MASS SPECTROMETRY OF 8-HYDROXYQUINOLINE DERIVATIVES*

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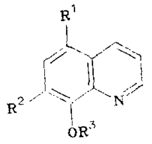
UDC 543.51:547.831.8

In contrast to the fragmentation of the corresponding alkyl aryl ethers, characteristic $[M - H]^+$ and $[M - H, - CO]^+$ fragments were observed in the fragmentation of 5-nitro(halo)-substituted 8-alkoxyquinolines. It was found by means of deuterium labeling that a hydrogen atom is split out primarily from the alkoxy group. It was demonstrated that an $[M - H, - CO]^+$ fragment was formed from the $[M - H]^+$ ion, which has a three-ring structure and a quaternary nitrogen atom. The formation of an $[M - CO]^+$ fragment is characteristic for the fragmentation of 5(7)-nitro(halo)-substituted 8-hydroxyquinolines. The interrelationship between the intensities of the $[M - H]^+$, $[M - H, - CO]^+$, and $[M - CO]^+$ ion peaks and the protonation constants (pK_a) of the investigated compounds is discussed.

Systematic studies of the mass-spectrometric fragmentation of quinolines have been made only for their simplest alkyl-substituted compounds [2, 3]. Less study has been devoted to the fragmentation under electron impact of other derivatives of this class. Primarily the mass spectra of the products of condensation of quinolines with various heterocycles [4] and complexes of some halo-substituted quinolines with metals [5, 6] have been investigated. 8-Hydroxyquinoline derivatives (for example, VIII, X, and XI, which were studied in the present research) have a broad spectrum of biological activity, and a number of medicinal preparations have been created from them [7]; their mass-spectrometric study is therefore of practical and theoretical interest.

In the present research we have studied the electron-impact mass spectra of functionally substituted quinolines I-XIII (Table 1).



I–XIII

I $R^1 = R^2 = H$, $R^3 = CH_3$, a $R^3 = CD_3$; II $R^1 = Cl$, $R^2 = H$, $R^3 = CH_3$, a $R^3 = CD_3$; III $R^1 = NO_2$, $R^2 = H$, $R^3 = CH_3$; IV $R^1 = Cl$, $R^2 = I$, $R^3 = CH_3$; V $R^1 = R^2 = H$, $R^3 = C_2H_5$, a $R^3 = C_2D_5$; VI $R^1 = Cl$, $R^2 = I$, $R^3 = C_2H_5$; VII $R^1 = Cl$, $R^2 = H$, $R^3 = C_6H_5$; VIII $R^1 = R^2 = R^3 = H$; IX $R^1 = Cl$, $R^2 = R^3 = H$; X $R^1 = Cl$, $R^2 = I$, $R^3 = H$; XI $R^1 = NO_2$, $R^2 = R^3 = H$; XII $R^1 = R^3 = H$; $R^2 = NO_2$; XIII $R^1 = R^2 = NO_2$, $R^3 = H$

The fragmentation of the compounds was studied in comparison with the corresponding substituted phenols and alkyl aryl ethers [8-10].

The spectra of 8-methoxyquinoline (I) and its deuterated analog Ia are presented in Fig. 1. The principal processes in the fragmentation of I take place with the formation of $[M - H]^+$ (158),[†] $[M - H, - 28]^+$ (130), $[M - CH_2O]^+$ (129), $[M - CH_3, - 28]^+$ (116), $[M - CH_2O - HCN]^+$ (102), and $[M - CH_3, - 28, - HCN]^+$ (89) ions.

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*Communication 4 from the series "Mass spectrometry of biologically active substances." See [1] for communication 3.

[†] Here and subsequently, the numbers that characterize the ions are the m/z values.

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0009-3122/84/2006-0637$08.50

TABLE 1. Mass Spectra of II-XIII

Compound	m/z values (relative intensities in percent relative to the maximum)*
II	196 (4), 195 (32), 193 (92), 192 (100), 191 (4), 167 (6), 166 (32), 165 (26), 164 (95), 163 (56), 162 (16), 158 (14), 152 (6), 151 (3), 150 (14), 149 (10), 130 (5), 128 (52), 123 (10), 116 (8), 115 (12), 114 (3), 102 (5), 101 (10), 100 (4), 99 (5)
IIa	198 (26), 197 (14), 196 (100), 195 (22), 194 (62), 193 (3), 169 (4), 168 (30), 166 (92), 165 (12), 164 (56), 161 (12), 152 (5), 151 (3), 150 (15), 130 (10), 129 (54), 123 (12), 116 (8), 115 (2), 114 (3), 102 (4), 101 (8), 100 (3), 99 (4)
III	205 (56), 204 (100), 203 (60), 176 (10), 175 (58), 174 (60), 173 (6), 172 (4), 160 (4), 159 (12), 158 (40), 157 (54), 156 (4), 155 (4), 146 (3), 145 (7), 144 (10), 131 (5), 130 (28), 129 (60), 128 (80), 117 (12), 116 (10), 115 (28), 104 (5), 103 (18), 102 (82), 101 (25), 90 (4), 89 (11), 88 (15), 79 (4), 78 (10), 77 (33), 39 (22)
IV	322 (4), 321 (27), 320 (22), 319 (78), 318 (34), 293 (3), 291 (8), 290 (60), 289 (3), 277 (2), 276 (6), 229 (4), 228 (4), 277 (6), 226 (5), 194 (12), 193 (8), 192 (48), 191 (12), 190 (13), 179 (6), 178 (3), 177 (17), 165 (16), 164 (42), 163 (55), 162 (100), 161 (3), 151 (10), 150 (6), 149 (4), 148 (6), 129 (8), 128 (26), 127 (36), 126 (32), 125 (5), 115 (8), 114 (55), 113 (4), 102 (5), 101 (10), 100 (12), 99 (12), 98 (3), 88 (17), 87 (16), 86 (8), 85 (2), 77 (3), 76 (6), 75 (12), 74 (8), 73 (2), 63 (25), 62 (12), 61 (2)
V	174 (3), 173 (10), 172 (12), 159 (4), 158 (100), 146 (3), 145 (12), 131 (2), 130 (9), 129 (40), 128 (4), 117 (20), 116 (10), 104 (2), 103 (4), 102 (2), 91 (2), 90 (8), 89 (12), 77 (4), 76 (2), 75 (4), 64 (3), 63 (8)
Va	179 (2), 178 (11), 177 (3), 176 (5), 161 (12), 160 (100), 148 (2), 147 (3), 146 (12), 145 (2), 132 (6), 131 (6), 130 (44), 118 (24), 117 (4), 116 (6), 104 (2), 103 (5), 102 (2), 91 (8), 90 (10), 89 (12), 64 (4), 63 (10), 62 (4)
VI	335 (6), 334 (2), 323 (12), 320 (32), 319 (4), 318 (100), 307 (10), 306 (12), 305 (32), 291 (3), 290 (2), 289 (10), 279 (2), 278 (2), 277 (6), 276 (3), 206 (4), 180 (4), 164 (5), 163 (4), 162 (20), 152 (4), 151 (4), 150 (16), 115 (6), 114 (10), 93 (4), 92 (3), 91 (2), 63 (4), 62 (3), 61 (2)
VII	257 (26), 256 (28), 255 (78), 180 (20), 179 (18), 178 (62), 152 (34), 151 (6), 150 (99), 141 (18), 125 (8), 124 (4), 123 (22), 116 (4), 115 (16), 114 (12), 90 (4), 89 (10), 78 (4), 77 (100)
VIII	146 (8), 145 (100), 117 (48), 116 (5), 90 (4), 89 (22), 70 (4), 69 (26), 68 (5)
IX	182 (6), 181 (34), 180 (10), 179 (100), 153 (12), 152 (4), 151 (32), 150 (6), 125 (4), 124 (6), 123 (4), 117 (4), 116 (25), 115 (6), 114 (4), 90 (6), 89 (16), 88 (6), 87 (7), 75 (4), 74 (5), 73 (7), 72 (2), 71 (4), 64 (4), 63 (12), 62 (4)
X	308 (4), 307 (30), 306 (12), 305 (100), 279 (7), 278 (2), 277 (26), 242 (4), 215 (5), 214 (2), 213 (7), 180 (3), 179 (4), 178 (12), 152 (14), 151 (8), 150 (48), 149 (8), 125 (4), 124 (4), 123 (12), 116 (4), 115 (28), 114 (16), 89 (4), 88 (12), 87 (8), 86 (4), 63 (8), 62 (7), 61 (3)
XI	191 (14), 190 (100), 174 (2), 161 (6), 160 (45), 145 (2), 144 (8), 132 (2), 117 (3), 116 (22), 104 (3), 89 (5)
XII	191 (12), 190 (100), 174 (1), 161 (4), 160 (26), 145 (2), 144 (5), 133 (2), 132 (22), 117 (2), 116 (20), 89 (2)
XIII	237 (2), 236 (12), 235 (100), 219 (3), 206 (3), 205 (22), 160 (8), 159 (6), 144 (3), 143 (9), 132 (6), 131 (5), 103 (8), 102 (2)

*Fragments, the intensities of the peaks of which exceed 2%, are presented in the table.

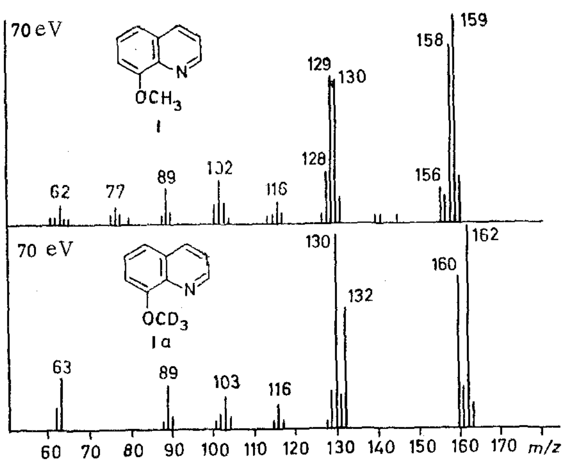
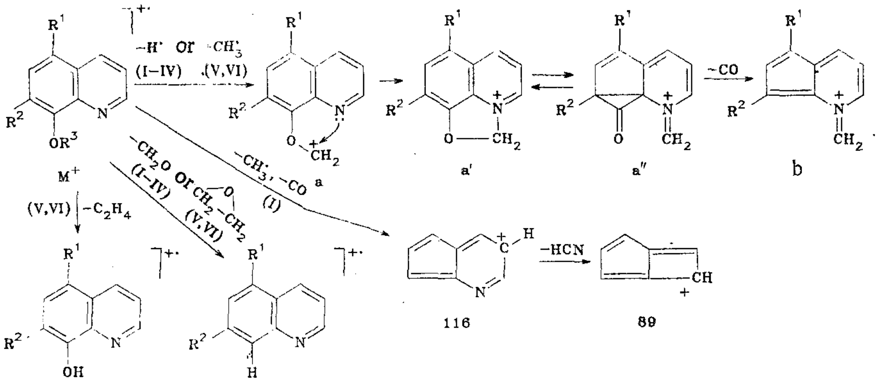


Fig. 1. Mass spectra of I and Ia.

Splitting out of CH_3 and CH_2O particles is observed in the fragmentation of α-methoxynaphthalene [10], whereas detachment of a molecule of HCN is characteristic for unsubstituted quinoline and its alkyl derivatives [2, 3]. However, in contrast to these compounds, peaks of $[M - H]^+$ and $[M - H, - 28]^+$ fragments are present in the spectrum of 8-methoxyquinoline. These fragments are formed in the fragmentation of all of the methoxy derivatives I-IV investigated in this research.

It follows from the spectrum of deutero analog Ia (see Fig. 1) that elimination of a hydrogen atom (80%) from the methoxy group occurs. The observed shifts of the m/z values of the $[M - H]^+$ ions from 158 to 160 and of the $[M - H, - 28]^+$ ions from 130 to 132 indicate that splitting out of a particle with 28 amu is realized from the $[M - H]^+$ fragment and that the particle split out is a molecule of CO, as shown in Scheme 1.

Scheme 1



Nitrogen-containing heterocycles are strong bases in the gas phase [11]. We therefore linked the formation of the $[M - H]^+$ (or $[M - CH_3]^+$) ion with transfer of the electron pair from the heteroatom to the cationic center with the formation of ion **a'** with a three-ring structure and a quaternary nitrogen atom. Sample and co-workers [3] have explained the formation of similar ions in the fragmentation of 8-propylquinoline from the assumption of charge localization on the ring nitrogen atom.

Opening of the five-membered ring of ion **a'** and subsequent splitting out of a stable CO molecule, which, as a rule, has a low energy of activation and a low frequency factor [12], lead to fragment b. It should be noted that the elimination of a molecule of CO from ions **a''** is similar to the analogous reactions under the conditions of photochemical transformations [13].

One should expect that the efficiency of the formation of the $[M - H]^+$ fragment should increase as the electron density on the ring nitrogen atom increases. We have made an attempt to explain the change in the relative intensities of the peaks of this fragment in the spectra of nitro- and halo-substituted 8-methoxyquinolines I-IV by means of protonation constants pK_a (Table 2). The pK_a values of derivatives I-IV are given for aqueous solutions. However, the basicity series constructed from pK_a data does not also comply with the proton affinities of molecules determined in the gas phase for all classes of organic compounds. Unfortunately, these data are not available in the literature for I-IV. However, there are a number of experimental facts [11] that constitute evidence for the absence of anomalies in the basicity series of pyridines, pyrroles, and other aromatic amines determined for aqueous solutions and the gas phase. If these conditions are satisfied for I-IV, one can draw the following conclusions from the data presented in Table 2. First, the intensities of the $[M - H]^+$ ion peaks and the $I_{[M - H]^+}/I_{[M - H, - CO]^+}$ ratios are directly proportional to the basicities of the compounds. Only the intensity of the $[M - H]^+$ ion peak for II deviates somewhat from the observed regularity. However, within the framework of the assumptions made, these data, upon the whole, constitute evidence in favor of the formation of ion **a'** with a three-ring structure. Second, the slight dependence of the intensities of the $[M - H, - CO]^+$ ion peaks on the pK_a values of the compounds may constitute evidence for energetically favorable splitting out of CO and the formation of amine fragment b. It is interesting to note that the stabilities of the molecules with respect to electron impact (the W_M values) decrease regularly on passing from I to disubstituted halogen analog IV.

TABLE 2. pK_a Constants, Stabilities with Respect to Electron Impact (W_M), Intensities of the Peaks of the Characteristic Fragments (in percent of the total ion current), and Their Ratios

Compound	pK_a	W_M	$[M-H]^+$	$[M-H, -CO]^+$	$\frac{I[M-H]^+}{I[M-H, -CO]^+}$	Compound	pK_a	W_M	$[M-CO]^+$	$\frac{IM^+}{I[M-CO]^+}$	Compound	pK_a	W_M	$[M-NO]^+$	$[M-NO, -CO]^+$
I	4,75	16,2	14,1	7,0	1,30	VIII	5,13	53,5	14,8	1,90	XI	2,88	46,3	20,4	1,4
II	4,13	14,6	15,3	15,0	1,16	IX	3,68	29,9	9,8	3,12	XII	1,94	50,5	13	11,0
III	3,55	11,3	6,8	6,7	1,07	X	2,53	24,4	1,2	20,0	XIII	−1,75	52,9	11,6	—
IV	2,95	8,0	3,4	6,1	0,59										

In the fragmentation of II-IV the NO_2 and Cl substituents are split out readily both from M^+ and from the fragment ions; fragments with both even and odd numbers of electrons are formed.

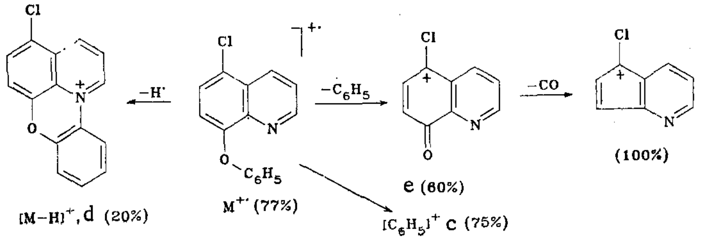
In addition to the formation of an $[M - H]^+$ ion, the competitive and favorable process $M^+ \rightarrow [M - CH_3]^+$ with splitting out of a more stable neutral particle occurs in the fragmentation of V and VI; however, the $[M - CH_3]^+$ ion peaks have low intensities (<6%).

It follows from the spectrum of deutero analog Va that splitting out of a hydrogen atom (62%) is realized from the ethyl group.

Let us note that a process with the formation of an $[M - CH_3]^+$ ion is not observed in the fragmentation of the corresponding ethyl aryl ether [14]. However, the $[M - C_2H_4]^+$ (145), $[M - OCH_2CH_2]^+$ (129), and $[M - C_2H_4, - CO]^+$ (117) fragments that are characteristic for the fragmentation of ethoxy-substituted hydrocarbon aromatic compounds are also observed in the fragmentation of heterocyclic analogs (Scheme 1); this is confirmed by the mass spectrum of deutero analog Va. The same fragmentation character is also retained for 5-chloro-7-iodo-8-ethoxyquinoline (VI).

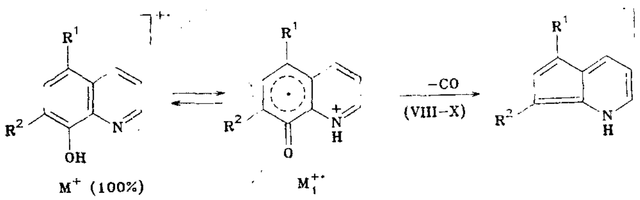
Splitting out of alkyl radicals R^3 with the formation of stable ions with a quinoid structure is not observed in the fragmentation of 8-alkoxy-substituted quinolines I-IV, whereas such processes are characteristic for the corresponding alkyl aryl ethers [10], and the charge may be retained on both the aryl fragment and on the $[M - Ar]^+$ fragment. The fragmentation of VII proceeds via the scheme

Scheme 2



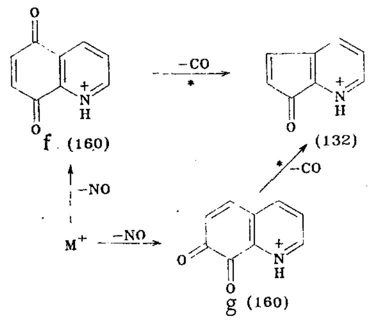
As in the case of alkoxy-substituted I-VI, the $[M - H]^+$ fragment in the fragmentation of derivative VII is evidently formed as a result of the loss of a hydrogen atom from the aryl substituent (ion d, Scheme 2), as well as from the quinoline ring. It should be noted that the fragmentation of VII with the formation of two charged fragments c and e with cleavage of the same bond also indicates charge localization in the region of the oxygen atom.

Processes that are more characteristic for the corresponding phenols [8] than the quinolines occur in the fragmentation of 8-hydroxyquinoline (VIII) and its halo derivatives IX and X. The maximum peaks in the mass spectra of VIII-X are the M^+ peaks. A peak of the $[M - HCN]^+$ fragment is absent, and the peaks of the $[M - CO]^+$, $[M - CO, - Cl]^+$, or $[M - CO, - I]^+$ ions have significant intensities. Splitting out of a molecule of CO from the molecular ions of phenols was proved by deuterium labeling and the high-resolution mass spectrum [8], Scheme 3



The absence of an $[M - HCN]^+$ fragment in the fragmentation of VIII-X can be explained by the existence of the molecular ions of these compounds in the M_1^+ form in analogy with the formation of zwitter ions in solutions of 8-hydroxyquinolines [15]. The M_1^+ ion should have a quinoid structure in the gas phase. In this case the intensity of the $[M - CO]^+$ ion peak will depend on the basicities of the compounds, i.e., on the ease of formation of the M_1^+ structure. In fact, it follows from the data in Table 2 that the intensity of the peak of the $[M - CO]^+$ fragment decreases as the electron density (the pK_a value) on the nitrogen atom of the quinoline ring decreases.

Scheme 4



The fragmentation of nitro derivatives XI-XIII consists in the successive elimination of NO and CO or NO_2 and CO particles; the intensities of the $[M - NO]^+$ (160) and $[M - NO, - CO]^+$ (132) ion peaks of isomers XI and XII differ substantially. The intensities of the peaks at m/z 160, 132, and 116 ($[M - NO_2, - CO]^+$) are considerably higher in the spectrum of para isomer XI than in the case of the ortho isomer (Table 2); this is due to the greater stability of the p-quinoid structure (ion f) as compared with the o-quinoid structure (ion g).

Thus, as a result of our research, we have established the principal regularities in the fragmentation of nitro- and halo-substituted derivatives of 8-hydroxyquinolines. An interrelationship between the peculiarities in the fragmentation of the investigated compounds and the ionization constants pK_a was demonstrated. The results obtained in this research are being used to monitor the quality of medicinal preparations created on the basis of 8-hydroxyquinolines and to establish the structures of new derivatives in this series of compounds.

EXPERIMENTAL

The mass spectra of the compounds were recorded with Varian MAT-112 (in the case of I-X) and MKh-1303 (in the case of XI-XIII) spectrometers. The operating conditions for the mass spectrometers were as follows: an accelerating voltage of 3 kV, an emission current of 1.0 mA, and an ionizing voltage of 70 eV in the case of the MAT-112 spectrometer, as compared with 2 kV, 1.5 mA, and 30 eV, respectively, in the case of the MKh-1303 spectrometer. The ionization constants (pK_a) of the investigated substances were measured spectrophotometrically by the method in [16] with a Perkin-Elmer 402 spectrophotometer. The pK_a values of VIII, X, and XI were in agreement with the literature data [17].

Ethers I-VIII were synthesized by known methods [18-20] by alkylation of the corresponding substituted 8-hydroxyquinolines with benzenesulfonic acid esters in aqueous NaOH solution. Commercial samples of VIII, IX, and XI, which were recrystallized from acetone (VIII and XI) or reprecipitated from DMF by means of methanol (IX and X) prior to recording of the spectra, were selected as the subjects of the investigation. Compounds XII and XIII, which are accompanying impurities in the manufacture of nitroxoline (XI), were obtained by the methods in [21, 22]; the constants of all of the synthesized substances were in agreement with the literature data.

In conclusion, the authors thank G. G. Paramonova and N. V. Karpova for their assistance in carrying out the experiments.

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