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# PECULIARITIES OF THE MASS-SPECTROMETRIC FRAGMENTATION OF (3-QUINUCLIDINYL)DIARYL(HETERYL)CARBINOLS

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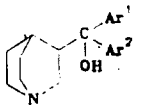
*The principal pathways of the fragmentation of (3-quinuclidinyl)diaryl(heteryl)carbinols that involve cleavage of the quinuclidine–carbinol C–C bond and the bridge bond in the quinuclidine ring containing the substituent were studied. In addition to the indicated fragmentation pathways, fragmentation proceeding with opening of the bridge bond of quinuclidine that does not contain a substituent is observed. The rearrangement of the molecular ion that precedes fragmentation via the indicated pathway is examined.*

The aim of the present research was to study the mass spectra of (3-quinuclidinyl)diaryl(heteryl)carbinols I-IX. A knowledge of the principles of the mass-spectrometric fragmentation of compounds of this series is important in connection with the study of their biotransformation in living organisms by mass spectrometry.* This research is also of independent interest from the point of view of mass-spectrometric behavior, since the presence of several charge-localization centers in the investigated molecules and the possibility of rearrangement of the molecular ions ($M^+$) prior to fragmentation make it possible to assume the realization of new specific fragmentation pathways.




I–IX

I, $Ar^1 = Ar^2$ = phenyl; II, $Ar^1 = Ar^2$ = 2-furyl; III, $Ar^1 = Ar^2$ =2-thienyl; IV, $Ar^1$ = 2-thienyl, $Ar^2$ = 2-furyl; V, $Ar^1 = Ar^2$ =o-tolyl; VI, $Ar^1$ = o-tolyl, $Ar^2$ = benzyl; VII, $Ar^1$ = phenyl, $Ar^2$ = 2-furyl; VIII, $Ar^1 = Ar^2$ =p-tolyl; IX, $Ar^1 = Ar^2$ =3-(o-xylyl).

Two principal fragmentation pathways are observed for most (3-quinuclidinyl)diaryl(heteryl)carbinols [1-4]. Fragmentation of the $M^+$ ion with the formation of $F_1$ and $F_2$ ions (Scheme 1) occurs as a result of the first pathway (A). It might be assumed that this process takes place from the open form of the $M^+$ ion via the mechanism described in [5, 6] for 3-substituted quinuclidines. This is indicated by both the one-step character of the formation of these ions directly from the $M^+$ ion, which was proved by direct analysis of the daughter ions (DADI), and by the similarity in the character of the fragmentation of the $F_1$ ion and the fragmentation of the analogous ions in the spectra of 3-quinuclidone and 3-acetoxyquinuclidine.

*Included among (3-quinuclidinyl)diaryl(heteryl)carbinols are the original antihistamine medicinal preparations fenkarol (I) and bikarfen (V), which are widely used in medical practice.

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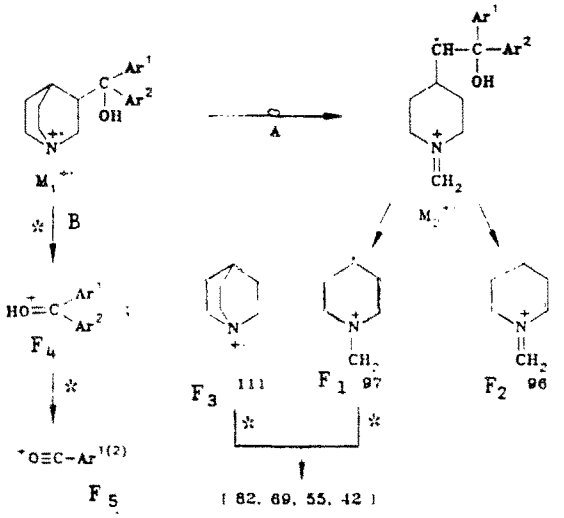
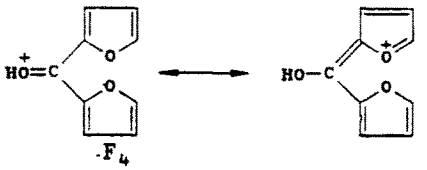
In the second pathway (B) the fragmentation of the $M^+$ ion proceeds with cleavage of the bond between the quinuclidine ring and the diarylcarbinol residue with localization of the charge on the nitrogen atom of the quinuclidine ring (the $F_3$ ion) or on the diarylcarbinol fragment ($F_4$, Scheme 1). The structure of the $F_3$ ion is, in all likelihood, similar to the structure of the molecular ion of unsubstituted quinuclidine. This follows from the identical character of their DADI spectra. The formation of the $F_4$ ion is particularly favorable in connection with the possibility of delocalization of the positive charge on the oxygen atom and in the aromatic system of the cation.

Scheme 1




The subsequent fragmentation of the $F_4$ ion proceeds with the formation of an ion with oxonium structure $F_5$, to which intense peaks correspond in all of the spectra. In the case of II, for which the $F_3$ and $F_5$ ions have the same mass number in the low-resolution spectra, the presence of the $F_5$ ion was established from the high-resolution mass spectrum. In the spectrum of II, 56% of the peak with m/z 111 corresponds to the $F_5$ ($C_5H_3SO^+$) ions, and 44% corresponds to the $F_3$ ($C_7H_{13}N^+$) ions.




Both of the examined pathways of fragmentation of the $M^+$ ions are dominant in the spectra of most of the investigated compounds and lead to the formation of ions that have the most intense peaks (Table 1).

However, it should be noted that the possibility of fragmentation via pathway B depends substantially on the aryl substituents. Thus, the intensities of the peaks of the $F_3$ and $F_4$ ions in the spectra of I-IV and VII-IX range from 33 to 100%, in the case of V the intensity of the peak of the $F_4$ ion does not exceed 13%, while the peak of an $F_3$ ion is altogether absent.

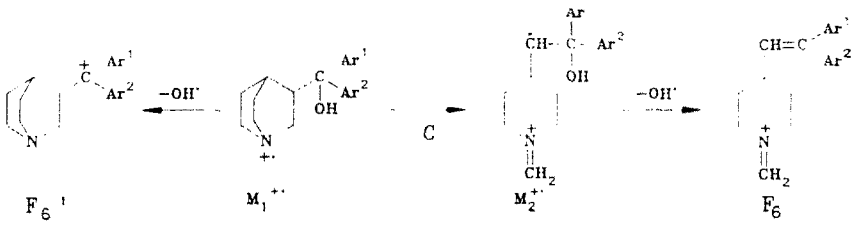
An analysis of molecular models of V showed that the o-methyl substituents are drawn very close to the protons of the quinuclidine ring in the 2 and 4 positions even in the case of the optimum orientation in space. The steric hindrance that develops evidently promotes cleavage of the $C_{(2)}$–$C_{(3)}$ bond in the molecular ion, and its fragmentation is realized primarily via pathway A.

When methyl substituents are present in the meta and para positions (VIII and IX) the steric hindrance is smaller, and fragmentation via pathway B (Scheme 1) with cleavage of the bond between the quinuclidine ring and the carbinol residue is realized to a greater extent than in the case of V: The intensity of the peaks of the $F_4$ ions is 100%, while the intensities of the peaks of the $F_3$ ions are 64 and 93%, respectively. The introduction of a benzyl group as one of the aryl substituents (VI) disrupts the conjugation chain in the $F_4$ ion and causes greater advantageousness of fragmentation via elimination of a benzyl radical with subsequent localization of the charge on the oxygen atom of the resulting ion with m/z 230 (100%).

*The structures of the ions with m/z 82, 69, 55, and 42 are discussed in [6, 7]. In the text and in the schemes the numbers that characterize the ions are the m/z values.

In addition to the examined principal fragmentation pathways A and B, elimination of a hydroxy group from the $M^+$ ion is characteristic for all of the investigated compounds (see Table 1 and Scheme 2).

Scheme 2

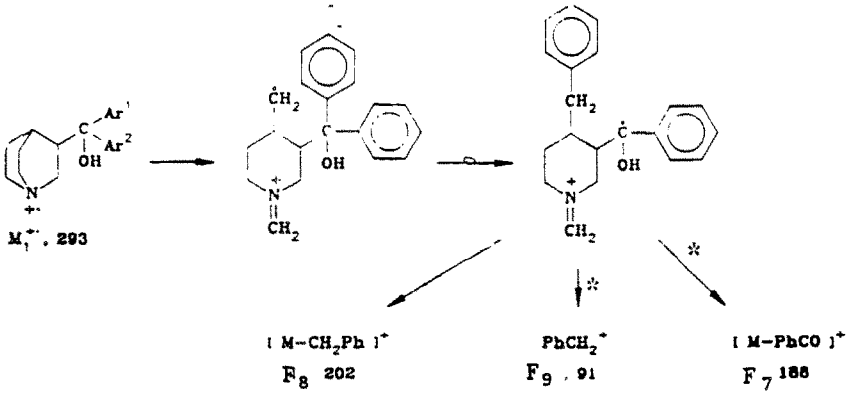


It might be assumed that elimination of a hydroxy radical takes place either from the open form of the molecular ion $M_2^+$ (pathway C) with the formation of the $F_6$ ion or from the closed form $M_1^+$ with the formation of the $F_6'$ carbonium ion. Unfortunately, the structure of the $[M - OH]^+$ ion cannot be proved on the basis of an analysis of its subsequent fragmentation in view of the absence of characteristic signals in the DADI spectrum.

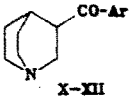
In addition to ions that correspond to the examined fragmentation pathways, peaks of $[M - ArCO]^+$ ($F_7$), $[M - ArCH_2]^+$ ($F_8$), and $ArCH_2^+$ ($F_9$) ions, the formation of which can be explained only by rearrangement of the $M^+$ ion prior to fragmentation that proceeds with opening of the bridge bond that does not contain a substituent, are also observed in the spectra of I-IX. This rearrangement has not been previously observed in series of other 3-substituted quinuclidines. The scheme of the fragmentation via this pathway in the case of I, for which it is expressed most clearly, is presented below (Scheme 3).

The observed rearrangement is realized for virtually all of the (3-quinuclidinyl)diaryl(heteryl)carbinols (Table 1). In the low-resolution spectrum of II, where Ar = 2-thienyl, the mass of the $F_9$ ion coincides with the mass of the $F_1$ ion – the quinuclidine cation radical. It was established from the high-resolution spectra that the ion with m/z 97 consists primarily of $F_1$ ions ($C_6H_{11}N^+$), while the percentage of $F_9$ ions ($C_6H_5S^+$) is 9.4%.

Scheme 3



It is important that this sort of rearrangement is characteristic only for (3-quinuclidinyl)diaryl(heteryl)carbinols and is absent in the spectra of the corresponding (3-quinuclidinyl)aryl(heteryl) ketones X-XII:



X Ar = 2-thienyl; XI Ar = O-tolyl; XII Ar = phenyl

The fragmentation of X-XII is characterized by either simple cleavage of the C–C bonds with the formation of the $F_5$ aroyl cation or by opening of the bridge bond containing the substituent with the formation of the $F_2$ and $F_{10}$ cations (Scheme 4).

Thus, an analysis of the data obtained makes it possible to assume that the fragmentation of the $M^+$ ions of (3-quinuclidinyl)diaryl(heteryl)carbinols occurs both from a structure corresponding to the starting molecule and with prior opening of the quinuclidine ring; in addition to cleavage of the bridge $C_{(2)}$–$C_{(3)}$ bond containing the substituent, competitive opening of

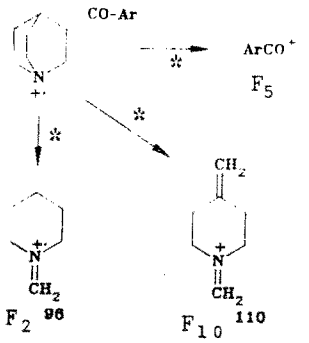
TABLE 1. Characteristic Ions in the Low-Resolution Mass Spectra of I-XII

| Compound | m/z ($I_{rel}$, %) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M·+ | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ | $F_9$ | $F_{10}$ | others |
| I | 293 (31) | 97 (100) | 96 (91) | 111 (31) | 183 (44) | 105 (68) | 276 (10) | 188 (12) | 202 (6) | 91 (20) | 110 (18), | 82 (27), 69 (17), 55 (28), 42 (61) |
| II | 305 (19) | 97 (100)* | 96 (61) | 111 (57)* | 195 (45) | 111 (57)* | 288 (4) | — | 208 (6) | 97 (100)* | 110 (1), | 82 (20), 69 (21), 55 (29), 42 (17) |
| III | 273 (47) | 97 (81) | 96 (61) | 111 (41) | 163 (100) | 95 (75) | 256 (7) | 178 (13) | 192 (15) | 81 (29) | 110 (45) | 82 (40), 69 (35), 55 (48), 42 (99) |
| IV | 283 (27) | 97 (100) | 96 (55) | 111 (53) | 179 (74) | 95 (42) | 272 (4) | — | 207 (4), 192 (5) | 81 (12) | 110 (19), | 82 (30), 69 (21), 55 (31), 42 (18) |
| V | 321 (13) | 97 (100) | 96 (61) | — | 211 (13) | 119 (33) | 304 (5) | 202 (16) | — | 105 (3) | 110 (13), | 82 (11), 69 (12), 55 (18), 42 (29) |
| VI | 321 (6) | 97 (10) | 96 (9) | 111 (5) | 211 (7) | 119 (38) | 304 (4) | 202 (3) | — | 105 (3) | 110 (11), | 82 (6), 69 (4), 55 (14), 42 (23) |
| VII | 283 (35) | 97 (100) | 96 (49) | 111 (33) | 173 (76) | 105 (22), 95 (54) | 266 (11) | 178 (10) | 202 (7) | 81 (10), 91 (7) | 110 (24), | 82 (41), 69 (28), 55 (44), 42 (74) |
| VIII | 321 (22) | 97 (49) | 96 (39) | 111 (64) | 211 (100) | 119 (80) | 304 (5) | 202 (6) | 216 (2) | 105 (12) | — | 82 (21), 69 (18), 55 (22), — |
| IX | 349 (17) | 97 (42) | 96 (58) | 111 (93) | 239 (100) | 133 (99) | 332 (4) | 216 (5) | — | 119 (12) | — | 82 (28), 69 (24), 55 (36), 42 (62) |
| X | 221 (74) | — | 96 (100) | — | — | 111 (56) | — | — | — | — | 110 (74), | 82 (43), — 55 (14), 42 (80) |
| XI | 229 (95) | — | 96 (84) | — | — | 119 (44) | — | — | — | — | 110 (100), | 82 (23), — 55 (19), 42 (90) |
| XII | 215 (100) | — | 96 (52) | — | — | 105 (37) | — | — | — | — | 110 (72), | 82 (26), — 55 (17), 42 (98) |

*The percentages of the $F_1$ and $F_9$ ions (m/z 97) and the $F_3$ and $F_5$ ions (m/z 111) of II were established from the high-resolution spectra.

the bridge bonds that do not contain a substituent, which is accompanied in part by rearrangement of the $M^+$ ion prior to fragmentation, occurs.

Scheme 4




## EXPERIMENTAL

The low-resolution mass spectra and the DADI spectra were obtained with a Varian MAT-112 chromatographic mass spectrometer with direct introduction of the samples; the temperature of the ionization chamber was 180°C, and the ionizing-electron energy was 70 eV. The high-resolution mass spectra were obtained with a Varian MAT-311A mass spectrometer with a resolution of 15,000 by the method of coincidence of the peaks; the ionizing-electron energy was 70 eV.

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