

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

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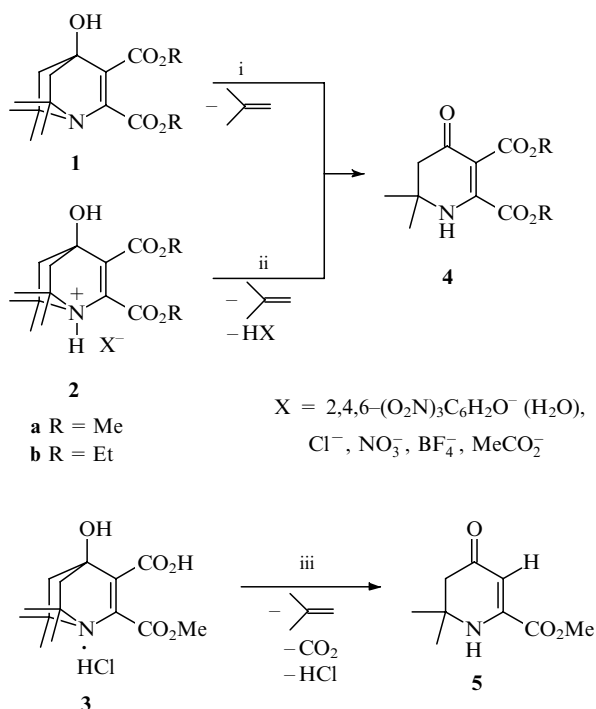
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The title quinuclidines undergo cleavage under the action of acids or H₂O to give Δ^2 -dehydro-4-piperidones **4**, **5** and isobutylene; the resulting redistribution of bond lengths upon N-protonation has been demonstrated by X-ray diffraction methods 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**[†] 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 H₂O 3 h or cat. **2** in MeOH, Et₂O or CHCl₃, boiling 5–10 h; ii, boiling in MeOH, EtOH or CHCl₃, 4–5 h; iii, boiling in MeOH, 5 h.

In the case of hydrochlorides **2a,b** the ¹H NMR spectra of the reaction mixtures in CDCl₃ 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 CDCl₃.

Quinuclidine bases **1a,b** remain unchanged after 5–10 h boiling in n-C₆H₁₄, C₆H₆ 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

[†] Spectroscopic data for: **1b**, from triacetoneamine and diethyl acetylenedicarboxylate in a mixture of Freon-113/CH₂Cl₂ (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). ¹H NMR (CDCl₃): 1.12 s and 1.57 s (Me₂C); 1.27 t and 1.33 t (MeCH₂, ³J 7.3); 1.73 s (CH₂); 2.70 br.s (HO); 4.26 q and 4.31 q (CH₂O). ¹H NMR ([²H₅]pyridine): 1.04 t and 1.13 t (MeCH₂, ³J 7.1), 1.08 s and 1.34 s (Me₂C), 1.83 q (CH₂, AB system, $\Delta\nu$ = 21.2, ²J = 10.7), 4.10 q and 4.25 q (CH₂O). ¹³C NMR (CDCl₃): 14.10 (MeCH₂, ¹J 129.3, ²J 2.9), 33.27 and 34.05 (Me₂C, ¹J 127.9, ³J 4.4), 48.53 (CH₂, ¹J 130.8, ³J 4.4), 60.13 (CMe₂), 61.15 and 61.39 (CH₂O, 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-(NO₃)₃C₆H₂O[−] (H₂O)], from **1b** and picric acid in MeOH, yield 58.2%, mp 95–98 °C (MeCO₂Et). ¹H NMR (CDCl₃): 1.43 s and 2.02 s (Me₂C), 2.06 q (CH₂, AB system, $\Delta\nu$ = 64.0, ²J = 11.9), 3.76 s and 3.90 s (MeO), 8.86 s (C₆H₂). ¹³C NMR ([²H₆]acetone): 28.86 (MeC, ¹J 130.4), 30.74 (MeC, ¹J 129.7), 45.63 (CH₂, ¹J 136.6), 52.73 (MeO, ¹J 149.1), 53.96 (MeO, ¹J 149.8), 72.20 (COH, ²J 4.9), 72.90 (CMe₂), 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).

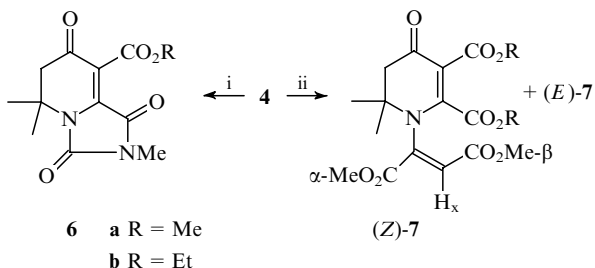
2b (X = Cl[−]), mp 127–129 °C (decomp.). ¹H NMR (CDCl₃): 1.34 t and 1.35 t (MeCH₂, ³J 7.3); 1.47 s and 2.12 s (Me₃C); 2.22 q (CH₂, $\Delta\nu$ = 144.0 ²J = 12.0) 4.35 and 4.37 q (CH₂O); 5.10 br.s (HO); 11.75 br.s (HN⁺). ¹H NMR (D₂O): 1.65 t and 1.71 t (MeCH₂, ³J 7.1), 1.72 s and 2.25 s (Me₂C), 2.53 q (CH₂, AB system, $\Delta\nu$ = 27.2, ²J = 12.0), 4.75 q and 4.79 q (CH₂O), 5.00 s (HO). ¹³C NMR (CDCl₃): 14.06 (MeCH₂, ¹J 129.3, ²J 2.9), 29.81 and 31.43 (Me₂C, ¹J 127.9, ³J 4.4), 46.48 (CH₂, ¹J 135.2, ³J 4.4), 62.35 and 63.13 (CH₂O, ¹J 148.2, ²J 4.4), 72.2 (COH, ²J 5.8), 72.3 (CMe₂), 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 (CO₂), 1720 (CO), 1640 (C = C). ¹H NMR (CDCl₃): 1.30 s (Me₂C), 2.40 s (CH₂), 3.62 s and 3.80 s (MeO), 6.01 br.s (HN). ¹³C NMR (CDCl₃): 25.45 (Me₂C, ¹J 127.9), 48.88 (CH₂, ¹J 130.8), 51.53 (MeO, ¹J 146.8), 52.90 (MeO, ¹J 148.2), 54.34 (CMe₂), 98.80 (3-C), 156.25 (2-C, ²J 2.9), 163.95 and 165.55 (CO₂, 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 MeCO₂Et–CCl₄). IR (KBr tablet), ν /cm^{−1}: 3230 (NH), 1770 (CO₂), 1720 (CO), 1635 (C = C). ¹H NMR (CDCl₃): 1.30 t and 1.34 t (MeCH₂, ³J 7.0), 1.35 s (Me₂C), 2.45 s (CH₂), 4.18 q and 4.30 q (CH₂O), 6.01 br.s (HN). ¹³C NMR (CDCl₃): 13.78 (MeCH₂, ¹J 127.9, ²J 3.0), 14.19 (MeCH₂, ¹J 126.1, ²J 2.9), 26.37 (Me₂C, ¹J 127.9, ³J 4.4), 48.70 (CH₂, ¹J 129.3, ³J 4.7), 54.10 (CMe₂), 60.70 and 63.10 (CH₂O, ¹J 148.2, ²J 4.7), 102.90 (3-C), 151.40 (2-C), 163.50 and 165.50 (CO₂Et, 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, Et₃N in CH₂Cl₂, boiling 5 h, yield 80–85.5%; ii, dimethyl acetylenedicarboxylate in Et₂O–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 Å for bond length and 1 kJ mol^{−1} for energy values (Table 1).

In the ¹H NMR spectra of quinuclidines in CDCl₃ 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 CO₂Et group.

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

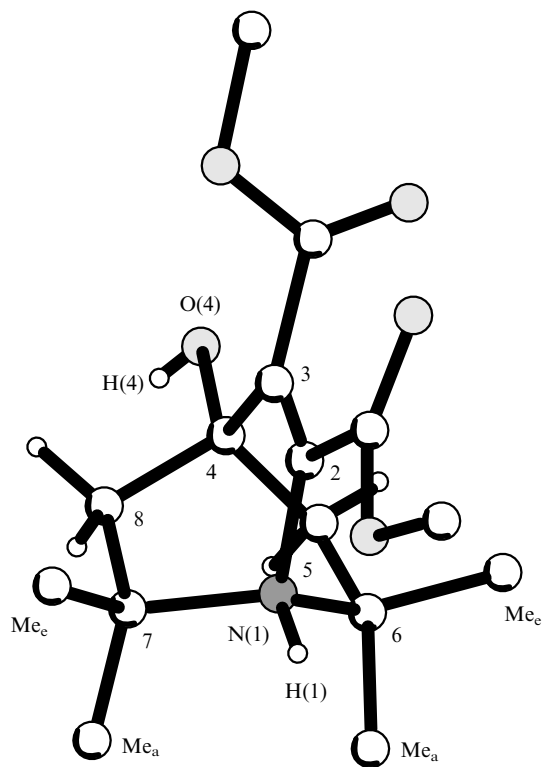


Figure 1 Molecular structure of the picrate **2a** cation. Methyl group hydrogens omitted. Bond lengths/Å: H(1)N(1) 0.89 (3), N(1)C(2) 1.476 (3), C(2)C(3) 1.325 (3), C(3)C(4) 1.496 (3), C(4)O(4) 1.400 (3), O(4)H(4) 0.87 (4), C(4)C(5) 1.541 (3), C(5)C(6) 1.522 (3), C(6)N(1) 1.581 (3), N(1)C(7) 1.566 (3), 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_c) 1.532 (3), C(7)C(Me_a) 1.518 (3), C(7)C(Me_c) 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_c) 112.7 (2), C(7)C(6)C(Me_a) 112.8 (2), C(7)C(6)C(Me_c) 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_c) 121.5, C(4)C(8)C(7)C(Me_a) 101.6, C(4)C(8)C(7)C(Me_c) 135.5.

[†] **5**, yield 84%, golden ductile crystals, mp 85 °C (from n-C₆H₁₄). IR (KBr tablet), ν/cm^{−1}: 3315 (NH), 1760 (CO₂), 1640 (C = C). ¹H NMR (CDCl₃): 1.27 s (Me₂C), 2.35 s (CH₂), 3.82 s (MeO), 5.34 br.s (HN), 5.64 d (HC =, ⁴J 1.6). ¹³C NMR (CDCl₃): 26.54 (Me₂C, ¹J 127.9, ³J 3.7), 49.04 (CH₂, ¹J 129.4, ³J 4.3), 53.27 (MeO, ¹J 147.7), 53.55 (CMe₂), 99.41 (3-C, ¹J 172.1, ³J 3.7), 146.22 (2-C), 164.04 (CO₂, ³J 2.8 and 4.4), 194.51 (CO, ²J 5.8). Mass spectrum (EI, 70 eV), *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 Et₂O–n-C₅H₁₂). ¹H NMR (CDCl₃): 1.62 t (Me₂C), 2.64 s (CH₂), 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 (Et₂O). ¹H NMR (CDCl₃): 1.32 t (MeCH₂, ³J 7.1), 1.62 s (Me₂C), 2.63 s (CH₂), 3.08 s (MeN), 4.35 q (CH₂O). ¹³C NMR (CDCl₃): 13.8 (MeCH₂, ¹J 126.9, ²J 2.8), 24.83 (MeN, ¹J 142.2), 25.55 (Me₂C, ¹J 128.3, ³J 4.2), 50.25 (CH₂, ¹J 131.1, ³J 4.2), 57.97 (CMe₂, ²J 3.5), 62.22 (CH₂O, 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 (CO₂, ³J 3.3), 188.74 (CO, ²J 6.6).

(*Z*)-**7**, large transparent crystals, mp 93–94 °C (Et₂O). ¹H NMR (CDCl₃): 1.19 t and 1.26 t (MeCH₂, ³J 7.1), 1.27 s and 1.51 s (Me₂C), 2.71 dd (CH₂, AB system, Δν = 428.0, ²J = 15.4), 3.78 s and 3.88 s (MeO), 4.17 q and 4.19 q (CH₂O), 7.01 (H_x). Part of the ¹³C NMR (CDCl₃): 162.72 (β-CO₂Me, ²J = ³J = 4.4), 163.43 (α-CO₂Me, ³J = ³J_{CHx} = 4.4), 189.02 (CO, ²J 5.8). IR (KBr tablet), ν/cm^{−1}: 1745 (CO), 1720 (CO₂), 1660, 1645 (C = C).

(*E*)-**7**, ¹H NMR (CDCl₃): 1.24 t and 1.29 t (MeCH₂, ³J 7.1), 1.25 s and 1.35 s (Me₂C), 2.71 q (CH₂, AB system, Δν = 428, ²J = 15.4), 3.80 s and 3.83 s (MeO), 4.20 q and 4.22 q (CH₂O), 6.38 s (H_x). Part of the ¹³C NMR (CDCl₃): 162.40 (β-CO₂Me, ²J_{Cx} = ³J = 4.4), 162.45 (α-CO₂Me, ³J 4.4, ³J_{CHx} 8.2), 187.65 (CO, ²J 5.8).

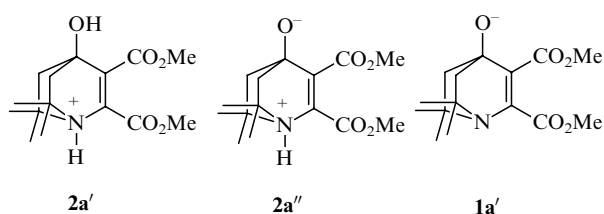
[‡] *X-Ray diffraction study*. Basic crystallographic data on the crystal of picrate **2a**: (C₁₅H₂₄NO₅)⁺(C₆H₂N₃O₇)[−]·H₂O, M 544.4, *a* = 8.132 (3), *b* = 12.792 (5), *c* = 13.894 (5) Å, α = 62.32 (4), β = 74.40, γ = 86.37 (3)°, *V* = 1229.5 (8) Å³, space group *P*1, *z* = 2, *d*_{calc} = 1.47 g cm^{−3}. Measurements of 2705 reflections with *I* > 4σ (*I*) were performed with four circle automatic diffractometer KM from Kuma Diffraction (Poland) using Mo(Kα)-irradiation [disregarding absorption, μ(MoKα) = 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 H₂O molecule are connected by a three-dimensional network of H-bonds, and the H₂O 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.

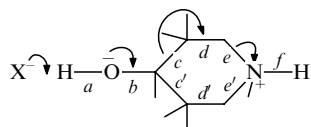
Table 1 Experimental and calculated bond lengths/Å and calculated values of relative energy/kJ mol⁻¹ (see Scheme 3).

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

^a Δ Bond length difference.

orientation of the CO₂Me 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 occurs¹), 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 CDCl₃ 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

**Scheme 3**

signal ($\Delta\delta = 2.4$ ppm) and high field shifts of the carbon signals: COH ($\Delta\delta = 2.4$ ppm), CH₂COH ($\Delta\delta = 2.0$ ppm) and =CCOH ($\Delta\delta = 14.3$ ppm) during the transition from the base **1b** to the quinuclidine hydrochloride **2b**.

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}

This work was carried out with financial support from the Russian Foundation for Basic Research (grant no. 94-03-08730) and the International Science Foundation (grant nos. MCO 000 and MCO 300).

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Received: Moscow, 14th December 1995
Cambridge, 9th January 1996; Com. 5/08219F