Synthesis, ^1H, ^{13}C-NMR and Mass Spectral Study of Aryloxyquinuclidinium Salts

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A series of 3-aryl-3-hydroxy-*N*-(4'-aryloxobutyl)quinuclidinium salts have been synthesized. The ^1H nmr, ^{13}C nmr and mass spectra of these compounds are described and discussed.

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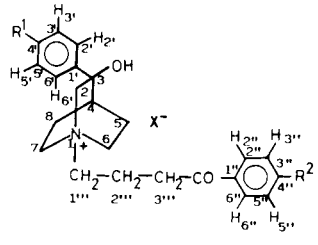
Introduction.

As a part of a research program related to the synthesis of anticholinergic compounds, we report in this paper the synthesis and structural analysis with the aid of ^1H and ^{13}C nmr spectroscopy of a series of 3-aryl-3-hydroxy-*N*-(4'-aryloxobutyl)quinuclidinium salts (Table 1), taking in mind the interesting cholinergic and anticholinergic properties shown by several quinuclidinium compounds [1-6].

The main fragmentation patterns of compounds **9**, **11**, **12**, **14**, **15**, and **18-22** are also described.

Table 1



Compound	R^1	R^2	X^-
1	Cl	Cl	Cl
2	Cl	F	Cl
3	Cl	Br	Cl
4	Cl	CH_3	Cl
5	Cl	OCH_3	Cl
6	F	Cl	Cl
7	F	F	Cl
8	F	Br	Cl
9	F	CH_3	Cl
10	F	OCH_3	Cl
11	CH_3	Cl	Cl
12	CH_3	F	Cl
13	CH_3	Br	Cl
14	CH_3	CH_3	Cl
15	CH_3	OCH_3	Cl
16	OCH_3	Cl	Cl
17	OCH_3	F	Cl
18	OCH_3	Br	Cl
19	OCH_3	CH_3	Cl
20	OCH_3	OCH_3	Cl
21	Cl	OCH_3	I
22	Cl	CH_3	I

Results and Discussion.

NMR Spectra.

The more significant magnetic parameters of compounds **1-22** correspond to the ^{13}C nmr data summarized in Table 2. Assignments of carbon resonances were made from the literature data of 3-*p*-tolyl-3-quinuclidinol [7] and several quinuclidine compounds [8,9] and related systems [10-12]. In the case of ^{13}C, substituent steric and electronic effects on ^{13}C chemical shifts 13 and signal multiplicity obtained from off-resonance decoupled spectra were also taken into consideration.

Table 2

Carbon-13 Chemical Shifts (δ, ppm) and (J_{C-F}, Hz) for Compounds 1-22

Compound	**1**	**2**	**3**	**4**	**5**	**6**
C-2	67.96	67.90	67.16	67.89	67.90	68.17
C-3	72.80	72.84	71.87	72.83	72.82	72.78
C-4	32.61	32.64	31.62	32.58	32.58	32.66
C-5	21.01	20.99	21.10	21.00	20.99	21.03
C-6 (7)	55.32	55.26	54.42	55.20	55.22	55.31
C-8	17.60	17.68	16.65	17.72	17.80	17.75
C-1'	143.20	143.20	142.28	143.22	143.19	140.64 J 2.81
C-2' (6')	128.92	128.94	128.95	128.94	128.92	129.26 J 8.15
C-3' (5')	129.82	129.79	127.96	129.81	129.80	116.39 J 21.67
C-4'	135.05	134.96	134.24	134.98	134.98	163.75 J 246.1
C-1'''	64.73	64.69	63.80	64.73	64.78	64.65
C-2'''	22.07	22.03	21.21	22.04	22.05	22.11
C-3'''	35.84	35.79	34.83	35.68	35.38	35.84
C = O	198.81	198.46	198.07	199.74	198.67	198.88
C-1''	136.36	134.43 J 2.99	135.87	135.35	131.51	136.38
C-2'' (6'')	130.03	132.06 J 9.48	129.98	129.98	129.29	130.02
C-3'' (5'')	130.03	116.68 J 22.09	132.21	130.43	114.96	130.83
C-4''	140.72	167.21 J 253.3	128.51	145.68	165.38	140.71
R^1						
R^2				21.73	56.16	

Table 2 (continued)

Compound	7	8	9	10	11	12
C-2	68.17	67.68	68.11	67.96	68.25	68.16
C-3	72.81	72.14	72.79	72.80	72.94	72.98
C-4	32.67	32.00	32.69	32.70	32.65	32.69
C-5	21.04	20.45	21.03	21.00	21.06	21.08
C-6 (7)	55.30	54.74	55.27	55.21	55.34	55.31
C-8	17.69	16.97	17.73	17.81	17.61	17.68
C-1'	140.50	139.53	140.51	140.49	141.30	141.32
	J 3.41	J 2.86	J 3.39	J 3.19		
C-2' (6')	129.28	128.64	129.28	129.28	126.91	126.94
	J 8.09	J 8.20	J 8.15	J 8.26		
C-3' (5')	116.39	115.83	116.37	116.34	130.41	130.39
	J 21.67	J 21.65	J 21.59	J 21.44		
C-4'	163.60	163.25	163.69	163.66	139.14	139.05
	J 247.8	J 246.1	J 246.1	J 247.5		
C-1'''	64.75	64.11	64.74	64.71	64.68	64.64
C-2'''	22.12	21.57	22.09	22.04	22.18	22.14
C-3'''	35.80	35.15	35.69	35.43	35.84	35.82
C = O	198.54	198.38	199.71	198.63	198.83	198.53
C-1''	134.42	136.19	135.36	131.51	136.39	134.43
	J 2.94					J 3.01
C-2'' (6'')	132.08	130.30	129.28	130.67	130.02	132.07
	J 8.55					J 9.42
C-3'' (5'')	116.70	132.52	130.42	114.95	130.83	116.68
	J 22.13					J 22.15
C-4''	116.93	128.82	145.65	165.26	140.72	167.16
	J 247.7					J 253.3
R^1					21.06	21.08
R^2			21.71	56.2		

Compound	13	14	15	16	17
C-2	67.47	68.18	68.18	68.38	68.24
C-3	72.02	72.96	72.96	72.78	72.83
C-4	31.68	32.65	32.62	32.66	32.69
C-5	20.15	21.09	21.07	21.06	21.04
C-6 (7)	54.49	55.30	55.33	55.35	55.31
C-8	16.68	17.72	17.81	17.58	17.68
C-1'	140.41	141.33	141.31	136.26	136.28
C-2' (6')	126.01	126.94	126.93	128.29	128.32
C-3' (5')	130.00	130.40	130.40	115.06	115.06
C-4'	138.33	139.04	139.08	160.86	160.75
C-1'''	63.81	64.70	64.78	64.64	64.64
C-2'''	21.32	22.13	22.15	22.23	22.18
C-3'''	34.86	35.70	35.41	35.83	35.81
C = O	198.10	199.74	198.72	198.82	198.54
C-1''	135.89	135.38	131.53	136.35	134.42
					J 3.05
C-2'' (6'')	129.54	129.29	130.75	129.87	132.06
					J 9.57
C-3'' (5'')	132.23	130.40	114.97	130.83	116.68
					J 22.10
C-4''	128.53	145.64	165.38	140.71	167.20
					J 253.5
R^1	20.15	21.09	21.07	55.83	55.87
R^2		21.71	56.17		

Table 2 (continued)

Compound	18	19	20	21	22
C-2	67.87	68.30	68.30	65.61	65.60
C-3	72.17	72.80	72.80	71.20	71.17
C-4	32.03	32.69	32.66	31.13	31.06
C-5	20.48	21.03	21.03	20.29	20.34
C-6 (7)	54.79	55.31	55.30	53.45	53.30
C-8	16.98	17.71	17.80	19.44	19.40
C-1'	136.20	136.29	136.28	142.73	142.66
C-2' (6')	127.68	128.32	128.31	128.06	127.96
C-3' (5')	114.51	115.07	115.07	128.19	128.11
C-4'	160.37	160.82	160.80	132.25	132.27
C-1'''	64.10	65.70	64.75	62.49	62.42
C-2'''	21.67	22.19	22.19	16.35	16.29
C-3'''	35.17	35.68	35.40	34.34	34.61
C = O	198.40	199.73	198.69	196.67	197.84
C-1''	135.66	135.39	131.53	130.17	133.73
C-2'' (6'')	130.30	129.29	130.74	129.17	128.40
C-3'' (5'')	132.52	130.43	114.96	113.87	129.21
C-4''	128.82	145.66	165.37	163.13	143.64
R^1		55.86	55.86		
R^2		21.69	56.17	55.60	21.12

The $\Delta\delta C5\text{-}\delta C8$ in compounds **1-22** can be attributed to the steric effect exerted by the aryl group on H8. This steric perturbation of the C-H bond leads to a drift of charge along the bond towards carbon, that causing orbital expansion and hence increase shielding.

The conjugation between the carbonyl and the aryl group in **1-22** is confirmed by δ C aromatic values.

By comparing the δ C values of compounds **1-22** with that of the corresponding bases [14], the following facts can be deduced. a) The $\Delta\delta C6(7)$ |**1-22**| - $\delta C6(7)$ |**bases**| $\cong$ 8.5 ppm is attributed to the more electron-attracting effect exerted by the nitrogen atom in the quaternized compounds; b) the $\Delta\delta C2$ |**1-22**| - $\delta C2$ |**bases**| $\cong$ 5.5 ppm is explained in the same way, the difference: 8.5-5.5 $\cong$ 3 ppm is attributed to more electron-deficient character of C2 with respect to C6 and C7 in the corresponding base.

Due to the complexity of the quinuclidine system, is it not possible the assignment of the protons of the quinuclidine system and the trimethylene chain that appear as a complex multiplet about 1.5-4.1 ppm at 80 MHz. Aromatic protons appear as a four spin AA'XX' system except when R^1 and/or R^2 are a fluorine atom (compounds **2,6-10,12** and **17**, Table 1). In the later cases the signals have been considered as a part of the five spin AA'MM'X system formed by the aromatic protons and the fluorine atom. The analysis of the corresponding signals allowed the establishment of the chemical shifts and coupling constants $J_{AX} + J_{AX'} = J_{A'X'} + J_{A'X}$ and $J_{H\text{-}F}$. Taking into account that $J_{AX'} = J_{A'X}$ is a long range ^5J coupling constant and must be very small, the deduced value should be adscribed to $J_{AX'} = J_{A'X'}$, corresponding to JH2'(6')-H3'(5') and JH2''(6'')-H3''(5'') (see Experimental).

Mass Spectra.

There are few data in the literature concerning to the mass spectra of quinuclidine derivatives [15-18] and quinuclidinium compounds [19]. The mass spectra of compounds **9, 11, 12, 14, 15,** and **18-22** were recorded and the main fragmentation patterns are discussed taking into consideration previous data for related compounds [15-19] and cyclic quaternary ammonium salts [20].

The line drawings of compounds **9, 11** and **18** are shown in Figures 1-3 as representative examples. The main frag-

ment ions along with their relative abundances are given in Table 3.

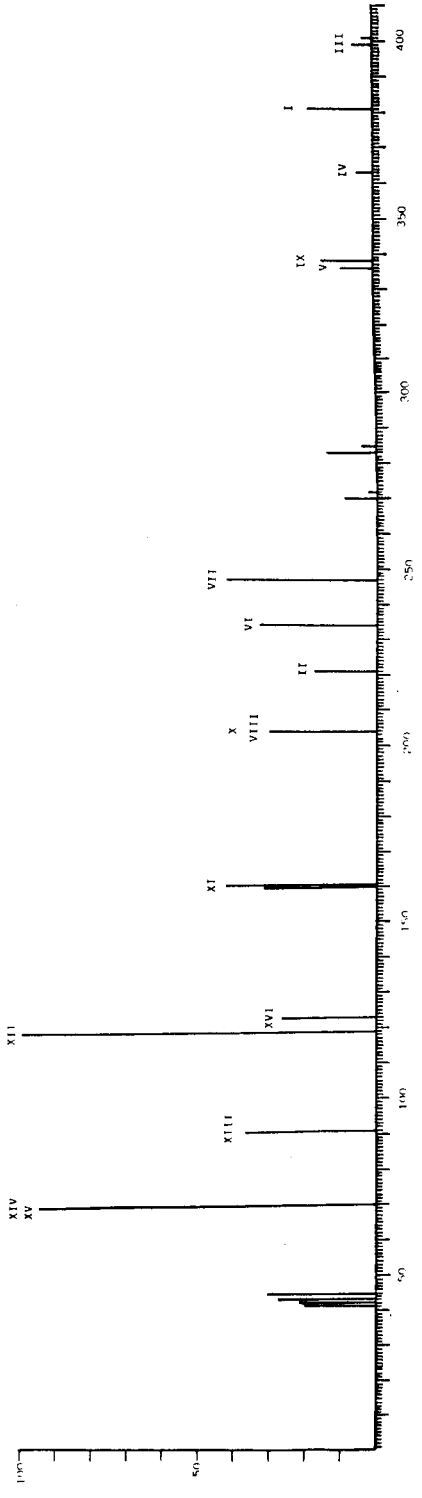


Figure 1. Mass Spectrum of Compound 9.

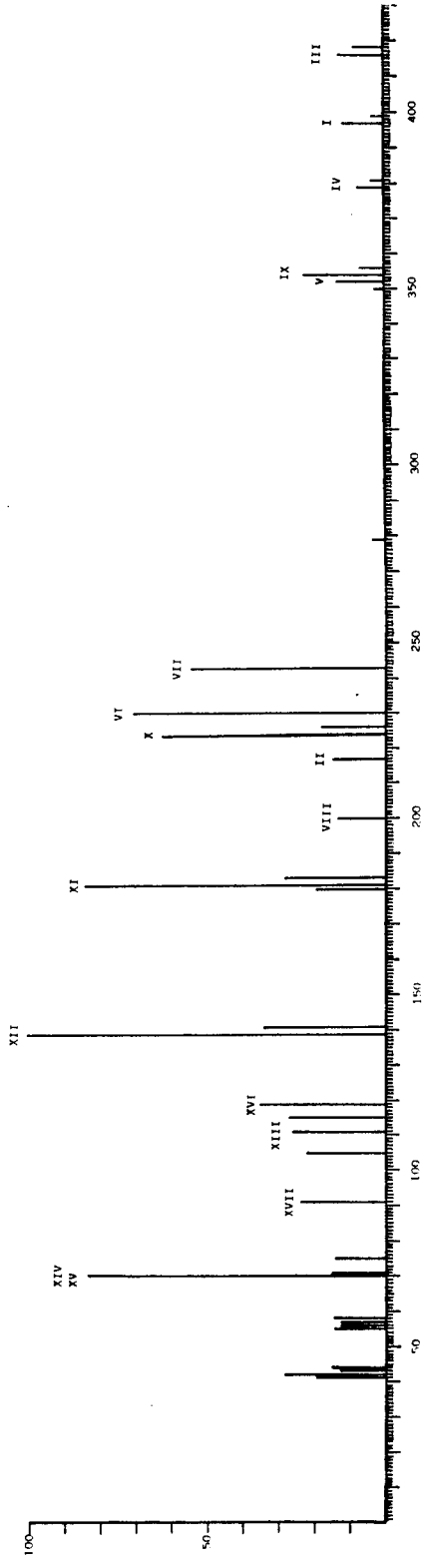


Figure 2. Mass Spectrum of Compound 11.

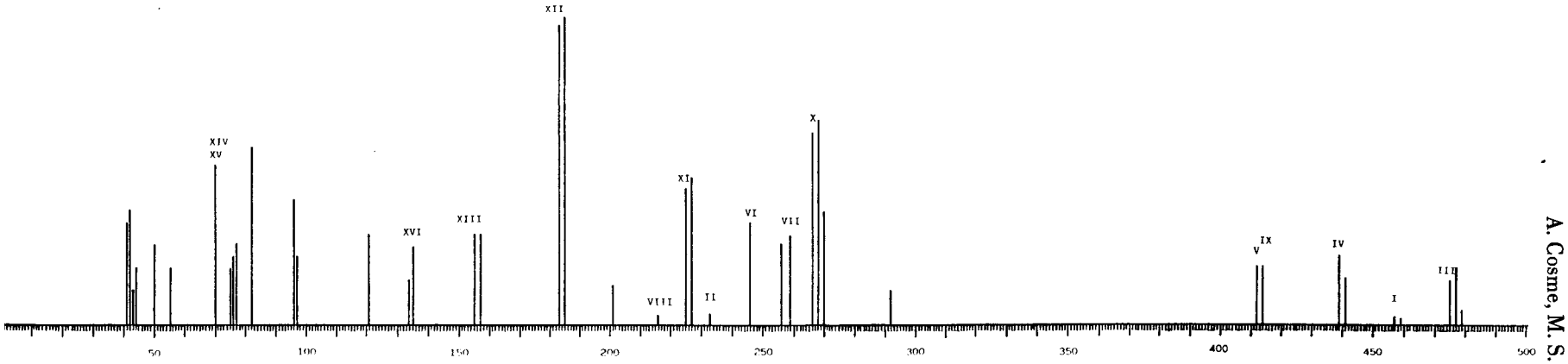


Figure 3. Mass Spectrum of Compound **18**.

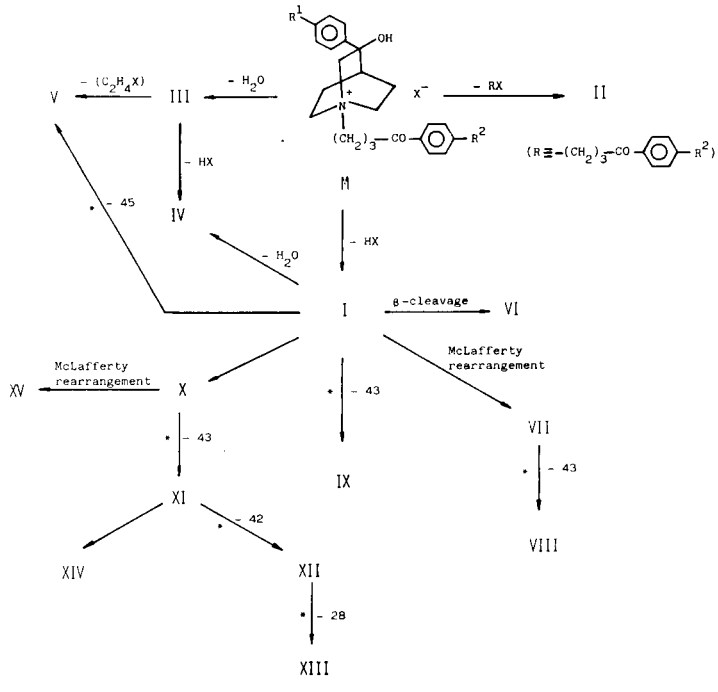
Table 3
Major Fragment Ions Along with t heir Relative Abundances (%) for Compounds **9**, **11**, **12**, **14**, **15** and **18-22**

Compound No.	M	R^1	R^2	X^-	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV XV	XIV	XVII
9	417	F	CH_3	Cl^-	381 (18)	221 (17)	399 (5)	363 (4)	336(9)	234 (32)	247 (42)	204 (23)	338 (15)	204 (23)	161 (42)	119((100)	91 (36)	70 (95)	123 (26)	95 (<1)
11	433	CH_3	Cl	Cl^-	397 (7)	217 (15)	415 (13)	379 (7)	352 (13)	230 (70)	243 (54)	200 (13)	354 (23)	224 (62)	181 (84)	139((100)	111 (26)	70 (84)	119 (35)	91 (24)
12	417	CH_3	F	Cl^-	381 (3)	217 (8)	399 (3)	363 (3)	336 (5)	230 (7)	243 (7)	200 (<1)	338 (11)	208 (8)	165 (13)	123 (100)	95 (20)	70 (57)	119 (6)	91 (6)
14	413	CH_3	CH_3	Cl^-	377 (12)	217 (16)	395 (16)	359 (6)	332 (21)	230 (69)	243 (91)	200 (10)	334 (26)	204 (41)	161 (74)	119 (100)	91 (36)	70 (65)	119 (100)	91 (36)
15	429	CH_3	OCH_3	Cl^-	393 (10)	217 (10)	411(<1)	375 (<1)	348 (2)	230 (16)	243 (27)	200 (10)	350 (4)	220 (8)	177 (25)	135 (100)	-	70 (63)	119 (18)	91 (<1)
18	493	OCH_3	Br	Cl^-	457 (2)	233 (3)	475 (14)	439 (22)	412 (19)	246 (33)	259 (30)	216 (4)	414 (18)	268 (67)	225 (44)	183 (97)	155 (30)	70 (52)	135 (26)	107 (<1)
19	429	OCH_3	CH_3	Cl^-	393 (3)	233 (10)	411 (15)	375 (3)	348 (16)	246 (11)	259 (17)	217 (11)	350 (4)	204 (21)	161 (80)	119 (100)	91 (43)	70 (74)	135 (18)	107 (<1)
20	445	OCH_3	OCH_3	Cl^-	409 (9)	233 (14)	427 (<1)	391 (<1)	364 (1)	246 (13)	259 (31)	216 (2)	366 (3)	220 (8)	177 (26)	135 (100)	107 (10)	70 (51)	135 (100)	107 (10)
21	541	Cl	OCH_3	I^-	413 (13)	237 (9)	523 (3)	395 (6)	368 (6)	250 (24)	263 (34)	220 (21)	370 (6)	220 (21)	177 (41)	135 (100)	107 (9)	70 (59)	139 (18)	111 (<1)
22 [a]	525	Cl	CH_3	I^-	396 (1)	237 (<<1)	507 (14)	378 (13)	352 (13)	250 (7)	263 (8)	220 (2)	354 (6)	204 (5)	161 (23)	119 (100)	91 (14)	70 (18)	139 (5)	111 (<1)

[a] In this case H_2I is lost.

All the spectra exhibit a common configuration suggesting the same essential fragmentation patterns for the studied compounds (Scheme I). In some cases, the corresponding metaestable peaks (indicated by * in the fragmentation schemes) confer validity to the proposed fragmentation pathways. The $M^{+\cdot}$ peak is practically absent, only traces have been detected in some espectra.

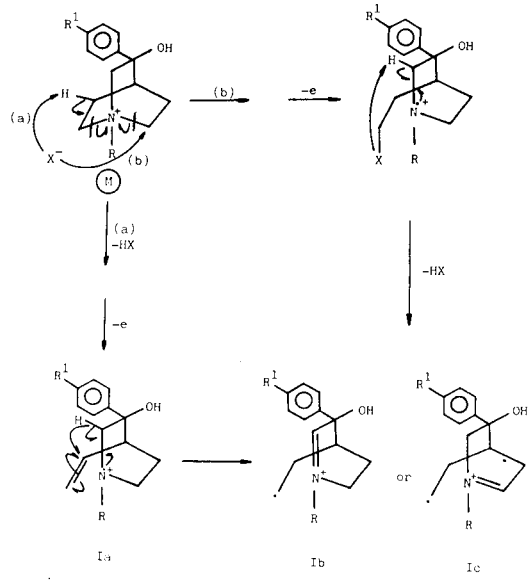
Scheme I



The study of the spectra points out the possibility of three pyrolitic reactions that lead to the conversion of the ammonium salts **9**, **11**, **12**, **14**, **15**, and **18-22** into non saline compounds which can be volatilized for their later ionization: 1) nucleophilic addition of the halide anion with opening of a ring and introduction of the halide anion in the molecule throughout a covalent bond; 2) direct loss of HX as a neutral molecule by a Hofmann elimination; 3) reaction of the halide anion with the *N*-(4′-aryloxobutyl) radical (R) and loss of the neutral molecule RX. These facts are in agreement with the previous studies of Hesse and coworkers [20] on cyclic quaternary ammonium salts.

The $[M - HX]^{+\cdot}$ fragment ion was detected in all the spectra. As it has been previously indicated, its formation can be explained through a Hofmann-like degradation [20-22] by HX loss which leads to a tertiary amine with an additional double bond (*via* (a), Scheme II). Its posterior vaporization and ionization gives rise to the fragment **Ia**. On the other hand, the covalent compound formed by introduction of the halide anion, volatilized and ionized, can also undergo HX elimination [20] originating the $[M - HX]^{+\cdot}$ ion for which the structures **Ia**, **Ib** and **Ic** are possible (*via* (b), Scheme II).

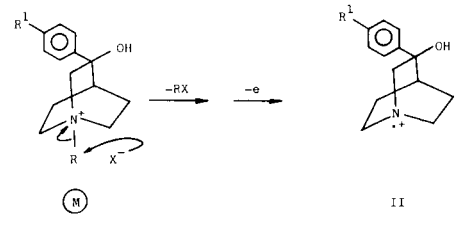
Scheme II



The $[M - HX]^{+\cdot}$ ion has been considered as the origin of important fragmentations (Scheme I) and the different structures proposed for this fragment allow their interpretation. Moreover, their interconversion can be easily rationalized, as it is indicated in Scheme II for the transformation of **Ia** into **Ib**.

The $[M - RX]^{+\cdot}$ fragment, **II**, is originated from the ammonium salt by nucleophilic attack of the halide anion upon the *N*-(4′-aryloxobutyl) radical and simple heterolitic excision [20-22], as is shown in Scheme III.

Scheme III

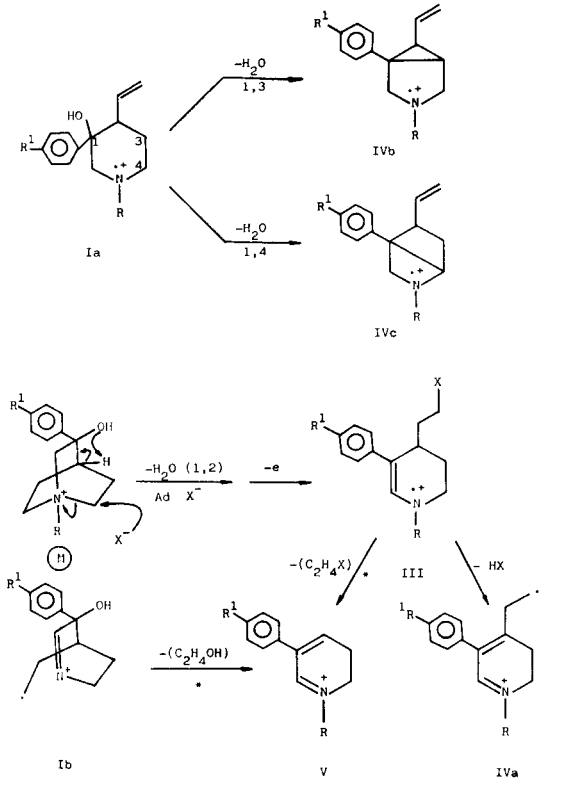


Moreover, the dehydration is other process that must be considered due to the presence of the hydroxyl group. The $[M - H_2O]^{+\cdot}$ and $[M - H_2O - HX]^{+\cdot}$ fragments observed in the spectra, make evident the water loss. Two patterns of dehydration are possible for these compounds: 1) a pyrolitic dehydration, simultaneously with the introduction of the halide anion on the molecule or the other pyrolitic reactions mentioned above; 2) dehydration of a positive ion in gaseous state once a neutral molecule was formed.

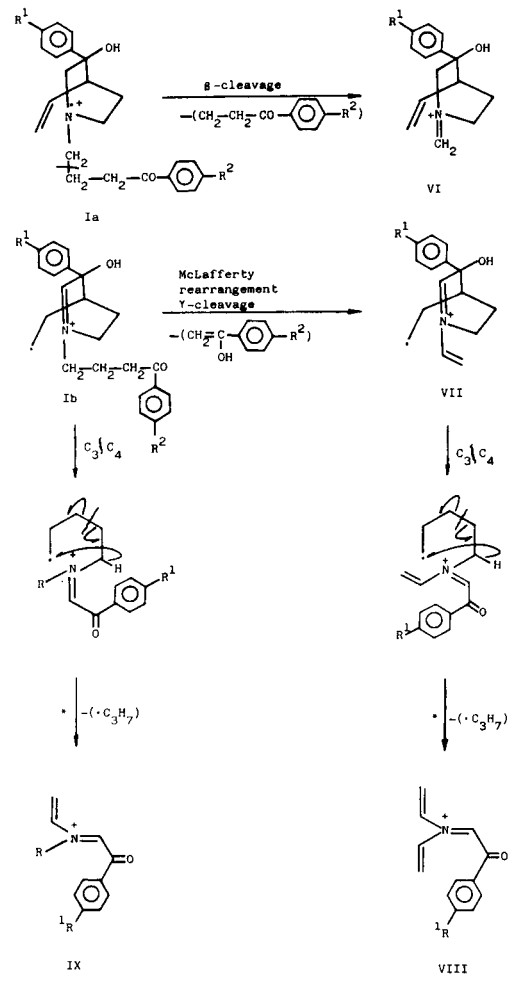
In the Scheme IV are shown the more probable mechanisms for water loss. From the quaternary ammonium salt (*M*), a pyrolitic process in which the 1, 2 water loss and nucleophilic addition of the halide anion take place simultaneously to achieve fragment **III**, has been proposed.

The losing of HX from **III** gives rise to $[M - H_2O - HX]^{+\cdot}$ fragment which can be also originated by 1,3 or 1,4 water elimination from $|M - HX|^{+\cdot}$ ion (formulated from the fragment **Ia**). Different structures are possible for $|M - H_2O - HX|^{+\cdot}$ fragment, represented in Scheme IV by **IVa, IVb** and **IVc**.

Scheme IV



Scheme V



Fragment **V** is originated from **III** by losing of (C_2H_4X), verified by a metaestable peak. Alternatively, other metaestable peak which would be associated to the loss from **I** of a fragment of 45 mass units, also would lead to **V**. This pathway seems to be more difficult to explain. Molecular rearrangement of hydroxyl group followed by loss of the $[\cdot C_2H_4OH]$ radical would be a hypothetical rationalization.

As it has been mentioned previously, important fragments are originated from $[M - HX]^{+\cdot}$ ion, **I**. Thus, the formation of fragments **VI** and **VII** can be easily rationalized from **I** by β-cleavage of **Ia** and γ-cleavage through a McLafferty rearrangement of **Ib** as is shown in Scheme V.

The decomposition of **VII** to **VIII** suppose the loss of a neutral radical with m/e = 43 which is confirmed by the corresponding metaestable peak observed in the spectra of the compounds **9, 11, 14, 15, 20,** and **21**. This is a complex fragmentation that would be explained by cleavage of the C_3-C_4 bond, followed by molecular rearrangement and concomitant cleavage as is represented in Scheme V. A similar fragmentation path of **Ib** (also demonstrated by the metaestable peak observed in the spectra of the same compounds indicated above) would also justify the formation of the fragment **IX** (Scheme V).

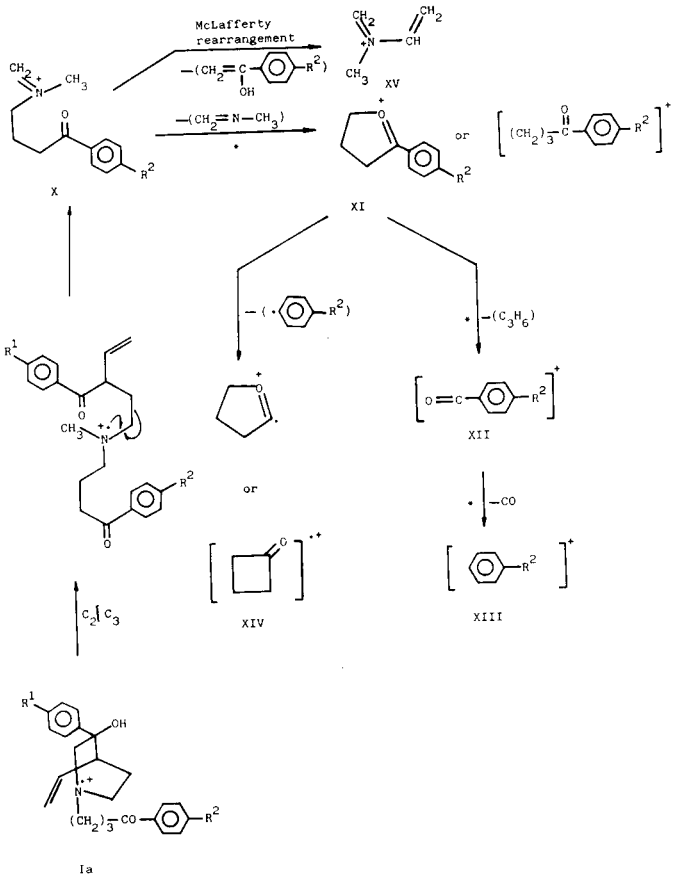
There is a fragmentation sequence from fragment **X** that gives rise to **XIII** through two ions **XI** and **XII** (Scheme I) and it is evidenced by the corresponding metaestable peaks. The structure of the fragment **XIII** results evident and, therefore, the structures of **XII** and **XI** can be also assigned (Scheme VI).

On this basis, a probable structure for the fragment **X** has been proposed which allow the rationalization of the fragmentation pathways leading to **XI, XII** and **XIII** (Scheme VI).

The fragment **XII** corresponds to the peak with the great abundance (base peak in all the cases except for compound **18**, Table 3). This fact can be associated to its great stability [21,22] and its easy formation by a simple excision.

The ion m/e = 70 is present in the spectra with high abundance (Table 3) and it can be originated from ions **X**

Scheme VI

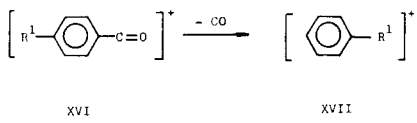


and **XI**. In Scheme VI are represented the respective fragmentations and the probable structures for this ion, **XIV** and **XV**.

Bearing in mind the structure of fragment **X**, there are multiple possibilities for its formation. It must be originated from fragments with a piperidine ring. A probable pathway from **Ia** is represented in Scheme VI.

Fragments **XVI** and **XVII** (Scheme VII) are also detected in practically all the spectra. The formation of **XVI** would take place in the molecular rearrangements with opening of a piperidine ring with hydrogen transfer, as for example from **VII**.

Scheme VII



From the fragmentation study of compounds **9**, **11**, **12**, **14**, **15**, and **18-22**, it can be concluded that all the quaternary ammonium salts present a similar behaviour, with the same essential fragmentation pathway. The presence of the $[M - HX]^+$ fragment in all the spectra confirms the attachment of the halide anion to the cyclic system through a C-X covalent bond and formation of a tertiary amine [20].

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were recorded on potassium bromide pellet on a Perkin-Elmer 883 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded on a Varian FT-80A (PFT) spectrometer at 303° K with TMS as the internal standard. The ^1H nmr spectra of *ca.* 6% w/v dimethyl sulfoxide-d_6 solutions were obtained at 80 MHz using sweep widths of 800 Hz and acquisition times of 2.047 s. over 50 transients. At these conditions, the quinuclidine proton signals and methylene protons of the aryloxoalkyl group appeared as complex multiplets in the range of *ca.* 1.5-4.1 ppm and could not be assigned.

The ^{13}C nmr spectra were recorded at 20 MHz using *ca.* 14% w/v Methanol-OD solutions. The spectral parameters included spectral width of 5000 Hz, acquisition time of 1.638 s., delay time of 1.64 s. and pulse width of 5 μs. Proton noise-decoupled and off-resonance decoupled spectra were obtained. The elemental analysis were performed in a Perkin-Elmer 240 B elemental analyzer.

The mass spectra were recorded in a Hitachi Perkin-Elmer RMU 6M spectrometer by E.I. All spectra were determined at 70 eV., 180° using a filament current of 3 A. Peaks whose intensities were less than 5% of the base peak were disregarded unless they appeared to have special significance. When chlorine and bromine are present the conventional molecular mass adopted corresponds to the isotopes 35 and 79 respectively.

Synthesis of Compounds. General Procedure.

To a solution of the corresponding 3-aryl-3-quinuclidinol (1.5 mmoles) [14] in anhydrous dimethylformamide (7 ml) was added a solution of the suitable 4-aryloxoalkyl chloride (1.5 mmoles) [23,24] in dimethylformamide (1 ml). The mixture was stirred at room temperature for 10 days. Then diethyl ether was added (20 ml) and the precipitated solid was filtered and recrystallized.

For the compounds **21** and **22** the reaction was carried out in the presence of potassium iodide (2.175 mmoles).

3-*p*-Chlorophenyl-3-hydroxy-*N*-(4'-*p*-chlorophenyl-4'-oxobutyl)quinuclidinium Chloride (**1**).

This compound was obtained in 73% yield, mp 234-236° (isopropyl alcohol-ethanol); ir: ν OH 3194, ν CO 1690 cm^{-1}; pmr: δ 7.96 (m, 2H, 2"- and 6"-H, J = 8.46 Hz), 7.63 (m, 2H, 3'- and 5'-H, J = 8.61 Hz), 7.57 (m, 2H, 3"- and 5"-H, J = 8.46 Hz), 7.42 (m, 2H, 2'- and 6'-H, J = 8.61 Hz), 6.32 ppm (s, 1H, OH); cmr: (see Table 2).

Anal. Calcd. for $C_{23}H_{26}Cl_3NO_2$: C, 60.72; H, 5.76; N, 3.08. Found: C, 60.58; H, 6.01; N, 2.98.

3-*p*-Chlorophenyl-3-hydroxy-*N*-(4'-*p*-fluorophenyl-4'-oxobutyl)quinuclidinium Chloride (**2**).

This compound was obtained in 72% yield, mp 187-189° (isopropyl alcohol); ir: ν OH 3219, ν CO 1686 cm^{-1}; pmr: δ 8.04 (m, 2H, 2"- and 6"-H, J = 9.12, J_{HF} = 5.14 Hz), 7.66 (m, 2H, 3'- and 5'-H, J = 8.90 Hz), 7.42 (m, 2H, 2'- and 6'-H, J = 8.90 Hz), 7.34 (m, 2H, 3"- and 5"-H, J = 9.12, J_{HF} = 9.24 Hz), 6.40 ppm (s, 1H, OH); cmr: (see Table 2).

Anal. Calcd. for $C_{23}H_{26}Cl_2FNO_2$: C, 63.01; H, 5.98; N, 3.19.

Found: C, 62.78; H, 6.26; N, 3.09.

3-*p*-Chlorophenyl-3-hydroxy-*N*-(4′-*p*-bromophenyl-4′-oxobutyl)-quinuclidinium Chloride (**3**).

This compound was obtained in 53% yield, mp 261-263° (isopropyl alcohol-ethanol); ir: ν OH 3105, ν CO 1690 cm^{-1}; pmr: δ 7.88 (m, 2H, 2″- and 6″-H, J = 8.59 Hz), 7.73 (m, 2H, 3″- and 5″-H, J = 8.59 Hz), 7.62 (m, 2H, 3′- and 5′-H, J = 8.90 Hz), 7.42 (m, 2H, 2′- and 6′-H, J = 8.90 Hz), 6.28 ppm (s, 1H, OH); cmr: (see Table 2).

Anal. Calcd. for $C_{23}H_{26}BrCl_2NO_2$: C, 55.32; H, 5.25; N, 2.80. Found: C, 55.03; H, 5.04; N, 2.74.

3-*p*-Chlorophenyl-3-hydroxy-*N*-(4′-*p*-methylphenyl-4′-oxobutyl)-quinuclidinium Chloride (**4**).

This compound was obtained in 48% yield, mp 212-214° (isopropyl alcohol); ir: ν OH 3100, ν CO 1680 cm^{-1}; pmr: δ 7.86 (m, 2H, 2″- and 6″-H, J = 8.12 Hz), 7.65 (m, 2H, 3′- and 5′-H, J = 8.67 Hz), 7.42 (m, 2H, 2′- and 6′-H, J = 8.67 Hz), 7.31 (m, 2H, 3″-and 5″-H, J = 8.12 Hz), 6.40 (s, 1H, OH), 2.37 ppm (s, 3H, CH_3); cmr: (see Table 2).

Anal. Calcd. for $C_{24}H_{29}Cl_2NO_2$: C, 66.35; H, 6.72; N, 3.22. Found: C, 66.41; H, 6.91; N, 3.27.

3-*p*-Chlorophenyl-3-hydroxy-*N*-(4′-*p*-methoxyphenyl-4′-oxobutyl)-quinuclidinium Chloride (**5**).

This compound was obtained in 69% yield, mp 206-208° (isopropyl alcohol); ir: ν OH 3171, ν CO 1680 cm^{-1}; pmr: δ 7.93 (m, 2H, 2″- and 6″-H, J = 8.85 Hz), 7.60 (m, 2H, 3′- and 5′-H, J = 8.82 Hz), 7.44 (m, 2H, 2′- and 6′-H, J = 8.82 Hz), 7.02 (m, 2H, 3″- and 5″-H, J = 8.85 Hz), 6.20 (s, 1H, OH), 3.83 ppm (s, 3H, $-OCH_3$); cmr: (see Table 2).

Anal. Calcd. for $C_{24}H_{29}Cl_2NO_3$: C, 63.99; H, 6.50; N, 3.11. Found: C, 63.58; H, 6.81; N, 3.09.

3-*p*-Fluorophenyl-3-hydroxy-*N*-(4′-*p*-chlorophenyl-4′-oxobutyl)quinuclidinium Chloride (**6**).

This compound was obtained in 64% yield, mp 246-248° (isopropyl alcohol); ir: ν OH 3112, ν CO 1690 cm^{-1}; pmr: δ 7.97 (m, 2H, 2″- and 6″-H, J = 8.53 Hz), 7.67 (m, 2H, 2′- and 6′-H, J = 8.71, J_{HF} = 5.25 Hz), 7.58 (m, 2H, 3″- and 5″-H, J = 8.53 Hz), 7.19 (m, 2H, 3′- and 5′-H, J = 8.71, J_{HF} = 9.09 Hz), 6.43 ppm (s, 1H, OH); cmr: (see Table 2).

Anal. Calcd. for $C_{23}H_{26}Cl_2FNO_2$: C, 63.01; H, 5.98; N, 3.19. Found: C, 62.75; H, 6.32; N, 3.09.

3-*p*-Fluorophenyl-3-hydroxy-*N*-(4′-*p*-fluorophenyl-4′-oxobutyl)quinuclidinium Chloride (**7**).

This compound was obtained in 81% yield, mp 222-224° (isopropyl alcohol); ir: ν OH 3168, ν CO 1680 cm^{-1}; pmr: δ 8.04 (m, 2H, 2″- and 6″-H, J = 8.75, J_{HF} = 5.64 Hz), 7.68 (m, 2H, 2′- and 6′-H, J = 8.70 J_{HF} = 5.48 Hz), 7.34 (m, 2H, 3″- and 5″-H, J = 8.75, J_{HF} = 8.87 Hz), 7.19 (m, 2H, 3′- and 5′-H, J = 8.70, J_{HF} = 8.88 Hz), 6.35 ppm (s, 1H, OH); cmr: (see Table 2).

Anal. Calcd. for $C_{23}H_{26}ClF_2NO_2$: C, 65.47; H, 6.21; N, 3.32. Found: C, 65.07; H, 6.47; N, 3.10.

3-*p*-Fluorophenyl-3-hydroxy-*N*-(4′-*p*-bromophenyl-4′-oxobutyl)quinuclidinium Chloride (**8**).

This compound was obtained in 42% yield, mp 260-262° (isopropyl alcohol-ethanol); ir: ν OH 3121, ν CO 1691 cm^{-1}; pmr: δ 7.88 (m, 2H, 2″- and 6″-H, J = 8.54 Hz), 7.73 (m, 2H, 3″- and 5″-H, J = 8.54 Hz), 7.64 (m, 2H, 2′- and 6′-H, J = 8.63, J_{HF} = 5.48 Hz), 7.19 (m, 2H, 3′- and 5′-H, J = 8.74, J_{HF} = 9.06 Hz), 6.22 ppm (s, 1H, OH); cmr: (see Table 2).

Anal. Calcd. for $C_{23}H_{26}BrClFNO_2$: C, 57.21; H, 5.43; N, 2.90. Found: C, 57.04; H, 5.62; N, 2.72.

3-*p*-Fluorophenyl-3-hydroxy-*N*-(4′-*p*-methylphenyl-4′-oxobutyl)-quinuclidinium Chloride (**9**).

This compound was obtained in 55% yield, mp 213-215° (isopropyl alcohol); ir: ν OH 3187, ν CO 1681 cm^{-1}; pmr: δ 7.86 (m, 2H, 2″- and 6″-H, J = 8.06 Hz), 7.67 (m, 2H, 2′- and 6′-H, J = 8.83, J_{HF} = 5.55 Hz), 7.31 (m, 2H, 3″- and 5″-H, J = 8.06 Hz), 7.20 (m, 2H, 3′- and 5′-H, J = 8.83, J_{HF} = 8.93 Hz), 6.35 (s, 1H, OH), 2.37 ppm (s, 3H, CH_3); cmr: (see Table 2); ms: (see Figure 1).

Anal. Calcd. for $C_{24}H_{29}ClFNO_2$: C, 68.96; H, 6.99; N, 3.35. Found: C, 68.86; H, 6.84; N, 3.19.

3-*p*-Fluorophenyl-3-hydroxy-*N*-(4′-*p*-methoxyphenyl-4′-oxobutyl)-quinuclidinium Chloride (**10**).

This compound was obtained in 76% yield, mp 205-207° (isopropyl alcohol); ir: ν OH 3272, ν CO 1681 cm^{-1}; pmr; δ 7.94 (m, 2H, 2″- and 6″-H, J = 8.54 Hz), 7.68 (m, 2H, 2′- and 6′-H, J = 8.62, J_{HF} = 5.54 Hz), 7.19 (m, 2H, 3′- and 5′-H, J = 8.62, J_{HF} = 8.71 Hz), 7.03 (m, 2H, 3″- and 5″-H, J = 8.74 Hz), 6.36 (s, 1H, OH), 3.83 ppm (s, 3H, $-OCH_3$); cmr: (see Table 2).

Anal. Calcd. for $C_{24}H_{29}ClFNO_3$: C, 66.42; H, 6.73; N, 3.22. Found: C, 66.45; H, 6.83; N, 3.20.

3-*p*-Methylphenyl-3-hydroxy-*N*-(4′-*p*-chlorophenyl-4′-oxobutyl)-quinuclidinium Chloride (**11**).

This compound was obtained in 68% yield, mp 242-244° (isopropyl alcohol); ir: ν OH 3103, ν CO 1690 cm^{-1}; pmr: δ 7.97 (m, 2H, 2″- and 6″-H, J = 8.51 Hz), 7.58 (m, 2H, 3″- and 5″-H, J = 8.51 Hz), 7.47 (m, 2H, 2′- and 6′-H, J = 7.66 Hz), 7.17 (m, 2H, 3′-and 5′-H, J = 7.66 Hz), 6.13 (s, 1H, OH), 2.30 ppm (s, 3H, CH_3); cmr: (see Table 2); ms: (see Figure 2).

Anal. Calcd. for $C_{24}H_{29}Cl_2NO_2$: C, 66.35; H, 6.73; N, 3.22. Found: C, 65.99; H, 7.01; N, 3.29.

3-*p*-Methylphenyl-3-hydroxy-*N*-(4′-*p*-fluorophenyl-4′-oxobutyl)quinuclidinium Chloride (**12**).

This compound was obtained in 69% yield, mp 208-210° (isopropyl alcohol); ir: ν OH 3195, ν CO 1680 cm^{-1}; pmr: δ 8.04 (m, 2H, 2″- and 6″-H, J = 8.87, J_{HF} = 5.66 Hz), 7.49 (m, 2H, 2′- and 6′-H, J = 8.37 Hz), 7.34 (m, 2H, 3″- and 5″-H, J = 8.87 Hz, J_{HF} = 9.09 Hz), 7.17 (m, 2H, 3′- and 5′-H, J = 8.37 Hz), 6.19 (s, 1H, OH), 2.30 ppm (s, 3H, CH_3); cmr (see Table 2); ms: (m/e) 401 (< 1), 399 (3), 381 (3), 363 (3), 338 (11), 336 (5), 243 (7), 230 (7), 217 (8), 208 (8), 200 (< 1), 165 (13), 164 (16), 163 (9), 124 (5), 123 (100), 119 (6), 95 (20), 91 (6), 75 (6), 71 (8), 70 (57), 69 (5), 58 (5), 55 (5), 43 (6), 42 (8), 41 (8).

Anal. Calcd. for $C_{24}H_{29}ClFNO_2$: C, 68.96; H, 6.99; N, 3.35. Found: C, 68.86; H, 7.04; N, 3.19.

3-*p*-Methylphenyl-3-hydroxy-*N*-(4′-*p*-bromophenyl-4′-oxobutyl)-quinuclidinium Chloride (**13**).

This compound was obtained in 60% yield, mp 254-256° (isopropyl alcohol-ethanol); ir: ν OH 3100, ν CO 1685 cm^{-1}; pmr: δ 7.88 (m, 2H, 2″- and 6″-H, J = 8.71 Hz), 7.73 (m, 2H, 3″- and 5″-H, J = 8.71 Hz), 7.45 (m, 2H, 2′- and 6′-H, J = 8.17 Hz), 7.18 (m, 2H, 3′- and 5′-H, J = 8.17 Hz), 6.02 (s, 1H, OH), 2.30 ppm (s, 3H, CH_3); cmr: (see Table 2).

Anal. Calcd. for $C_{24}H_{29}BrClNO_2$: C, 60.19; H, 6.10; N, 2.92. Found: C, 60.46; H, 6.35; N, 3.12.

3-*p*-Methylphenyl-3-hydroxy-*N*-(4′-*p*-methylphenyl-4′-oxobutyl)-quinuclidinium Chloride (**14**).

This compound was obtained in 66% yield, mp 218-210° (isopropyl alcohol); ir: ν OH 3110, ν CO 1680 cm^{-1}; pmr: δ 7.86 (m, 2H, 2″- and 6″-H, J = 8.19 Hz), 7.49 (m, 2H, 2′- and 6′-H, J = 8.18 Hz), 7.31 (m, 2H, 3″- and 5″-H, J = 8.19 Hz), 7.17 (m, 2H, 3′-and 5′-H, J = 8.18 Hz), 6.20 (s, 1H, OH), 2.37 (s, 3H, CH_3), 2.29 ppm (s, 3H, CH_3); cmr: (see Table 2); ms: (m/e) 397 (6), 395 (16), 377 (12), 359 (6), 334 (26), 332 (21), 330 (7), 279 (7), 266 (6), 244 (14), 243 (91), 231 (7), 230 (69), 217 (16), 204 (41), 202 (14), 200 (10), 162 (17), 161 (74), 128 (13), 120 (14), 119 (100), 115 (12), 105 (12), 96 (12), 91 (36), 71 (14), 70 (65), 65 (16), 64 (9), 58 (20), 57 (12), 56 (8), 55 (23), 44 (13), 43 (16), 42 (13), 41 (13), 38 (93), 36 (21).

Anal. Calcd. for $C_{25}H_{32}ClNO_2$: C, 72.53; H, 7.79; N, 3.38. Found: C, 72.57; H, 7.96; N, 3.42.

3-*p*-Methylphenyl-3-hydroxy-*N*-(4′-*p*-methoxyphenyl-4′-oxobutyl)-quinuclidinium Chloride (**15**).

This compound was obtained in 69% yield, mp 209-211° (isopropyl alcohol); ir: ν OH 3200, ν CO 1675 cm^{-1}; pmr; δ 7.94 (m, 2H, 2″- and 6″-H, J = 8.78 Hz), 7.48 (m, 2H, 2′- and 6′-H, J = 8.18 Hz), 7.17 (m, 2H, 3′- and 5′-H, J = 8.18 Hz), 7.03 (m, 2H, 3″-and 5″-H, J = 8.78 Hz), 6.17 (s, 1H, OH), 3.83 (s, 3H, -OCH_3), 2.29 ppm (s, 3H, CH_3); cmr: (see Table 2); ms: (m/e) 411 (< 1), 393 (10), 375 (< 1), 350 (4), 348 (2), 243 (27), 230 (16), 220 (8), 217 (10), 200 (10), 177 (25), 176 (36), 175 (28), 135 (100), 119 (18), 77 (13), 71 (14), 70 (63), 45 (13), 41 (16).

Anal. Calcd. for $C_{25}H_{32}ClNO_3$: C, 69.83; H, 7.50 N, 3.25. Found: C, 69.91; H, 7.14; N, 3.22.

3-*p*-Methoxyphenyl-3-hydroxy-*N*-(4′-*p*-chlorophenyl-4′-oxobutyl)-quinuclidinium Chloride (**16**).

This compound was obtained in 65% yield, mp 220-222° (isopropyl alcohol-ethanol); ir: ν OH 3095, ν CO 1695 cm^{-1}; pmr: δ 7.97 (m, 2H, 2″- and 6″-H, J = 8.57 Hz), 7.58 (m, 2H, 3″- and 5″-H, J = 8.57 Hz), 7.52 (m, 2H, 2′- and 6′-H, J = 8.78 Hz), 6.91 (m, 2H, 3′- and 5′-H, J = 8.78 Hz), 6.12 (s, 1H, OH), 3.75 ppm (s, 3H, -OCH_3); cmr: (see Table 2).

Anal. Calcd. for $C_{24}H_{29}Cl_2NO_3$: C, 63.99; H, 6.49; N, 3.11. Found: C, 63.62; H, 6.76; N, 3.11.

3-*p*-Methoxyphenyl-3-hydroxy-*N*-(4′-*p*-fluorophenyl-4′-oxobutyl)-quinuclidinium Chloride (**17**).

This compound was obtained in 62% yield, mp 177-176° (isopropyl alcohol); ir: ν OH 3100, ν CO 1685 cm^{-1}; pmr; δ 8.05 (m, 2H, 2″- and 6″-H, J = 8.76, J_{HF} = 5.58 Hz), 7.53 (m, 2H, 2′- and 6′-H, J = 8.68 Hz), 7.34 (m, 2H, 3″- and 5″-H, J = 8.76, J_{HF} = 8.82 Hz), 6.92 (m, 2H, 3′- and 5′-H, J = 8.68 Hz), 6.16 (s, 1H, OH), 3.75 ppm (s, 3H, -OCH_3); cmr: (see Table 2).

Anal. Calcd. for $C_{24}H_{29}ClFNO_3$: C, 66.62; H, 6.73; N, 3.22. Found: C, 66,66; H, 7.01; N, 3.07.

3-*p*-Methoxyphenyl-3-hydroxy-*N*-(4′-*p*-bromophenyl-4′-oxobutyl)-quinuclidinium Chloride (**18**).

This compound was obtained in 54% yield, mp 231-233° (isopropyl alcohol-ethanol); ir: ν OH 3103, ν 1691 cm^{-1}; pmr: δ 7.89 (m, 2H, 2″- and 6″-H, J = 8.62 Hz), 7.73 (m, 2H, 3″- and 5″-H, J = 8.62 Hz), 7.50 (m, 2H, 2′- and 6′-H, J = 8.73 Hz), 6.93 (m, 2H, 3′- and 5′-H, J = 8.73 Hz), 6.02 (s, 1H, OH), 3.75 ppm (s, 3H, -OCH_3); cmr (see Table 2); ms: (see Figure 3).

Anal. Calcd. for $C_{24}H_{29}BrClNO_3$: C, 58.25; H, 5.90; N, 2.83. Found: C, 57.92; H, 6.21; N, 2.69.

3-*p*-Methoxyphenyl-3-hydroxy-*N*-(4′-*p*-methylphenyl-4′-oxobutyl)-quinuclidinium Chloride (**19**).

This compound was obtained in 69% yield, mp 208-210° (isopropyl alcohol); ir: ν OH 3115, ν CO 1683 cm^{-1}; pmr: δ 7.86 (m, 2H, 2″- and 6″-H, J = 8.14 Hz), 7.53 (m, 2H, 2′- and 6′-H, J = 8.74 Hz), 7.31 (m, 2H, 3″- and 5″-H, J = 8.14 Hz), 6.92 (m, 2H, 3′-and 5′-H, J = 8.74 Hz), 6.16 (s, 1H, OH), 3.74 (s, 3H, -OCH_3), 2.37 ppm (s, 3H, CH_3); cmr: (see Table 2); ms: (m/e) 413 (5), 412 (4), 411 (15), 393 (3), 375 (3), 350 (4), 349 (4), 348 (16), 259 (17), 246 (11), 233 (10), 217 (11), 204 (21), 202 (10), 161 (80), 160 (17), 135 (18), 121 (15), 119 (100), 91 (43), 83 (18), 71 (18), 70 (74), 65 (14), 55 (14), 43 (14), 42 (18), 41 (17).

Anal. Calcd. for $C_{25}H_{32}ClNO_3$: C, 69.82; H, 7.50: N, 3.25. Found: C, 69.53; H, 7.67; N, 2.97.

3-*p*-Methoxyphenyl-3-hydroxy-*N*-(4′-*p*-methoxyphenyl-4′-oxobutyl)quinuclidinium Chloride (**20**).

This compound was obtained in 69% yield, mp 176-178° (isopropyl alcohol); ir: ν OH 3200, ν CO 1680 cm^{-1}; pmr: δ 7.93 (m, 2H, 2″- and 6″-H, J = 8.85 Hz), 7.52 (m, 2H, 2′- and 6′-H, J = 8.79 Hz), 7.03 (m, 2H, 3″- and 5″-H, J = 8.85 Hz), 6.92 (m, 2H, 3′-and 5′-H, J = 8.79 Hz), 6.11 (s, 1H, OH), 3.83 (s, 3H, -CH_3), 3.74 ppm (s, 3H, -OCH_3); cmr: (see Table 2); ms: (m/e) 427 (< 1), 409 (9), 391 (< 1), 366 (3), 364 (1), 259 (31), 246 (13), 233 (14), 220 (8), 177 (26), 176 (38), 175 (29), 136 (11), 135 (100), 107 (10), 92 (12), 77 (18), 71 (12), 70 (51), 55 (8), 50 (7), 45 (8), 43 (8), 42 (8), 41 (9).

Anal. Calcd. for $C_{25}H_{32}ClNO_4$: C, 67.32; H, 7.23; N, 3.14. Found: C, 67.68; H, 7.21; N, 3.34.

3-*p*-Chlorophenyl-3-hydroxy-*N*-(4′-*p*-methoxyphenyl-4′-oxobutyl)-quinuclidinium Iodide (**21**).

This compound was obtained in 43% yield, mp 194-196° (water); ir: ν OH 3250, ν CO 1670 cm^{-1}; pmr: δ 7.94 (m, 2H, 2″-and 6″-H, J = 8.75 Hz), 7.62 (m, 2H, 3′- and 5′-H, J = 8.70 Hz), 7.44 (m, 2H, 2′- and 6′-H, J = 8.70 Hz), 7.03 (m, 2H, 3″- and 5″-H, J = 8.75 Hz), 6.12 (s, 1H, OH), 3.83 ppm (s, 3H, -OCH_3); cmr: (see Table 2); ms: (m/e) 523 (3), 413 (13), 395 (6), 370 (6), 368 (6), 265 (10), 263 (34), 252 (8), 250 (24), 239 (5), 237 (9), 222 (7), 220 (21), 177 (41), 176 (21), 175 (21), 150 (12), 142 (23), 141 (5), 139 (18), 136 (12), 135 (100), 128 (10), 127 (12), 121 (12), 107 (9), 103 (9), 92 (15), 77 (22), 70 (59), 58 (14), 42 (15), 41 (7).

Anal. Calcd. for $C_{24}H_{29}ClINO_3$: C, 53.19; H, 5.39; N, 2.58. Found: C, 52.83; H, 5.53; N, 2.79.

3-*p*-Chlorophenyl-3-hydroxy-*N*-(4′-*p*-methylphenyl-4′-oxobutyl)quinuclidinium Iodide (**22**).

This compound was obtained in 56% yield, mp 204-206° (water); ir: ν OH 3245, ν CO 1670 cm^{-1}; pmr: δ 7.87 (m, 2H, 2″-and 6″-H, J = 8.29 Hz), 7.64 (m, 2H, 3′- and 5′-H, J = 9.07 Hz), 7.44 (m, 2H, 2′- and 6′-H, J = 9.07 Hz), 7.32 (m, 2H, 3″- and 5″-H, J = 8.29 Hz), 6.10 (s, 1H, OH), 2.37 ppm (s, 3H, CH_3); cmr: (see Table 2); ms: (m/e) 509 (5), 508 (5), 507 (14), 396 (< 1), 378 (13), 354 (6), 352 (13), 263 (8), 250 (7), 237 (< < 1), 232 (6), 220 (2), 204 (5), 161 (23), 139 (5), 134 (13), 131 (27), 128 (11), 119 (100), 91 (14), 70 (18), 65 (7).

Anal. Calcd. for $C_{24}H_{29}ClINO_2$: C, 54.81; H, 5.55; N, 2.66. Found: C, 54.67; H, 5.67; N, 2.81.

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