APPLICATION OF MASS SPECTROMETRY IN STRUCTURAL AND STEREOCHEMICAL INVESTIGATIONS

V.* MASS SPECTRA OF β-HYDROXYQUINUCLIDINES AND β-HYDROXYBENZO[b]QUINUCLIDINES

A. I. Ermakov, Yu. N. Sheinker,
E. E. Mikhlina, A. D. Yanina,
V. Ya. Vorob'eva, L. I. Mastafanova,
and L. N. Yakhontov

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The peculiarities of fragmentation in various substituted quinuclidines and benzo[b]quinuclidines with an OH group in the β position when model compounds, deutero analogs, and low-voltage mass spectra are used are discussed.

The mass spectra of β-hydroxyquinuclidines and β-hydroxybenzo[b]quinuclidines, which have not been previously studied, are examined in the present communication.

The fundamental principles of fragmentation of α-substituted β-hydroxyquinuclidines follow from an examination of the mass spectra of structural isomers of 2-carbomethoxy-3-hydroxyquinuclidine (I), 2-carbethoxy-3-hydroxy quinuclidine (II) (Fig. 1), and 2-carbomethoxy- (III) and 2-carbethoxy-5-hydroxyquinuclidines (IV) (Fig. 2). The similarity in the mass spectra of I-IV is due to the formation of fragments with identical mass numbers (m/e 170, 156, and 126), which can be explained by proceeding from the open form of molecular ions A_1 and A_2 (scheme 1), which develop during cleavage of the bridge bond containing the hydroxyl group. Molecular ions A_1 and A_2 are fragmented via three principal pathways. Elimination of alkyl radicals (R = CH_3, C_2H_5) during the fragmentation of I and II (scheme 1) occurs from the ester grouping to give electron-saturated fragment a (m/e 170). The energetic advantageousness of the process $A_1 \rightarrow a$ and its rearrangement character are confirmed by the fact that the ion peaks with m/e 170 in the spectra of I and II at 70 and 12 eV are characterized by high intensities.

*See [1] for communication IV.

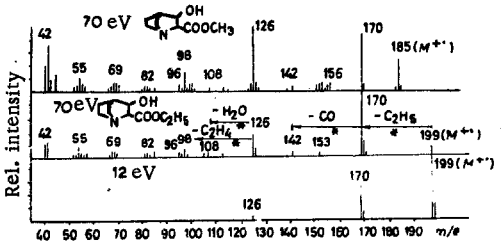


Fig. 1

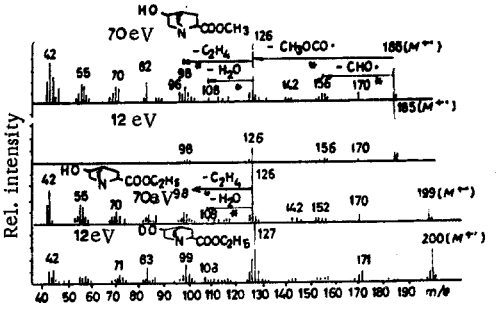
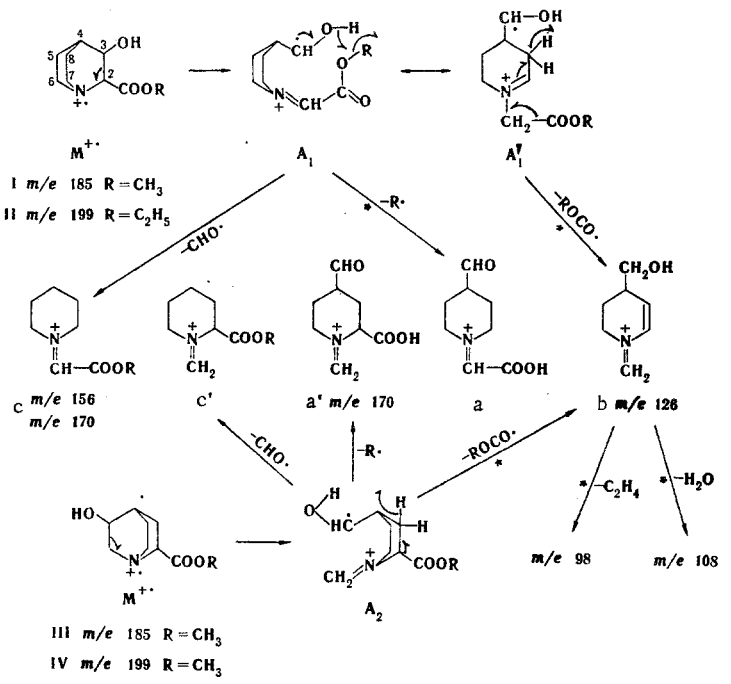


Fig. 2

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1376-1383, October, 1975. Original article submitted July 10, 1974.

The detachment of an alkyl radical (process $A_2 \rightarrow a'$) is expressed extremely weakly in the fragmentation of III and IV (scheme I). The energetically advantageous elimination of R· from A_2 is impossible in view of steric hindrance, as shown by an analysis of molecular models, which evidently hinder the formation of a stable transition state for migration of the labile hydrogen atom to the COO· group.

Scheme 1



The second pathway of fragmentation of A_1 and A_2 is elimination of an ester group. Because of isomerization of the $A_1 \longleftrightarrow A'_1$ type (see [1, 2]), detachment of an ester group from A_1 with simultaneous migration of H· leads to the formation of stable cyclic ion b (m/e 126).

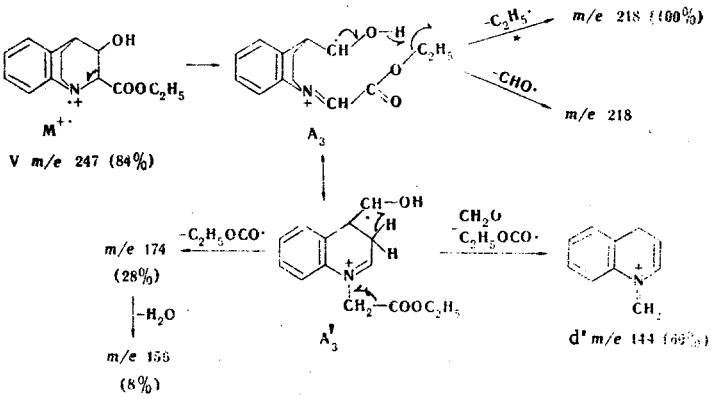
The elimination of a carbalkoxyl group from A_2 also leads to the appearance of intense peaks with m/e 126 in the spectra of quinuclidines III and IV. This sort of detachment from A_2 is energetically advantageous, inasmuch as a rearrangement similar to the process $A_1 \longleftrightarrow A'_1$ is not required in this case. The peak with m/e 126 in the low-voltage mass spectra of III and IV therefore is of high intensity. The subsequent fragmentation of fragments with m/e 126 is realized with splitting out of H_2O and C_2H_4 molecules. These processes constitute evidence for the identical character of the structures of fragments b with m/e 126 formed in the fragmentation of I, II and III, IV.

The third pathway for fragmentation of A_1 and A_2 – elimination of CHO groups – is expressed weakly: The peaks with m/e 156 in the spectra of I and III are characterized by low intensity. This process is interesting in that the migration of a hydrogen atom from the hydroxyl group to C-4 leads to retention of the monocyclic structure with the formation of fragments c and c'. The mass spectrum of deutero analog IVa with respect to the hydroxyl group is in conformity with the proposed mechanisms for the fragmentation of I-IV.

Fragmentation processes characteristic for 2-carbethoxy-3-hydroxyquinuclidine appear during the fragmentation of 2-carbethoxy-3-hydroxybenzo[b]quinuclidine V* (scheme 2). The principal mechanisms of fragmentation of V, which are confirmed by the metastable ions and the mass spectrum of deuterium analog Va, are presented in scheme 2. As for II, the $(M-C_2H_5)^+$ ion peak with m/2 218 has the maximum intensity in the spectrum of V. The formation of a stable fragment with m/e 144 seems of interest. It is most likely that the fragment with m/e 144 arises from A_3 during the simultaneous splitting out of C_2H_5OCO· and CH_2O particles to give structure d'. It is apparent that the stabilizing property of the benzene ring, which shows up clearly on comparison of the fragmentation of 3-hydroxyquinuclidine (VI), 3-hydroxybenzo-[b]quinuclidine (VII), and some of their analogs (schemes 3 and 4), promotes the process $A_3 \rightarrow d'$ to an important extent.

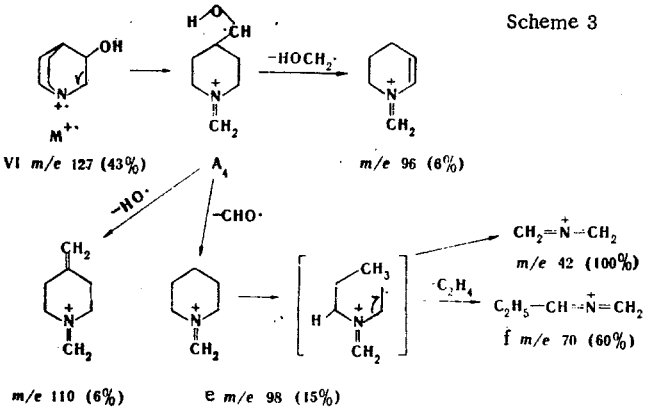
*If the mass spectra are not presented in the figures, the relative intensities of the ion peaks are indicated in parentheses in the fragmentation scheme.

Scheme 2

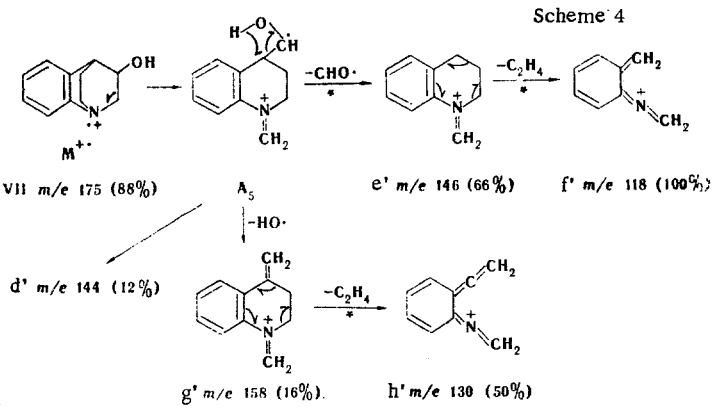


It follows from an examination of schemes 3 and 4 and the intensities of the peaks of the characteristic ions that the benzene ring has a pronounced effect on the fragmentation of the quinuclidine ring. The characteristic detachment of a CHO· radical from A_4 to A_5 is expressed most clearly in the fragmentation of VII. In contrast to the peak of ion e with m/e 98 for VI, the peak of the fragment with a cyclic structure (e' with m/e 146) in the spectrum of VII is of high intensity. The subsequent detachment of a C_2H_4 molecule as a result of a concerted shift of electrons leads to stable ion f' with m/e 118, the peak of which is a maximum in the spectrum. We detected similar fragmentation processes during a study of the mass spectra

Scheme 3



Scheme 4



of β-oxobenzo[b]quinuclidines and 3-substituted benzo[b]quinuclidines [1, 3]. It is interesting to compare the two similar rearrangement processes $A_5 \rightarrow e' \rightarrow f'$ and $A_5 \rightarrow g' \rightarrow h'$ observed in the fragmentation of VIII (scheme 4). One should evidently assume that the first process has a considerably lower activation energy than the reaction to form the ion with m/e 130. This probably is also responsible for the relatively low intensities of the peaks of the fragments with m/e 158 and 130, which have stable structures.

The effect of the benzene ring on a process of the $A_4 \rightarrow e$ type shows up particularly distinctly on comparison of the fragmentation of 3-ethyl- (VIII), 3-phenyl- (IX), 3-benzyl-3-hydroxyquinuclidine (X), and the corresponding benzo analogs XI-XIII. The presence in the 3 position of VIII-X of strong electron-donor

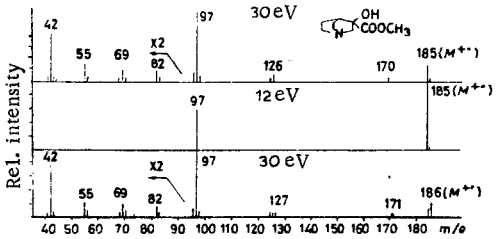


Fig. 3

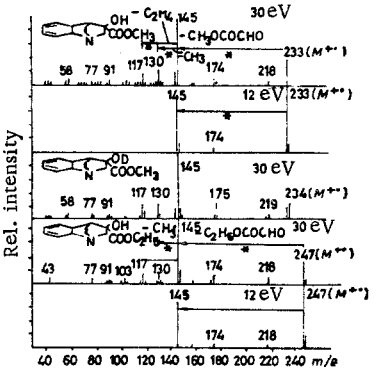
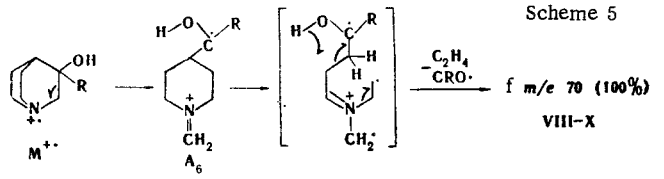


Fig. 4

substituents is responsible for the fact that their fragmentation proceeds practically in a single direction to give an ion with m/e 70. The primary formation of a fragment with m/e 70 can evidently be explained as follows. First, the presence of two substituents attached to one C atom weakens the bridge bond to a considerable extent [3] and therefore promotes the facile formation of the A_6 ion (scheme 5). Second, cleavage of the C-3–C-4 bond with simultaneous migration of the labile H* atom from the α position to C-4 with subsequent one-step splitting out of two stable C_2H_4 and O=C–R particles leads to stable ion f with m/e 70.

Scheme 5

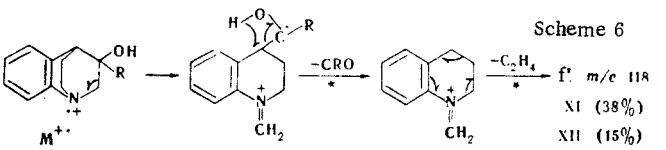


VIII m/e 155 R = C_2H_5 (44%)
IX m/e 203 R = C_6H_5 (16%)
X m/e 217 R = $CH_2C_6H_5$ (32%)

The rearrangement character of the process $A_6 \rightarrow f$ is confirmed by the fact that the peak of the fragment with m/e 170 in the spectra of VIII-X at 12 eV retains its high intensity.

The fragmentation of 3-methyl- (XI), 3-phenyl- (XII), and 3-benzyl-3-hydroxybenzo[b]quinuclidine (XIII) is realized practically only in a single direction (scheme 6).

Scheme 6



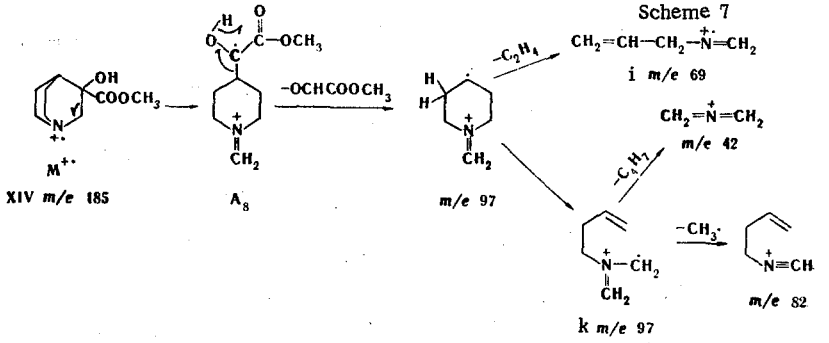
XI m/e 189 R = CH_3 (26%)
XII m/e 251 R = C_6H_5 (20%)
XIII m/e 256 R = $CH_2C_6H_5$ (14%)

The stabilizing properties of the benzene ring are responsible for the fact that the successive detachment of two stable O=C–R and C_2H_4 particles from A_7 leads to the formation of ions with m/e 146 and 118. In this case, the peak of fragment e' is of maximum intensity in the spectra at 30 and 12 eV, and this confirms the energetic advantageousness of the rearrangement. In addition, the mass spectrum of deuterium analog XIa shows that H* migrates exclusively from the OH group to C-4 in open molecular ion A_7.

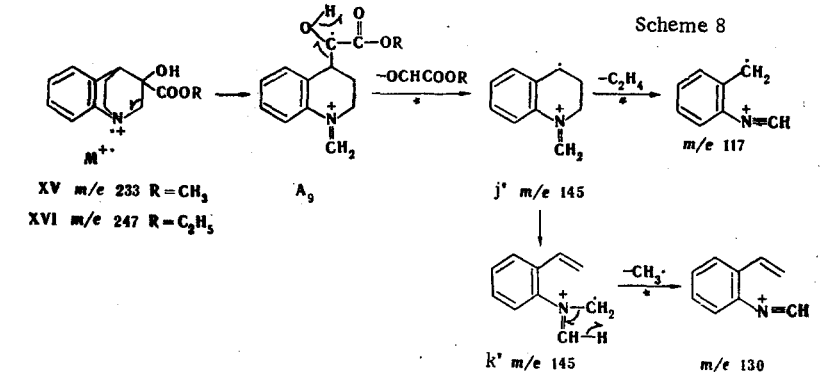
In contrast to this, in the fragmentation of 3-hydroxy-3-carbomethoxyquinuclidine (XIV), 3-hydroxy-3-carbomethoxybenzo[b]quinuclidine (XV), and 3-hydroxy-3-carbethoxybenzo[b]quinuclidine (XVI) (Figs. 3 and 4) one does not observe the characteristic (for VIII-XIII) migration of H* from the hydroxyl group to C-4. This feature of the fragmentation of VIII-XIII is explained by fragmentation from the open form of the molecular ion with subsequent rearrangement $A_8 \rightarrow j \rightarrow k$ and, respectively, $A_9 \rightarrow j' \rightarrow k'$ (schemes 7 and 8). The absence of migration of H* of the hydroxyl group to C-4 is graphically illustrated by a comparison of the mass spectra of deuterium analogs XIVa and XVa and, respectively, XIV and XV, in which the peaks of ions k and k', with m/e 97 and 145, have identical parameters (Figs. 3 and 4). It was shown in [1, 2, 4] that the formation of ions k and k' also occurs by fragmentation of 3-oxoquinuclidine and 3-oxobenzo[b]quinuclidine by direct splitting out of a CO molecule from the open molecular ion. In this case,

on the basis of a study of the ionization and appearance potentials for the dissociative fragmentation of 3-oxoquinuclidine we interpreted the process j → k or j' → k' as a rearrangement with a low activation energy and a low frequency factor. A similar situation evidently also holds for the fragmentation of XIV and XV. The high intensities of the peaks with m/e 97 and 145 at 12 eV may serve as a confirmation of this.

Scheme 7



Scheme 8



Thus, the fragmentation of β-hydroxyquinuclidines and β-hydroxybenzo[b]quinuclidines under the influence of electron impact is realized from the open form of the molecular ion formed by cleavage of the bridge bond containing the functional group. This process is also common to all of the previously investigated quinuclidine derivatives [1-6]. Cleavage of the C-3—C-4 bond in the open molecular ion with subsequent elimination of stable neutral particles and formation of stable ions is characteristic for the fragmentation of the investigated compounds.

EXPERIMENTAL*

The mass spectra of the compounds were investigated with an MKh-1303 mass spectrometer with evaporation of the sample near the ionization region at ionizing voltages of 70, 50, 30, and 12 eV and an emission current of 75 mA. The injection temperature was 20-50°, and the ionization chamber temperature was 125°. Prior to recording of the spectra, we purified the compounds by vacuum distillation or recrystallization. The mass spectra of I, III, and IV were studied with an LKV-9000 chromatographic mass spectrometer. The substances were introduced through a 3.4 m-long chromatographic column with an inner diameter of 2 mm; the column filling was Chromosorb W with an Se-30 (5%) phase. The ionizing voltages were 20 and 70 eV, the accelerating voltage was 3.5 kV, the emission current was 60 μA, and the ionization chamber temperature was 270°.

Methyl 3-Hydroxyquinuclidine-2-carboxylate (I). A 0.05-g sample of Na metal was added to a solution of 3 g of II in 60 ml of methanol, after which the mixture was refluxed for 5 h. It was then vacuum-evaporated, and the residue was dissolved in 15 ml of water. The aqueous solution was made alkaline with 50% K_2CO_3 and extracted with chloroform. The dried chloroform extract was evaporated, and the residue was triturated with ether to give 1.75 g (63%) of cis-I with mp 92-97°.

Ethyl 5-Hydroxyquinuclidine-2-carboxylate (IV). A 1-g sample of ethyl 5-oxoquinuclidine-2-carboxylate was dissolved in 50 ml of anhydrous ethanol, and the compound was hydrogenated in the presence of

*The results of the elementary determination of C, H, and S for the described substances are in good agreement with the calculated values.

0.1 g of an Adams platinum catalyst. The reaction was carried out at room temperature with an excess pressure of 20-30 cm (water gage). At the end of the reaction the catalyst was removed by filtration, the solution was vacuum evaporated, and the residue was fractionated at 115-117° (0.5 mm) to give 0.69 (69%) of IV.

Compounds XI, XII, and XIII were synthesized by a general method. A solution of 8 g (46 mmole) of 3-oxobenzo[b]quinuclidine [8] in 30 ml of ether was added at 5° to an RLi or RMgX derivative prepared from 72 mmole of RX and the appropriate amount of Li or Mg in 60 ml of ether. The mixture was allowed to stand at room temperature for 20 h, after which it was refluxed for 2 h. Extraction with benzene gave the following substances (the yields indicated are based on the sum of the separated diastereoisomers): XI 45%, XII 63%, XIII 47%; anti-XI had mp 156-157° (from ethyl acetate), syn-XI had mp 145-146° (dec., from ether–ethyl acetate), and anti-XII had mp 160-162° (from ethyl acetate), anti-XIII had mp 139-140° (from ethyl acetate), and syn-XIII had mp 116-118° (from ether).

Previously described methods were used to synthesize II [9], III [10], IV [11], VI [12], VII [11], VIII-X [13], and XIV and XV [14].

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