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TETRAHEDRON: *ASYMMETRY*

Synthesis of 10,11-didehydro- and 10,11-dihydro-Quincorine and of the Quincoridine analogs: functionalized and enantiopure 1-azabicyclo[2.2.2]-octanes with four stereogenic centers

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Abstract

The convenient synthesis of 10,11-didehydro-QCI (**2**) and of 10,11-didehydro-QCD (**4**) as well as 10,11-dihydro-QCI (**5**) and 10,11-dihydro-QCD (**6**) is described. Conversion of the olefinic double bond of Quincorine® **1** and Quincoridine® **3** into the corresponding alkynes **2** and **4** involves twofold dehydrobromination, and an important application of the solid KOH/aliquat 336 system in the key step. The structure of didehydro-QCI (**2**) has been elucidated by X-ray crystal diffraction. The new alkynes **2** and **4** are more polar and more basic than QCI and QCD, respectively.

1. Introduction

Quincorine® **1** and Quincoridine® **3** are two new scalemic β-amino alcohols containing four stereogenic centers each, including the N-chiral 1*S*-configurated bridgehead. Because of their compact azabicyclic structure and their low molecular weight, both **1** and **3** are of general interest and use.[1,2] We now report the preparation of the four derived title compounds.

2. Results and discussion

The acetylenes **2** and **4** were prepared via a bromination–double dehydrobromination sequence. This was accomplished by isolating the intermediate vinylic bromides (method a) and by a simple one-pot procedure (method b).

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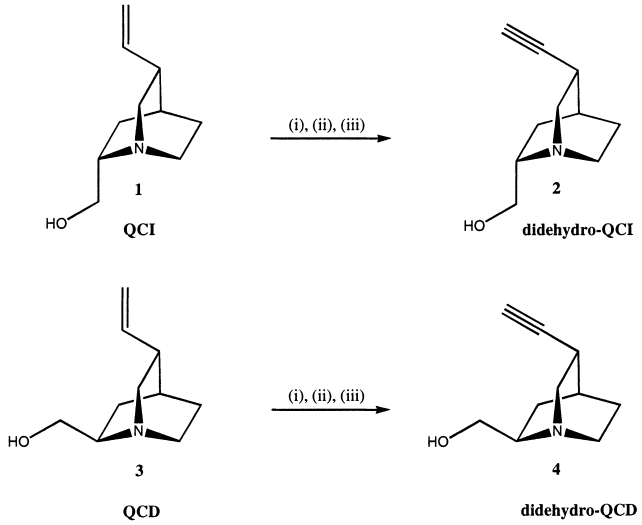
QCI **1** and QCD **3** were brominated rapidly by addition of bromine in solvent tetrachloromethane. The resulting precipitate then underwent self-induced mono-dehydrobromination giving a mixture of the corresponding vinylic bromides. This first dehydrobromination was caused by the basicity of the bridgehead nitrogen. Subsequent addition of triethylamine shortened the reaction time. The second dehydrobromination to the corresponding alkynes was more demanding, as expected. Orientating initial experiments with different bases such as $KOBu^t$ were not satisfactory. Use of the highly lipophilic methyltrioctylammonium chloride (aliquat 336) in catalytic amount together with 2 equiv. of solid KOH simplified the procedure and alkyne formation was feasible under mild conditions, with best overall results.[3] The two step sequence (method a), which included a purification of the vinylic bromides, provided overall yields of 78%, whereas the simple one-pot reaction (method b) without purification of intermediates gave a slightly lower yield of 68% (Scheme 1).

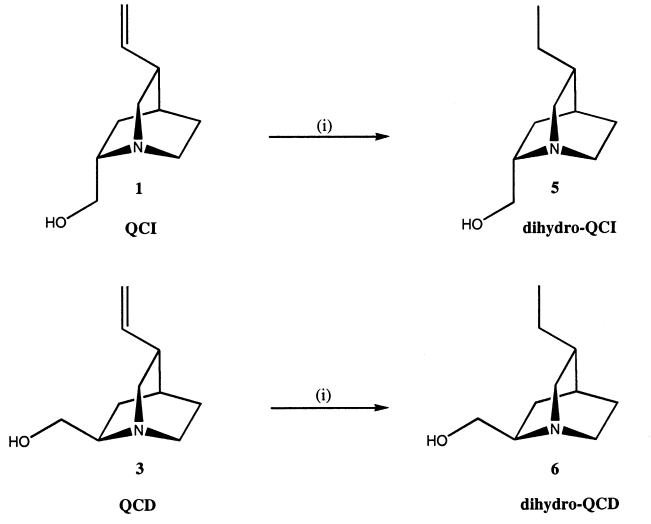


Reagents and conditions: (i) 1.8 eq. Br_2, CCl_4, rt, 1 h; (ii) 2 eq. Et_3N, $CHCl_3$, rt, 1 d; (iii) 2 eq. KOH, 0.2 eq. aliquat 336, THF, reflux, 4 h

Scheme 1.

We also prepared the related dihydro-derivatives of QCI and QCD in order to evaluate the properties of the alkynes. The hydrogenation was advantageously carried out homogenously with Wilkinson's catalyst to afford dihydro-QCI (**5**) and dihydro-QCD (**6**) in high yields (Scheme 2).

QCI **1**[4] and QCD **3** and their respective dihydro analogs **5** and **6** are highly viscous liquids at room temperature. We were pleased to find that the new alkynes **2** (mp 67°C) and **4** (mp 44°C) could readily be isolated as crystalline solids. On TLC the parent QCI **1** and QCD **3** are less polar than the four title compounds (R_f-values).[5] Thus the remote C5-substituent has a significant impact[6] not only on melting points, but also on chemical properties, i.e. basicity. It is assumed that the distortion of the azabicyclic cage affects the basicity of the bridgehead nitrogen. By comparison, the distortion of the azabicyclic cage in the alkynes of QCI **2** and QCD **4** is less than in dihydroquinine and dihydroquinidine.[7] The structure of 10,11-didehydroquincorine **2** was corroborated by X-ray crystal diffraction (see Experimental).



(i) $Rh(PPh_3)_3Cl$, H_2, toluene, ethanol (1:1)

Scheme 2.

3. Conclusion

We have described four new members of the Quincorine® and Quincoridine® family, including **2** and **4**. In view of the high synthetic flexibility of alkynes, the scope of these attractive chiral building blocks and chiral auxiliaries has been widened. To our knowledge the solid KOH/aliquat 336 system has previously been used for the preparation of simple alkynes.[3] We have shown that the conversion of functionalized alkenes into alkynes works well and utilizes inexpensive reagents. It is therefore the procedure of choice.

4. Experimental section

Melting points were determined on a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1710 infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer in deuterated chloroform unless otherwise stated, with tetramethylsilane as internal standard. Mass spectra were recorded on a Finnigan MAT 312 (70 eV) or a VG Autospec spectrometer at rt unless otherwise stated. Microanalyses were performed in the Department of Organic Chemistry of the University of Hannover. Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30–60 μm). Analytical TLC was carried out on aluminum-backed 0.2 mm silica gel 60 F_{254} plates (E. Merck). R_f-values were determined by using MTBE:methanol (20 ml, 5:1) and conc. NH_3 (0.2 ml). THF was distilled over sodium and benzophenone before use. CH_2Cl_2 (DCM) was distilled over CaH_2 before use. CCl_4 and $CHCl_3$ were distilled before use.

*4.1. (1S,2S,4S,5R)-2-Hydroxymethyl, 5-ethynyl-[2.2.2]-1-azabicyclooctane **2** and (1S,2R,4S,5R)-2-hydroxymethyl, 5-ethynyl-[2.2.2]-1-azabicyclooctane **4***

4.1.1. Method a

QCI **1** and QCD **3**, respectively (2.0 g, 12.0 mmol) were dissolved in dry CCl_4 (15 ml). Bromine (1.1 ml, 21.5 mmol) was added neat at 0°C. The reaction mixture was stirred for 1 h. After work-up ($CHCl_3$ and $Na_2S_2O_3$ solution) the resulting yellow solid was dissolved in $CHCl_3$ (25 ml). Et_3N (3.1 ml, 24 mmol) was added and the mixture was then stirred for 4 h at rt. Work-up ($CHCl_3$ and sat. $NaHCO_3$) and column chromatography (MTBE:methanol=5:1) furnished the yellowish vinylic bromides in 98% yield (2.80 g, 11.8 mmol).

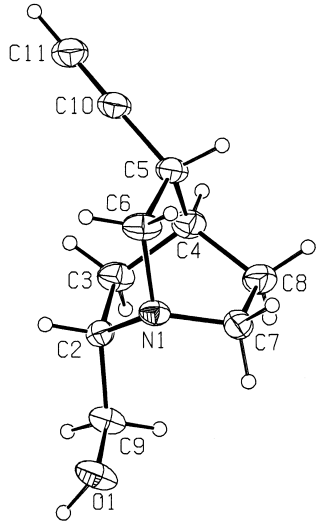
The vinylic bromides (200 mg, 0.81 mmol) were dissolved under argon in THF (10 ml), followed by addition of KOH (116 mg, 2.0 mmol) and aliquat 336 (0.73 ml, 0.16 mmol). The reaction mixture was then heated at reflux for 20 h. Work-up ($CHCl_3$ and sat. $NaHCO_3$) and column chromatography (MTBE:methanol=5:1) furnished the alkynes **2** and **4** in 78% overall yield (105 mg, 0.64 mmol).

4.1.2. Method b

QCI **1** and QCD **3**, respectively (2.0 g, 12.0 mmol) were dissolved in dry CCl_4 (15 ml). Bromine (1.1 ml, 21.5 mmol) was added neat at 0°C. The reaction mixture was stirred for 1 h. After removal of the solvent at reduced pressure the yellow solid was dissolved in $CHCl_3$ (25 ml). Et_3N (3.1 ml, 24 mmol) was added and the mixture was then stirred for 4 h at rt. After work-up ($CHCl_3$ and sat. $NaHCO_3$) the crude vinylic bromides (200 mg, 0.81 mmol) were dissolved under argon in THF (10 ml), followed by addition of KOH (116 mg, 2.0 mmol) and aliquat 336 (0.73 ml, 0.16 mmol). The reaction mixture was then heated at reflux for 20 h. Work-up ($CHCl_3$ and sat. $NaHCO_3$) and column chromatography (MTBE:methanol=5:1) furnished the alkynes **2** and **4** in 68% overall yield (1.35 g, 8.2 mmol).

Data for **2**. Solid, mp 67°C, $[\alpha]_D$ 35 (*c* 1.005; $CHCl_3$). IR ($CHCl_3$) ν 3304 (s), 3000 (m), 2940 (s), 2868 (m), 1620 (w), 1452 (m), 1412 (m), 1376 (w), 1336 (m), 1324 (m), 1300 (w), 1264 (m), 1228 (m), 1164 (w), 1132 (w), 1100 (w), 1020 (m), 996 (m), 960 (m), 936 (w), 864 (w) cm^{-1}; ^1H NMR (400 MHz) δ 3.51 (dd, 1H, *J*=10 Hz, *J*=7.4 Hz, H-9), 3.45 (dd, 1H, *J*=8 Hz, *J*=5 Hz, H-9), 3.26 (dd, 1H, *J*=13.2 Hz, *J*=9.8 Hz, H-6), 3.15–3.05 (m, 1H, H-2), 2.62–2.52 (ddd, *J*=10.7 Hz, *J*=4.8 Hz, *J*=2 Hz, H-3), 2.58–2.52 (m, 1H, H-5), 2.14–2.05 (m, 1H, H-3), 2.11 (d, 1H, *J*=2.5 Hz, H-11), 1.96–1.90 (m, 1H, H-4), 1.55–1.35 (m, 2H, H-8, H-8), 0.87–0.80 (m, 1H, H-3); ^{13}C NMR (100 MHz) δ 87.75 (C-10), 68.74 (C-11), 62.77 (C-9), 57.0 (C-2), 56.73 (C-6), 39.65 (C-7), 27.76 (C-5), 26.50 (C-4), 26.29 (C-8), 24.81 (C-3); MS *m/z* 165 (M^+, 19.46), 148 (6.53), 136 (6.63), 135 (12.09), 134 (100.00), 126 (15.83), 124 (10.18), 120 (4.09), 106 (19.17), 96 (6.64), 91 (7.98), 82 (17.09), 77 (21.37), 72 (22.39), 67 (5.86); HRMS calcd for $C_{10}H_{15}NO$: 165.1154, found 165.1142. X-Ray crystal structure, see Scheme 3.

Data for **4**. Solid, mp 44°C, $[\alpha]_D$ 92 (*c* 1.005; $CHCl_3$); mp 67°C. IR (cap. film) ν 3288 (s), 2940 (s), 2872 (s), 2108 (w), 1648 (w), 1452 (m), 1412 (m), 1388 (m), 1324 (m), 1256 (w), 1200 (w), 1136 (w), 1096 (m), 1072 (m), 1036 (s), 908 (m), 628 (s) cm^{-1}; ^1H NMR (400 MHz) δ 4.49 (s, 1H, OH), 3.64 (dd, 1H, *J*=11.7 Hz, *J*=10.3 Hz, H-9), 3.49 (dd, 1H, *J*=11.7 Hz, *J*=5.2 Hz, H-9), 3.11–2.84 (m, 5H, H-7, H-7, H-6, H-6, H-2), 2.60–2.52 (m, 1H, H-5), 2.12 (d, 1H, *J*=2.4 Hz, H-11), 1.95 (m, 1H, H-3), 1.72–1.64 (m, 1H, H-4), 1.63–1.53 (m, 2H, H-8, H-8), 1.51–1.43 (m, 1H, H-3); ^{13}C NMR (100 MHz) δ 88.68 (C-10), 69.76 (C-11), 62.03 (C-9), 57.83 (C-2), 48.45 (C-6), 47.76 (C-7), 28.08 (C-5), 27.32 (C-4), 25.32 (C-8), 24.02 (C-3); MS *m/z* 165 (M^+, 19.46), 148 (6.46), 135 (12.41), 134 (100.00), 132 (2.83), 126 (12.57), 124 (9.75), 120 (3.73), 108 (6.86), 106 (18.2), 94 (6.44), 91 (8.58), 84 (11.61), 82 (18.71), 80 (9.86), 79 (16.27), 77 (21.72), 72 (24.53); HRMS calcd for $C_{10}H_{15}NO$: 165.1154, found 165.1155.



X-ray crystal structure of 10,11-didehydro-QCI 2

10,11-didehydro-QCI **2**		torsion angles[8] of *vs.*	(p-chlorobenzoyl) 10,11-dihydroquinine:[7]	
N1-C2-C3-C4	6.1°		N1-C2-C3-C4	10°
N1-C6-C5-C4	11.0°		N1-C6-C5-C4	15°
N1-C8-C7-C4	9.7°		N1-C8-C7-C4	20°

Scheme 3. [7,8]

*4.2. (1S,2S,4S,5R)-2-Hydroxymethyl, 5-ethyl-[2.2.2]-1-azabicyclooctane **5** and (1S,2R,4S,5R)-2-hydroxymethyl, 5-ethyl-[2.2.2]-1-azabicyclooctane **6***

QCI **1** and QCD **3**, respectively (2.5 g, 15 mmol) and $Rh(PPh_3)_3Cl$ (250 mg, 10 wt%) were dissolved in a 1:1 mixture of ethanol:toluene (40 ml) and stirred under an H_2 atmosphere for 3 days. Work-up ($CHCl_3$ and sat. $NaHCO_3$) and column chromatography (MTBE:methanol=5:1) furnished dihydro-QCI (**5**) and dihydro-QCD (**6**) with yields in the range 97% (2.46 g, 14.55 mmol).

Data for **5**. Oil, $[\alpha]_D$ 11 (*c* 0.1, $CHCl_3$). IR ($CHCl_3$) ν 3332 (b), 2964 (s), 2880 (w), 1600 (m), 1461 (m), 1384 (m), 1340 (m), 1236 (m), 1120 (w), 1072 (m), 612 (m), 544 (m), 512 (m) cm^{-1}; ^1H NMR (400 MHz) δ 4.24 (s, 1H, OH), 3.48 (dd, 1H, J_2=11.6 Hz, J_3=10.3 Hz, H-9), 3.39 (dd, 1H, J_2=11.6 Hz, J_3=4.8 Hz, H-9), 3.15 (dd, 1H, *J*=13.4 Hz, *J*=9.6 Hz, H-2), 3.02–2.36 (m, 4H, H-7, H-7, H-6, H-6), 1.81–1.67 (m, 2H, H-5, H-4), 1.53–1.43 (m, 3H, H-8, H-8, H-3), 1.38 (q, 2H, *J*=7.2 Hz, H-10, H-10), 0.89 (t, 3H, *J*=7.2 Hz, H-11), 0.79–0.72 (m, 1H, H-3); ^{13}C NMR (100 MHz) δ 62.97 (C-9), 57.45 (C-2), 57.10 (C-6), 40.26 (C-7), 37.58 (C-5), 28.44 (C-8), 27.58 (C-10), 24.90 (C-4), 24.31 C-3), 12.13 (C-11); MS *m/z* 169 (M^+, 52.76), 152 (34.70), 138 (100.00), 126 (22.11), 121 (5.55), 110 (32.27), 105 (5.61), 97 (19.49), 91 (8.76), 82 (47.94)), 79 (10.00) 77 (7.83), 72 (46.13), 67 (17.74).

Data for **6**. Oil, $[\alpha]_D$ 147 (*c* 1.005; $CHCl_3$). IR ($CHCl_3$) ν 3356 (b), 2932 (s), 2868 (s), 1664 (m), 1460 (m), 1376 (m), 1320 (m), 1200 (w), 1148 (w), 1076 (m), 1040 (s), 932 (m), 908 (m), 860 (m) cm^{-1}; ^1H

NMR (400 MHz) δ 4.43 (s, 1H, OH, 3.50 (dd, 1H, J_2=11.4 Hz, J_3=10 Hz, H-9), 3.38 (dd, 1H, J_2=11.4 Hz, J_3=4.6 Hz, H-9), 2.94–2.80 (m, 4H, H-7, H-7, H-6, H-2), 2.43 (ddd, 1H, J_2=14.8 Hz, J=7.8 Hz, J=3 Hz, H-6), 1.69–1.60 (m, 2H, H-5, H-4), 1.59–1.50 (m, 1H, H-8), 1.48–1.39 (m, 2H, H-8, H-3), 1.31 (q, 2H, J=7.4 Hz, H-10, H-10), 1.15–1.06 (m, 1H, H-3), 0.86 (t, 3H, J=7.4 Hz, H-11); ^{13}C NMR (100 MHz) δ 62.13 (C-9), 57.74 (C-2), 48.93 (C-6), 48.30 (C-7), 37.50 (C-5), 27.61 (C-8), 25.74 (C-4), 25.49 (C-10), 23.61 (C-3), 11.92 (C-11); MS *m/z* 169 (M^+, 53.57), 152 (29.55), 138 (100.00), 128 (15.56), 122 (3.05), 110 (32.75), 101 (3.22), 96 (8.28), 86 (7.06), 82 (39.01), 77 (3.35), 72 (36.73).

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8. The angles given in the left hand column correspond to those on the right, but are numbered according to different conventions (IUPAC for 1-azabicyclo[2.2.2]octanes and traditional nomenclature for cinchona alkaloids). Detailed X-ray diffraction data will be submitted to Z. Krist-NCS.