Heterolytic fragmentation of 4-hydroxy-6,6,7,7-tetramethyl-Δ^2-dehydroquinuclidine-2,3-dicarboxylic acid esters

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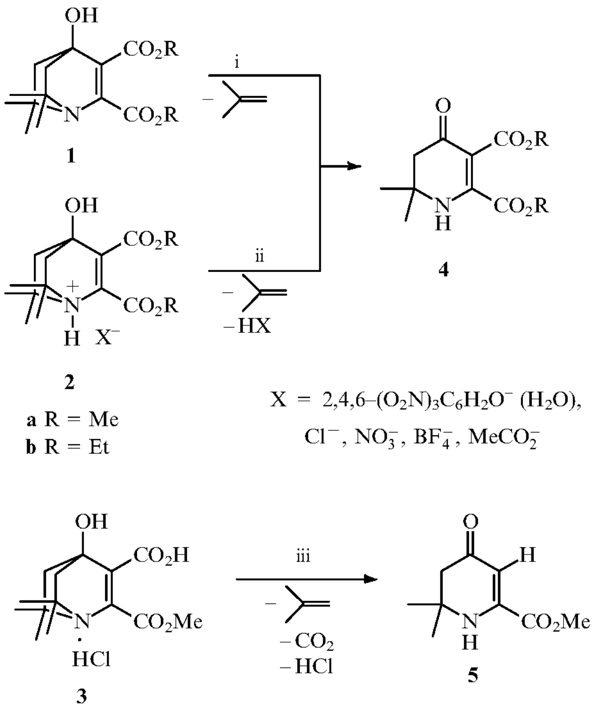
The title quinuclidines undergo cleavage under the action of acids or H_2O to give Δ^2-dehydro-4-piperidones 4, 5 and isobutylene; the resulting redistribution of bond lengths upon N-protonation has been demonstated by X-ray diffraction methods for picrate 2a as well as by *ab initio* calculations for quinuclidine 1a, cation 2a′ and zwitterion 2a″, the latter being the most suitable as an intermediate of the fragmentation.

Acid-catalysed heterolytic fragmentation of quinuclidines **1**–**3**[1] was found to be accompanied by elimination of isobutylene and formation of Δ^2-dehydro-4-piperidones **4** (yields 92–96%) and **5** (yield 84%) (Scheme 1).



Scheme 1 *Reagents and conditions*: i, boiling in H_2O 3 h or cat. **2** in MeOH, Et_2O or $CHCl_3$, boiling 5–10 h; ii, boiling in MeOH, EtOH or $CHCl_3$, 4–5 h; iii, boiling in MeOH, 5 h.

In the case of hydrochlorides **2a,b** the ^{1}H NMR spectra of the reaction mixtures in $CDCl_3$ indicate that isobutylene and *tert*-butyl chloride are formed. It should be noted that the hydrochloride of 2,2,6,6-tetramethylquinuclidine remains unchanged after boiling for 20 h in $CDCl_3$.

Quinuclidine bases **1a,b** remain unchanged after 5–10 h boiling in n-C_6H_{14}, C_6H_6 or PhMe, *i.e.* the fragmentation is initiated by N-protonation. It also occurs smoothly in the presence of catalytic quantities of acids or hydrochlorides **2a,b**. The fragmentation of **3** is accompanied by decarboxylation to monoester **5** (Scheme 1). Δ^2-Dehydro-6,6-dimethyl-4-piperidone, *i.e.* the 2-unsubstituted analogue of **5**, was reported earlier but was obtained by different methods.[2,3]

All starting compounds and products were characterized by spectroscopic methods.† The structures of **1a**[1] and picrate hydrate **2a** were unambiguously determined by the X-ray

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† *Spectroscopic data for*: **1b**, from triacetonamine and diethyl acetylenedicarboxylate in a mixture of Freon-113/CH_2Cl_2 (3 : 1), 2 h at 20 °C, yield 83.5%, mp 119–120 °C (with sublimation). IR, ν/cm^{-1}: 3350 (OH), 1735, 1725 and 1720 (CO), 1627 (C = C). ^{1}H NMR ($CDCl_3$): 1.12 s and 1.57 s (Me_2C); 1.27 t and 1.33 t (*Me*CH_2, ^3J 7.3); 1.73 s (CH_2); 2.70 br.s (HO); 4.26 q and 4.31 q (CH_2O). ^{1}H NMR ([$^2H_5$]pyridine): 1.04 t and 1.13 t (*Me*CH_2, ^3J 7.1), 1.08 s and 1.34 s (Me_2C), 1.83 q (CH_2, AB system, $\Delta\nu$ = 21.2, ^2J −10.7), 4.10 q and 4.25 q (CH_2O). ^{13}C NMR ($CDCl_3$): 14.10 (*Me*CH_2, ^1J 129.3, ^2J 2.9), 33.27 and 34.05 (*Me*$_2$C, ^1J 127.9, ^3J 4.4), 48.53 (CH_2, ^1J 130.8, ^3J 4.4), 60.13 (*C*Me_2), 61.15 and 61.39 (CH_2O, ^1J 148.2, ^2J 4.4), 74.64 (COH, ^2J 5.8), 142.93 (3-C), 144.74 (2-C), 163.31 and 166.39 (CO, ^3J 2.9). Mass spectrum (EI, 70 eV), *m*/*z* (relative intensity, %): 325 (39), 310 (19), 269 (16), 252 (64), 241 (71), 196 (43), 167 (100), 58 (45).

2a [X = 2,4,6-$(NO_3)_3C_6H_2O^-(H_2O)$], from **1b** and picric acid in MeOH, yield 58.2%, mp 95–98 °C ($MeCO_2Et$). ^{1}H NMR ($CDCl_3$): 1.43 s and 2.02 s (Me_2C), 2.06 q (CH_2, AB system, $\Delta\nu$ = 64.0, ^2J −11.9), 3.76 s and 3.90 s (MeO), 8.86 s (C_6H_2). ^{13}C NMR ([$^2H_6$]acetone): 28.86 (*Me*C, ^1J 130.4), 30.74 (*Me*C, ^1J 129.7), 45.63 (CH_2, ^1J 136.6), 52.73 (MeO, ^1J 149.1), 53.96 (MeO, ^1J 149.8), 72.20 (COH, ^2J 4.9), 72.90 (CMe_2), 125.24 (3′-C, ^1J 169.2, ^3J 5.6), 127.81 (4′-C), 128.22 (2′-C), 142.17 (3-C), 147.08 (2-C, ^2J 6.2), 159.26 (3-CO, ^3J 4.2), 160.33 (1′-C, ^3J 6.2), 162.26 (2-CO, ^3J 4.2).

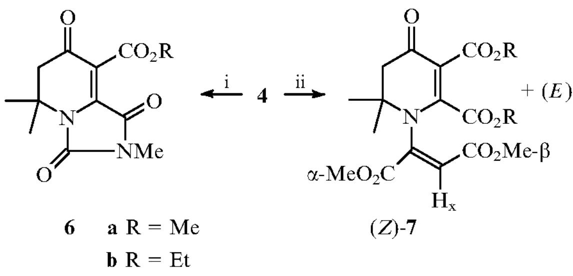
2b (X = Cl^-), mp 127–129 °C (decomp.). ^{1}H NMR ($CDCl_3$): 1.34 t and 1.35 t (*Me*CH_2, ^3J 7.3); 1.47 s and 2.12 s (Me_3C); 2.22 q (CH_2, $\Delta\nu$ = 144.0 ^2J −12.0) 4.35 and 4.37 q (CH_2O); 5.10 br.s (HO); 11.75 br.s (HN^+). ^{1}H NMR (D_2O): 1.65 t and 1.71 t (*Me*CH_2, ^3J 7.1), 1.72 s and 2.25 s (Me_2C), 2.53 q (CH_2, AB system, $\Delta\nu$ = 27.2, ^2J −12.0), 4.75 q and 4.79 q (CH_2O), 5.00 s (HO). ^{13}C NMR ($CDCl_3$): 14.06 (*Me*CH_2, ^1J 129.3, ^2J 2.9), 29.81 and 31.43 (Me_2C, ^1J 127.9, ^3J 4.4), 46.48 (CH_2, ^1J 135.2, ^3J 4.4), 62.35 and 63.13 (CH_2O, ^1J 148.2, ^2J 4.4), 72.2 (COH, ^2J 5.8), 72.3 (*C*Me_2), 128.6 (3-C), 146.43 (2-C), 164.20 and 165.82 (CO, ^3J 3.0).

4a, yield 92%, white prismatic crystals, mp 150–151 °C (from MeOH–EtOH), IR (KBr tablet), ν/cm^{-1}: 3235 (NH), 1770 and 1735 (CO_2), 1720 (CO), 1640 (C = C). ^{1}H NMR ($CDCl_3$): 1.30 s (*Me*$_2$C), 2.40 s (CH_2), 3.62 s and 3.80 s (MeO), 6.01 br.s (HN). ^{13}C NMR ($CDCl_3$): 25.45 (Me_2C, ^1J 127.9), 48.88 (CH_2, ^1J 130.8), 51.53 (MeO, ^1J 146.8), 52.90 (MeO, ^1J 148.2), 54.34 (*C*Me_2), 98.80 (3-C), 156.25 (2-C, ^2J 2.9), 163.95 and 165.55 (CO_2, ^3J 4.4), 189.1 (CO, ^2J 5.8). Mass spectrum (EI, 70 eV), *m*/*z* (relative intensity, %): 241 M^+ (94), 226 (40), 210 (79), 194 (100), 166 (19), 126 (53), 83 (46).

4b, yield 96%, white acicular crystals, mp 108–109 °C (from $MeCO_2Et$–CCl_4). IR (KBr tablet), ν/cm^{-1}: 3230 (NH), 1770 (CO_2), 1720 (CO), 1635 (C = C). ^{1}H NMR ($CDCl_3$): 1.30 t and 1.34 t (*Me*CH_2, ^3J 7.0), 1.35 s (*Me*$_2$C), 2.45 s (CH_2), 4.18 q and 4.30 q (CH_2O), 6.01 br.s (HN). ^{13}C NMR ($CDCl_3$): 13.78 (*Me*CH_2, ^1J 127.9, ^2J 3.0), 14.19 (*Me*CH_2, ^1J 126.1, ^2J 2.9), 26.37 (*Me*$_2$C, ^1J 127.9, ^3J 4.4), 48.70 (CH_2, ^1J 129.3, ^3J 4.7), 54.10 (CMe_2), 60.70 and 63.10 (CH_2O, ^1J 148.2, ^2J 4.7), 102.90 (3-C), 151.40 (2-C), 163.50 and 165.50 (CO_2Et, ^3J 2.9), 189.30 (CO, ^2J 5.8). Mass spectrum (EI, 70 eV), *m*/*z* (relative intensity, %): 269 M^+ (72), 254 (21), 224 (100), 208 (67), 196 (62), 182 (67), 180 (95), 153 (41), 140 (57), 136 (38), 125 (52), 83 (81), 68 (80), 55 (71).

diffraction method (Figure 1).‡

Derivatives such as **6a**,**b**, (*Z*)- and (*E*)-**7** (ratio $Z/E = 2$) were obtained from the products of fragmentation **4** (Scheme 2) and were characterized by spectroscopic methods.† The structure of (*Z*)-**7** was also unambiguously confirmed by the X-ray diffraction method (results will be reported separately).



Scheme 2 *Reagents and conditions*: i, MeNCO, Et_3N in CH_2Cl_2, boiling 5 h, yield 80–85.5%; ii, dimethyl acetylenedicarboxylate in Et_2O–MeOH, 1 month at 20 °C, total yield 63%.

When comparing the X-ray diffraction data for quinuclidine **1a**[1] and its picrate **2a** it is evident that N-protonation leads to a redistribution of bond lengths corresponding to the fragmentation under examination. Similar changes in bond lengths are predicted by calculations for the free molecules **1a**, cation **2a′**, zwitterion **2a″**, and O-deprotonated anion **1a′** using *ab initio* methods (DFT Becke 3LYP/6-31 G*)[4] with optimization of structures up to the maximum errors of 0.01 A for bond length and 1 kJ mol^{-1} for energy values (Table 1).

In the ^1H NMR spectra of quinuclidines in $CDCl_3$ a broad signal is observed [for **1b** at 1.27, 1.73 and 4.26 ppm, for **2b** (X = Cl) at 2.41 ppm], which disappears during heating (from 16 to 60 °C). This indicates the hindered rotation of the CO_2Et group.

All experimental and calculated structures (see ref. 1 and Figure 1) are substantially unsymmetric due to the different

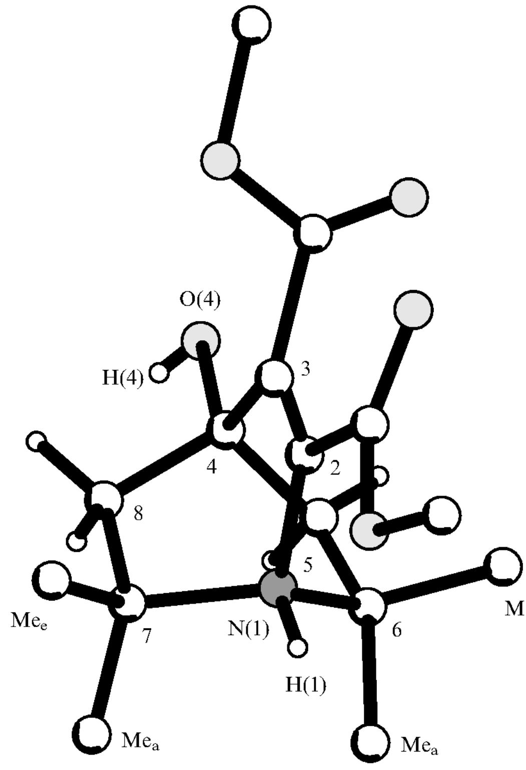


Figure 1 Molecular structure of the picrate **2a** cation. Methyl group hydrogens omitted. Bond lengths/A: H(1)N(1) 0.89 (3), N(1)C(2) 1.476 (3), C(2)C(3) 1.325 (3), C(3)C(4) 1.496 (3), C(4)O(4) 1.400 (3), O(4)H(4) 0.87 (4), C(4)C(5) 1.541 (3), C(5)C(6) 1.522 (3), C(6)N(1) 1.581 (3), N(1)C(7) 1.566 (3), C(7)C(8) 1.535 (3), C(8)C(4) 1.544 (3), C(2)C(O) 1.470 (3), C(3)C(O) 1.490 (3), C(6)C(Me_a) 1.521 (3), C(6)C(Me_e) 1.532 (3), C(7)C(Me_a) 1.518 (3), C(7)C(Me_e) 1.523 (3). Bond angles/°: H(1)N(1)C(2) 110 (2), H(1)N(1)C(6) 109 (2), H(1)N(1)C(7) 108 (2), C(2)N(1)C(6) 105.3 (2), C(2)N(1)C(7) 107.5 (2), C(6)N(1)C(7) 116.7 (2), N(1)C(2)C(3) 112.4 (2), C(2)C(3)C(4) 114.9 (2), C(3)C(4)C(5) 108.1 (2), C(4)C(5)C(6) 111.2 (2), C(5)C(6)N(1) 105.2 (2), C(6)N(1)C(7) 116.7 (2), N(1)C(7)C(8) 105.4 (2), C(7)C(8)C(4) 111.5 (2), C(8)C(4)C(5) 108.1 (2), C(3)C(4)C(8) 106.0 (2), C(5)C(4)C(8) 108.1 (2), H(4)O(4)C(4) 106 (2), O(4)C(4)C(3) 108.9 (2), O(4)C(4)C(5) 112.6 (2), O(4)C(4)C(8) 112.9 (2), C(5)C(6)C(Me_a) 113.8 (2), C(5)C(6)C(Me_e) 112.7 (2), C(7)C(6)C(Me_a) 112.8 (2), C(7)C(6)C(Me_e) 113.3 (2). Dihedral angles/°: N(1)C(6)C(5)C(4) 13.0, N(1)C(7)C(8)C(4) 0.4, N(1)C(2)C(3)C(4) 2.9, C(4)C(5)C(6)C(Me_a) 115.8, C(4)C(5)C(6)C(Me_e) 121.5, C(4)C(8)C(7)C(Me_a) 101.6, C(4)C(8)C(7)C(Me_e) 135.5.

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† **5**, yield 84%, golden ductile crystals, mp 85 °C (from n-C_6H_{14}). IR (KBr tablet), ν/cm^{-1}: 3315 (NH), 1760 (CO_2), 1640 (C = C). ^1H NMR ($CDCl_3$): 1.27 s (Me_2C), 2.35 s (CH_2), 3.82 s (MeO), 5.34 br.s (HN), 5.64 d (HC = , ^4J 1.6). ^{13}C NMR ($CDCl_3$): 26.54 (*Me*$_2$C, ^1J 127.9, ^3J 3.7), 49.04 (CH_2, ^1J 129.4, ^3J 4.3), 53.27 (MeO, ^1J 147.7), 53.55 (*C*Me_2), 99.41 (3-C, ^1J 172.1, ^3J 3.7), 146.22 (2-C), 164.04 (CO_2, ^3J 2.8 and 4.4), 194.51 (CO, ^2J 5.8). Mass spectrum (EI, 70eV), *m*/*z* (relative intensity, %): 183 M^+ (40), 168 (100), 140 (22), 136 (40), 108 (52), 100 (23), 68 (59), 41 (48).

6a, yield 80%, acicular crystals, mp 184–185 °C (with sublimation) (from Et_2O–n-C_5H_{12}). ^1H NMR ($CDCl_3$): 1.62 t (Me_2C), 2.64 s (CH_2), 3.09 s (MeN), 3.88 s (MeO). Mass spectrum (EI, 70 eV), *m*/*z* (relative intensity, %): 266 M^+ (35), 251 (56), 235 (34), 194 (69), 179 (27), 166 (20), 135 (18), 89 (33), 83 (64), 69 (34), 55 (54), 45 (100), 43 (82), 41 (62).

6b, yield 85.5%, white fluffy acicular crystals, mp 146–147 °C (Et_2O). ^1H NMR ($CDCl_3$): 1.32 t ($MeCH_2$, ^3J 7.1), 1.62 s (Me_2C), 2.63 s (CH_2), 3.08 s (MeN), 4.35 q (CH_2O). ^{13}C NMR ($CDCl_3$): 13.8 (*Me*CH_2, ^1J 126.9, ^2J 2.8), 24.83 (MeN, ^1J 142.2), 25.55 (*Me*$_2$C, ^1J 128.3, ^3J 4.2), 50.25 (CH_2, ^1J 131.1, ^3J 4.2), 57.97 (*C*Me_2, ^2J 3.5), 62.22 (CH_2O, ^1J 148.4, ^2J 4.5), 111.80 (3-C, ^3J 1.5), 139.04 (2-C), 152.23 and 159.23 (1-CO and 2-CO, ^3J 2.9), 161.93 (CO_2, ^3J 3.3), 188.74 (CO, ^2J 6.6).

(*Z*)-**7**, large transparent crystals, mp 93–94 °C (Et_2O). ^1H NMR ($CDCl_3$): 1.19 t and 1.26 t (*Me*CH_2, ^3J 7.1), 1.27 s and 1.51 s (Me_2C), 2.71 dd (CH_2, AB system, $\Delta\nu = 428.0$, ^2J −15.4), 3.78 s and 3.88 s (MeO), 4.17 q and 4.19 q (CH_2O), 7.01 (H_X). Part of the ^{13}C NMR ($CDCl_3$): 162.72 (β-*C*O_2Me, $^2J = {}^3J = 4.4$), 163.43 (α-*C*O_2Me, $^3J = {}^3J_{CHx} = 4.4$), 189.02 (CO, ^2J 5.8). IR (KBr tablet), ν/cm^{-1}: 1745 (CO), 1720 (CO_2), 1660, 1645 (C = C).

(*E*)-**7**, ^1H NMR ($CDCl_3$): 1.24 t and 1.29 t (*Me*CH_2, ^3J 7.1), 1.25 s and 1.35 s (Me_2C), 2.71 q (CH_2, AB system, $\Delta\nu = 428$, ^2J −15.4), 3.80 s and 3.83 s (MeO), 4.20 q and 4.22 q (CH_2O), 6.38 s (H_x). Part of the ^{13}C NMR ($CDCl_3$): 162.40 (β-*C*O_2Me, $^2J_{CX} = {}^3J = 4.4$), 162.45 (α-*C*O_2Me, ^3J 4.4, $^3J_{CHx}$ 8.2), 187.65 (CO, ^2J 5.8).

‡ *X-Ray diffraction study*. Basic crystallographic data on the crystal of picrate **2a**: $(C_{15}H_{24}NO_5)^+(C_6H_2N_3O_7)^-H_2O$, M 544.4, $a = 8.132$ (3), $b = 12.792$ (5), $c = 13.894$ (5) A, $\alpha = 62.32$ (4), $\beta = 74.40$, $\gamma = 86.37$ (3)°, $V = 1229.5$ (8) A^3, space group $P1$, $z = 2$, $d_{calc} = 1.47$ g cm^{-3}. Measurements of 2705 reflections with $I > 4\sigma(I)$ were performed with four circle automatic diffractometer KM from Kuma Diffraction (Poland) using Mo(K_α)-irradiation [disregarding absorption, $\mu(MoK_\alpha) = 12.4$ cm^{-1}]. The structure was determined by direct methods using the SHELX-86 program.[8] Location of H atoms was defined from the differencing syntheses. Refinement by the LSM was carried out in a full-matrix anisotropic approximation for atoms C, N and O and in isotropic one for atoms H using the SHELX-93 program.[9] The value of *R* was finalized to 0.038.

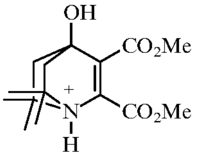
In the independent part of the unit cell, cation, anion and H_2O molecule are connected by a three-dimensional network of H-bonds, and the H_2O molecule forms three H-bonds while the cation also forms one H-bond with another anion.

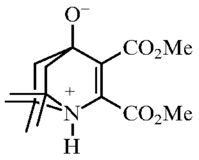
Full lists of bond lengths, bond angles, atomic coordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see Notice to Authors, *Mendeleev Communications*, 1996, Issue 1. Any request to the CCDC should include the full literature citation and the reference number 1135/5.

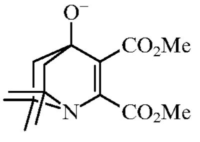
Table 1 Experimental and calculated bond lengths/ Å and calculated values of relative energy/kJ mol^{-1} (see Scheme 3).

Molecule (method)	a	b	c (c′)	d (d′)	e (e′)	f	Relative energy
picrate **2a**	0.87	1.400	1.541	1.522	1.560	0.89	–
(exp.)			(1.544)	(1.535)	(1.581)		
cation **2a′**	0.976	1.396	1.552	1.549	1.587	1.032	−1053.8
(calc.)			(1.559)	(1.551)	(1.593)		
zwitter-							
ion **2a″**	–	1.279	1.615	1.536	1.593	1.028	159.9
(calc.)			(1.616)	(1.538)	(1.593)		
anion **1a′**	–	1.300	1.600	1.554	1.530	–	1574.5
(calc.)			(1.604)	(1.554)	(1.529)		
1a	0.83	1.430	1.526	1.572	1.530	–	–
(exp.[1])			(1.536)	(1.573)	(1.537)		
1a	0.976	1.410	1.549	1.565	1.530	–	0.0
(calc.)			(1.553)	(1.567)	(1.534)		
Δ^a **2a′**–**1a**	0.04	−0.03	0.015	−0.050	0.036	–	–
(exp.)			(0.008)	(−0.038)	(0.044)		
Δ^a **2a″**–**1a**	–	−0.014	0.066	−0.029	0.063	–	–
(calc.)			(0.063)	(−0.029)	(0.059)		

^{a} Δ Bond length difference.

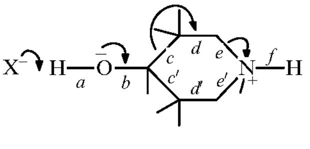

2a′


2a″


1a′

orientation of the CO_2Me groups in relation to the double bond. Therefore, the bond lengths of two saturated bridges are different from each other. Nevertheless the conformation of these bridges in the molecule of picrate **2a** is almost staggered (Figure 1), and is perfectly suitable for the development of a stereoelectronic effect involving displacement of electron density along the system of σ-bonds from donor atom O to acceptor protonated atom N (Scheme 3). A decrease in the accepting properties of N in the quinuclidine base **1** results in a lack of fragmentation (see above) even when anion **1a′** is generated on boiling with excess alkali (saponification of just the carboxy groups occurs[1]), which agrees with the calculations for this anion (Table 1). A decrease in the donating properties of atom O also results in retarded fragmentation, and the picrate of the *O*-methylcarbamoyl derivative of quinuclidine **1a** gives **4a** after 20 h boiling in $CDCl_3$ with elimination of isobutylene and methyl isocyanate.

Thus the most probable fragmentation intermediate is zwitterion **2a″**. Its generation under the action of anion X^- (Scheme 3) can explain the observed low field shift of the OH signal ($\Delta\delta = 2.4$ ppm) and high field shifts of the carbon signals: COH ($\Delta\delta = 2.4$ ppm), *C*H_2COH ($\Delta\delta = 2.0$ ppm) and = *C*COH ($\Delta\delta = 14.3$ ppm) during the transition from the base **1b** to the quinuclidine hydrochloride **2b**.



Scheme 3

Viewed in terms of the stereoelectronic effect discussed here, heterolytic fragmentation[5,6] of the quinuclidine nucleus differs from known examples of quinuclidine fragmentation.[5] Thus, the donor centre in 4-tosyloxy- and 4-halogenoquinuclidines is atom N, and the acceptor centre is the 4-substituent. Therefore the fragmentation proceeds with elimination of 4-substituent as an anion, cleavage of the central bond of the bridge, and formation of the 1,4-bismethylenepiperidiniminium salt.[7,8]

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