional group (for example, C=O) directly in the bridge chain in the 3 position [1]. The unsubstituted and substituted bonds are consequently commensurable with respect to the energy of cleavage in this case. As should be expected, the molecular ion peak (scheme 5) is the peak of maximum intensity in the mass spectrum of benzo[b]quinuclidine. The ions with m/e 158, 131, and 130 correspond to structures c, b, and e, respectively (scheme 1).

Scheme 5



The disintegration of the β-dimethylaminoethyl benzo[b]quinuclidine-3-carboxylate (VIII) (Fig. 2) is determined by the stability of the charged and neutral fragments that are formed during the cleavage of the substituent bonds (scheme 6).

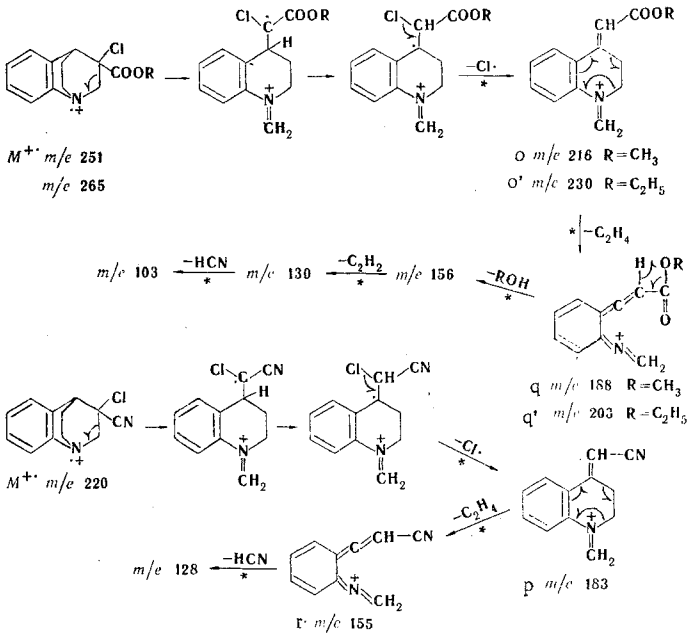
Scheme 6



The intensity of the peaks with m/e 158 and 130 that are characteristic for I-IV is insignificant in the mass spectrum of this compound because the charge is concentrated primarily on the nitrogen atom of the substituent. Consequently, as in the fragmentation of aliphatic amines [6, 7], the most probable process is the formation of ions m with m/e 58 and n with m/e 71, which are obtained as a result of α and β cleavages, respectively. In the second case, the cleavage is accompanied by migration of a hydrogen atom from the α position to the COO· group and detachment of a neutral benzo[b]quinuclidine-3-carboxylic acid molecule. When the ionizing voltage is lowered to 12 eV, the intensities of the peaks of fragments m and n are redistributed. The peak of the fragment with m/e 71 becomes the maximum peak in the spectrum, while the intensity of the peak with m/e 58 is 36%. This fact may evidently explain the growing role of the frequency factor at low ionizing voltages for rearrangements that are accompanied by the cleavage of neutral molecules [9].

In the case of 3,3-disubstituted benzo[b]quinuclidines (Fig. 3), when one of the substituents is a chlorine atom, the migration (characteristic for I-IV) of a hydrogen atom in the open molecular ion from the 4 position to the radical center in the 3 position is most clearly expressed. The weakest bond in the open molecular ions of these compounds is the C–Cl bond. The peaks of fragments o with m/e 216 (m* =186), of o' with m/e 230 (m* =200), and of p with m/e 183 (m* =153) (scheme 7) in the mass spectra of 3-chloro-3-carbomethoxybenzo[b]quinuclidine (V), 3-chloro-3-carbethoxybenzo[b]quinuclidine (VI), and 3-chloro-3-cyanobenzo[b]quinuclidine (VII) (Fig. 3) are therefore the maximum peaks in the spectra, not only at 30 eV but also at 12 eV. The presence of metastable ions in the spectra of V and VI makes it possible to conceive of further disintegration of fragments o, o', and p to form ions with m/e 188 (m*=163), 156 (m* = 129), 203 (m* =178), 130 (m* =106.5), 103 (m* =81.5) for V and with m/e 155 (m* =130) and 128 (m* = 105.5) for VI.

Scheme 7



Thus an examination of the results obtained makes it possible to assume that the fragmentation of the investigated compounds is realized from the open form of the molecular ion, which is formed primarily in the cleavage of the bridge bond that contains a substituent. Subsequent detachment of a substituent from the 3 position is a characteristic process in the disintegration of the investigated compounds.

EXPERIMENTAL

The mass spectra of the compounds were investigated with an MKh-1303 mass spectrometer with introduction of the sample within the ion source. The ionizing voltages were 50, 30, and 12 eV, and the emission current was 75 mA. The admission temperature was 20°, and the ionizing-chamber temperature was 125°. The substances were purified prior to recording their spectra by vacuum distillation or recrystallization.

Compounds I (syn and anti isomers),* III (syn isomer), IV (a mixture of syn and anti isomers), V (anti isomer), VI (anti isomer), and VII were described in [10-12].

3-Ethoxycarbonylbenzo[b]quinuclidine (II, mixture of syn and anti isomers). A 1-g sample of a mixture of the hydrochlorides of syn- and anti-benzo[b]quinuclidine-3-carboxylic acids was refluxed for 5 h with 10 ml of ethanol and 1 ml of concentrated sulfuric acid. The alcohol was removed by distillation, and the residue was treated with ice, made alkaline with 50% potassium carbonate solution, and extracted with ether to give 0.6 g (53%) of a product with bp 123-126° (1 mm). Found: C 72.6; H 7.6; N 6.3%. $C_{14}H_{17}NO_2$. Calculated: C 72.7; H 7.4; N 6.1%.

β-Dimethylaminoethyl Benzo[b]quinuclidine-3-carboxylate (VIII, mixture of syn and anti isomers). A 3-g sample of a mixture of the methyl esters of syn- and anti-benzo[b]quinuclidine-3-carboxylic acids and 30 ml of dimethylaminoethanol, to which 0.05 g of sodium had been added, was refluxed with simultaneous removal of the methanol formed. When the temperature of the mixture reached 133-135°, it was allowed to stand at this temperature for 4 h. The solution was evaporated in vacuo, and 20 ml of 25% potassium carbonate solution was added to it. The alkaline mixture was extracted with benzene to give 2.25 g (59%) of a product with bp 136-139° (0.6 mm). Found: C 69.8; H 8.0%. $C_{16}H_{22}N_2O_2$. Calculated: C 70.0; H 8.1%.

*In the formation of the open form of the molecular ion of benzo[b]quinuclidines, the asymmetry of the molecules, which is caused by the syn or anti orientation of the bridge substituent relative to the benzene ring, vanishes as a result of cleavage of the bridge bond containing the substituent [1, 2]. We therefore deemed it possible throughout this paper to disregard the stereochemistry of the investigated compounds and to omit from their names the prefixes anti and syn, retaining them only in the experimental portion of the study.

LITERATURE CITED

1. A. I. Ermakov, Yu. N. Sheinker, E. E. Mikhlina, L. I. Mastafanova, V. Ya. Vorob'eva, A. D. Yanina, L. N. Yakhontov, and R. G. Kostyanovskii (Kostyanovski), Org. Mass Spectrometry, 5, No. 9, 1029 (1971).
2. A. I. Ermakov, Yu. N. Sheinker, E. E. Mikhlina, A. D. Yanina, V. Ya. Vorob'eva, L. N. Yakhontov, and R. G. Kostyanovskii, Khim. Geterotsikl. Soedin. (1972, in press).
3. R. G. Kostyanovskii, Dissertation [in Russian], Inst. Khim. Fiziki, Moscow (1968).
4. R. G. Kostyanovskii (Kostyanovski), E. E. Mikhlina, E. N. Levkoeva, and L. N. Yakhontov, Org. Mass Spectrometry, 3, 1023 (1970).
5. E. E. Mikhlina, K. F. Turchin, V. Ya. Vorob'eva, A. I. Ermakov, R. G. Kostyanovskii, Yu. N. Sheinker, and L. N. Yakhontov, Dokl. Akad. Nauk SSSR, 195, 1347 (1970).
6. R. S. Gohlke and F. W. McLafferty, Anal. Chem., 34, 1281 (1962).
7. H. Budzikiewicz, C. Djerassi, and D. Williams, Interpretation of the Mass Spectra of Organic Compounds [Russian translation], Mir, Moscow (1966).
8. P. M. Draper and D. B. Macleam, Can. J. Chem., 46, 1499 (1968).
9. D. H. Williams and R. G. Gooks, Chem. Comm., 563 (1966).
10. A. D. Yanina, K. F. Turchin, E. E. Mikhlina, L. N. Yakhontov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., 222 (1972).
11. K. F. Turchin, E. E. Mikhlina, A. D. Yanina, V. Ya. Vorob'eva, L. N. Yakhontov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., 981 (1971).
12. E. E. Mikhlina and M. V. Rubtsov, Zh. Obhsch. Khim., 30, 2970 (1960).