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Autoassembling of the quinuclidine nucleus: one-step synthesis, structure and properties of dimethyl 4-hydroxy-6,6,7,7-tetramethyl-Δ^2-dehydroquinuclidine-2,3-dicarboxylate

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Triacetonamine reacts with dimethyl acetylenedicarboxylate in MeOH to give an ordinary adduct, aminomaleate 2, while in aprotic solvents quinuclidine 1 is formed under mild conditions and in high yield; its structure is confirmed by spectroscopic methods as well as X-ray diffraction analysis. A mechanism of autoassembling is proposed, and chemical transformations of 1 with retention of quinuclidine nucleus are studied.

It was earlier presumed that quinuclidines are formed by the one-step reaction of triacetonamine (TAA) with dialkyl acetylenedicarboxylates in ether or hexane (24–36 h, 20 °C, yields 58–70%); however, the structures of the products were not proved rigorously.[1–3]

It has been established in this work that the above-mentioned reaction with dimethyl acetylenedicarboxylate (DMAD) in aprotic solvents (CH_2Cl_2, $CHCl_3$, or CCl_4, 18–20 h, 20 °C) leads to quinuclidine **1** in high yield (85–86.5%) while in protic solvent (MeOH) an ordinary adduct, triacetonoaminomaleate **2** is formed with a yield of 51.5% (*cf.*[4,5]) (Scheme 1).

The structures of products **1**, **2** have been unambiguously determined by spectroscopic methods,† and the structure of quinuclidine **1** has been confirmed by X-ray diffraction analysis‡ (Figure 1).

† *Spectroscopic data*: **1** White acicular crystals, mp 140–142 °C, mass spectrum (EI, 70 eV), *m*/*z* (relative intensity): 297 M^+(34) 282 (20) 241 (20) 238 (46) 213 (82) 182 (100) 58 (56). IR ($CHCl_3$), ν/cm^{-1}: 3500 (OH), 1730, 1715 (CO), 1623 (C = C). ^{1}H NMR (C_6D_5N): 1.22 s and 1.50 s (Me_2C); 2.02 q (CH_2, AB system, $\Delta\nu$ = 60.0; ^2J −11.4); 3.75 s and 3.90 s (MeO). ^{1}H NMR ($CDCl_3$): 1.10 s and 1.57 s (Me_2C); 1.73 s (CH_2); 2.69 (OH); 3.79 s and 3.86 s (MeO). ^{13}C NMR ($CDCl_3$): 32.74 and 34.07 (*Me*$_2$C, ^1J 128.2; ^3J 4.9); 48.52 (CH_2, ^1J 131.8; ^3J 3.7); 52.40 and 52.53 (MeO, ^1J 147.7); 60.3 (*C*Me$_2$); 74.8 (4-C, ^2J 4.9); 142.9 (3-C); 145.6 (2-C); 163.8 and 166.8 (CO, ^3J 3.7).

2 White acicular crystals, mp 65 °C, from *n*-C_6H_{14}–CCl_4. IR (CCl_4), ν/cm^{-1}: 1740 and 1720 (CO), 1600 (C=C). ^{1}H NMR ($CDCl_3$): 1.33 s (Me_2C); 2.21 s (CH_2); 3.67 s and 3.80 s (MeO); 5.67 (=CH).

3 White acicular crystals, mp 128–129 °C (from MeOH–Et_2O). ^{1}H NMR (CD_3OD): 1.37 s and 1.89 s (Me_2C); 2.10 q (CH_2, AB system, $\Delta\nu$ = 100.0; ^2J −11.9); 3.92 s and 3.93 s (MeO).

4 Yield 96%, white ductile crystals, mp 134–136 °C (decomp.). ^{1}H NMR (CD_3OD): 1.37 s and 1.89 s (Me_2C); 2.10 q (CH_2, AB system, $\Delta\nu$ = 92; ^2J −12.0); 3.93 and 3.94 s (MeO).

5 Yield 95%, mp 133–138 °C (decomp.). ^{1}H NMR (CD_3OD): 1.31 s and 1.83 s (Me_2C); 2.04 q (CH_2, AB system, $\Delta\nu$ = 96, ^2J −12.0); 3.87 s and 3.88 s (MeO).

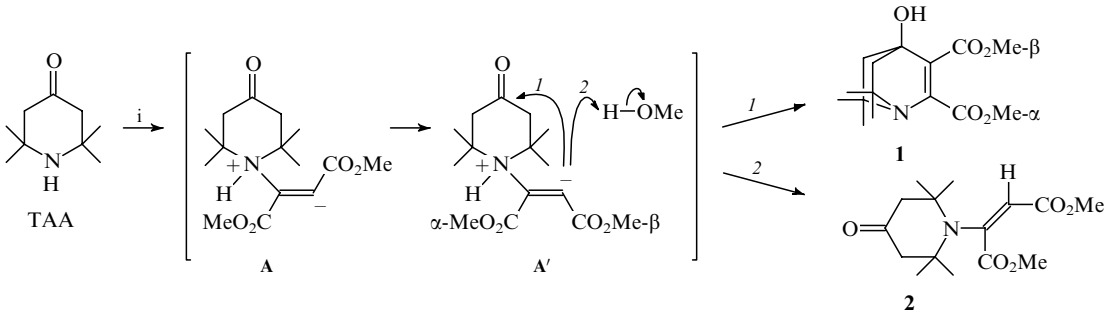
6 Yield 64%, bright lemon-yellowish crystals, mp 143–144 °C (decomp.), from $MeCO_2Et$. ^{1}H NMR ($CDCl_3$): 1.41 s and 1.96 s (Me_2C); 2.35 q (CH_2, AB system, $\Delta\nu$ = 148.0; ^2J −11.2); 2.75 d (MeN, ^3J 4.9); 3.76 s and 3.83 s (MeO); 4.75 br. (HN); 8.93 s (C_6H_2). ^{13}C NMR ($CDCl_3$): 26.85 (MeN, ^1J 138.7); 29.44 and 31.19 (*Me*$_2$C, ^1J 129.7); 42.94 (CH_2, ^1J 137.3); 52.94 (MeO, ^1J 149.1); 53.98 (MeO, ^1J 149.8); 71.31 (*C*Me$_2$); 76.29 (4-C, ^2J 4.9); 125.85 (3′-C, ^1J 169.2; ^3J 5.6); 127.52 (4′-C, ^2J 4.2); 130.3 (2′-C); 141.10 (3-C, ^3J 5.6); 141.74 (2-C, ^2J 3.5); 154.12 (O = CN, $^2J = {}^3J \sim 4.2$); 158.98 (3-CO, ^3J 4.2); 161.10 (1^1-C, ^3J 6.2); 161.62 (2-CO, ^3J 4.2). IR ($CHCl_3$), ν/cm^{-1}: 1570 (C = C, picrate), 1627 (C = C), 1640 (CONH), 1750 (CO), 3100 (NH).

7 Yield 65%, white fluffy crystals, mp 195–198 °C (from EtOH–*n*-C_6H_{14}). ^{1}H NMR (D_2O): 1.23 s and 1.72 s (Me_2C); 1.91 q (CH_2, AB system, $\Delta\nu$ = 44.0; ^2J −11.9); 4.02 s (MeO). ^{1}H NMR ($CDCl_3$): 1.10 s and 1.53 s (Me_2C); 1.71 s (CH_2); 2.52 br. s (HO); 3.88 s (MeO); 5.54 br. s and 5.76 br. s (NH_2).

8 Yield 95%, white crystals, mp 228–230 °C (from MeCN). ^{1}H NMR (CD_3OD): 1.39 s and 1.88 s (Me_2C), 2.12 q (CH_2, AB system, $\Delta\nu$ = 32.0; ^2J −11.9). IR (KBr pellet), ν/cm^{-1}: 3340 (OH), 3260, 3220, 3190 (NH_2), 1682, 1670 (CON), 1628 (C = C).

9 Yield 85%, white acicular crystals, mp 115–117 °C (from MeOH–CCl_4). ^{1}H NMR (CD_3OD): 1.38 s and 1.90 s (Me_2C); 2.12 q (CH_2, AB system, $\Delta\nu$ = 92.0, ^2J −11.9); 3.93 s (MeO).

10 Yield 79%, white fluffy crystals, mp 128–129 °C (from Et_2O–MeOH). ^{1}H NMR (CD_3OD): 1.30 s and 1.80 s (Me_2C); 2.00 q (CH_2, $\Delta\nu$ = 80.0; ^2J −12.0).



Scheme 1 *Reagents and conditions*: i, DMAD. Route 1: in CH_2Cl_2, $CHCl_3$ or CCl_4, 18–20 h, 20 °C; in Et_2O or *n*-C_6H_{14}, 24–36 h, 20 °C. Route 2: in MeOH, 44 h, 20 °C.

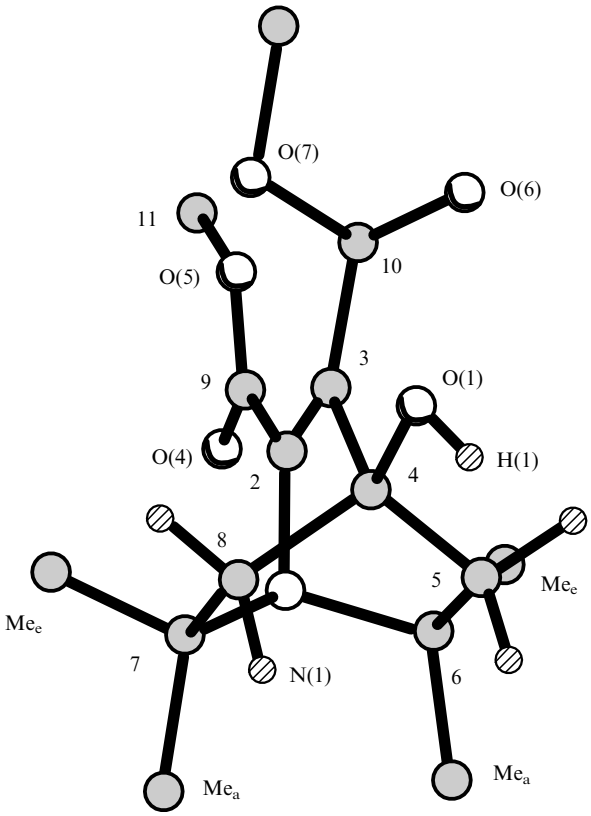


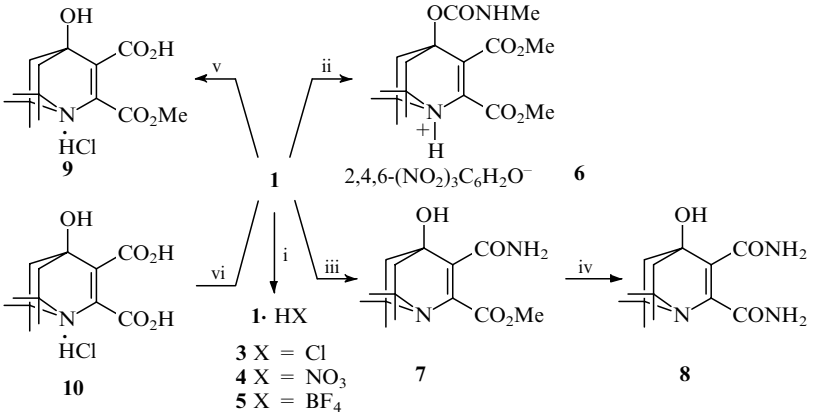
Figure 1 Molecular structure of **1**. Bond lengths/A: N(1)–C(2) 1.447 (1) N(1)–C(7) 1.530 (1) N(1)–C(6) 1.537 (1) C(2)–C(3) 1.359 (1) C(3)–C(4) 1.523 (1) C(4)–C(8) 1.536 (1) C(4)–C(5) 1.526 (1) C(5)–C(6) 1.572 (1) C(7)–C(8) 1.573 (1) C(2)–C(=O) 1.490 (1) C(3)–C(=O) 1.490 (1) C(4)–O 1.430 (1) O–H 0.83 (2) C(6)–C(Me$_a$) 1.542 (1) C(7)–C(Me$_a$) 1.532 (1) C(6)–C(Me$_e$) 1.532 (1) C(7)–C(Me$_e$) 1.533 (1).
Bond angles/°: C(2)N(1)C(6) 105.2 (1) C(2)N(1)C(7) 104.9 (1) C(6)N(1)C(7) 114.0 (1) C(3)C(4)C(5) 106.1 (1) C(3)C(4)C(8) 106.3 (1) C(5)C(4)C(8) 108.7 N(1)C(2)C(3) 116.1 (1) C(2)C(3)C(4) 113.4 (1) C(4)C(5)C(6) 110.5 (1) C(4)C(8)C(6) 109.7 (1) N(1)C(2)C(=O) 116.5 91) N(1)C(6)C(5) 108.7 (1) N(1)C(7)C(8) 109.4 (1) N(1)C(6)C(Me$_a$) 112.0 (1) N(1)C(7)C(Me$_a$) 112.3 (1) N(1)C(6)C(Me$_e$) 106.1 (1) N(1)C(7)C(Me$_e$) 105.9 (1) C(3)C(2)C(=O) 127.4 (1) C(2)C(3)C(=O) 129.7 (1) C(Me$_a$)C(6)C(Me$_e$) 106.1 (1) C(Me$_a$)C(7)C(Me$_e$) 106.2 (1) C(3)C(4)O 109.1 (1).
Dihedral angles/°: N(1)C(2)C(3)C(4) 1.0; C(4)C(5)C(6)N(1) 5.3; N(1)C(7)C(8)C(4) 4.1; H$_a$C(5)C(6)C(Me$_a$) 9.9; H$_a$C(8)C(7)C(Me$_a$) 7.8; H$_e$C(5)C(6)C(Me$_e$) 12.3; H$_e$C(8)C(7)C(Me$_e$) 9.1; C(3)C(2)C(=O) 173.0; C(2)C(3)C(=O) 85.8; C(3)C(4)OH 162.4.

The results obtained can be explained as follows. Under the influence of a strongly delocalising group, β-CO_2Me,[8] the original anion **A** is isomerized readily into the sterically more preferable anion **A′**. The latter is quickly protonated in MeOH to form adduct **2** but in aprotic media an intramolecular attack at the carbonyl group occurs that results in the formation of quinuclidine **1** (Scheme 1, routes 2 and 1, respectively). Similar reactions of dialkyl acetylenedicarboxylates with α- and β-aminoketones followed by dehydration are known to give pyrroles and pyridines, respectively.[9–11]

One of the principal considerations in constructing quinuclidines according to Scheme 1 is the presence of a strongly electron-delocalising substituent in the activated acetylene. This provides a formation of anion **A′** that is necessary for the cyclization. Indeed, when TAA interacts with dicyanoacetylene containing a poorly delocalising group such as CN[12,13] only the ordinary adduct is formed.[4–5] At the same time TAA does not react at all with hexafluorobut-2-yne (in a mixture of Et_2O–CH_2Cl_2, 1 month, 20 °C) possibly due to steric hindrance.

Normal *E*-adducts are also formed when diethyl acetylenedicarboxylate interacts with 2,2,5-trimethyl-4-piperidone or TAA reacts with methyl acetylenecarboxylate.[4,5]

‡ *X-Ray diffraction study of* **1**. Basic crystallographic data on $C_{15}H_{23}NO_5$, $M = 297.4$; $a = 9.005$ (3); $b = 14.206$ (4); $c = 13.208$ (2) A; $\beta = 100.20$ (2)°, $V = 1662.9$ (8) A^3, space group $P2/b$, $Z = 4$, $d_{calc} = 1.19$ g cm^{-3}. Measurements of 2602 reflections with $I > 3\sigma(I)$ were performed with a three-circle automatic diffractometer DAR--UM using Cu K_α-irradiation disregarding absorption, μ(Cu-K_α) = 7.4 cm^{-1}. The structure was determined by direct methods followed by a series of Fourier syntheses. Location of H atoms was defined from the differencing syntheses. Refinement by the LSM was carried out in full matrix anisotropic approximation for atoms C, N, and O and in isotropic one for H. The value of the *R*-factor was finalized to be equal to 0.040. Calculations were verified by the program 'ROENTGEN-75'.
Full lists of bond angles, bond lengths, atomic coordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, 1996, issue 1. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/7.
The saturated six-membered ring of **1** is a practically non-distorted bath. The bicyclic skeleton from the side of N is described by a Newman projection with angles C(1)N(1)C(5) 119.0°; C(2)N(1)C(7) 118.6°; C(5)N(1)C(7) 122.4°. The orientation of groups CO_2Me and **1** (Figure 1) is close to the optimal one for n_σ[O(5)]–π*[C(10)=O(6)] interaction: O(5)...C(10) 2.826 (1) A; C(3)C(10)...O(5) 74.5 (2)°; O(6)C(10)...O(5) 102.5 (2)°; O(7)C(10)...O(5) 95.6 (2)°; C(11)O(3)...C(10) 148.0 (2)° (*cf.* refs. 6, 7).
The molecules of **1** in the crystal are arranged in continuous chains due to the intermolecular H-bonds: H(1)...N(1) 2.16 (1) A; O(1)...N(1) 2.911 (1) A; O(1)H(1)...N(1) 149 (1)°; C(1)N(1)...H(1) 119 (1)°; C(6)N(1)...H(1) 112 (1)°, and C(7)N(1)...H(1) 106 (1)°.



Scheme 2 *Reagents and conditions*: i, **3** from **1** and dry HCl in Et_2O at 20 °C; **4** from **3** and $AgNO_3$ in MeOH at 20 °C; **5** from **3** and $AgBF_4$ in a mixture of MeOH–CH_2Cl_2 at 20 °C; ii, excess MeNCO in CH_2Cl_2, cat. Et_3N, 10 days at 20 °C, boiling 5 h, then 2,4,6-$(NO_3)_2C_6H_2OH$ in a mixture of Et_2O–MeOH; iii, excess NH_3, cat. MeONa in MeOH, 36 h at 20 °C; iv, excess NH_3, cat. MeONa in MeOH, 156 h at 20 °C; v, 1.5-fold excess KOH in MeOH, 72 h at 20 °C, then dry HCl in EtOH; vi, 18-fold excess KOH in MeOH, 72 h at 20 °C, then dry HCl in EtOH.

Therefore, it is evident that another condition for the formation of quinuclidine according to Scheme 1 is the presence of two substituents in activated acetylene as well as a complete substitution of the α-position in the source 4-piperidone. Then in anion **A′** the only degree of freedom for the *N*-substituent bearing a carbanionic centre is oriented in the gap between α-substituents, and the anion attack is directed strictly on the carbonyl carbon.

Thus, a one-step reaction for the construction of polyfunctional quinuclidines has been found. All other methods of preparing quinuclidines are complex and multi-step syntheses.[14,15] Quinuclidines bearing only some elements of the structure **1** were reported earlier. They are 4-quinuclidol, 2,2,6,6-tetramethylquinuclidine,[14] alkyl Δ^2-dehydroquinuclidine-2- and -3-carboxylates[16] as well as -2,3-dicarboxylates.[17]

Quinuclidine **1** forms salts **3**–**5**, it can be carbamoylated at the OH group giving a product isolated as picrate **6**, and it also undergoes ammonolysis to yield amides **7**, **8** and hydrolysis to yield acids **9**, **10**. Unlike Δ^2-dehydroquinuclidine-2,3-dicarboxylates[17] these reactions proceed firstly at the β-carboxy group and then at the more sterically shielded α-carboxy group (Scheme 2).

Quinuclidine **1** does not react with MeI in MeOH, Et_2O or in the absence of solvent (5–60 days at 20 °C), with MeCOCl and Et_3N in CH_2Cl_2 or with MeCOBr in C_5H_5N at 20 °C, with ClCN (in $CHCl_3$, 60 days at 20 °C) and BrCN (in $CHCl_3$, boiling 30 h), $HC{\equiv}CCO_2Me$ (boiling 48 h) and CH_2N_2 in Et_2O.

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