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New hydrogenated and didehydrogenated 1,2-diamines of quincorine and quincoridine

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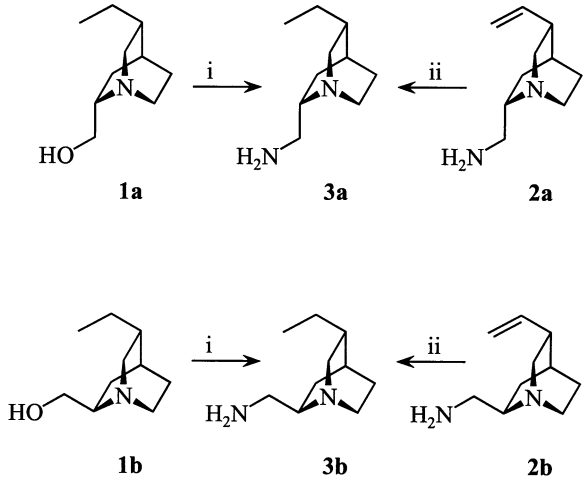
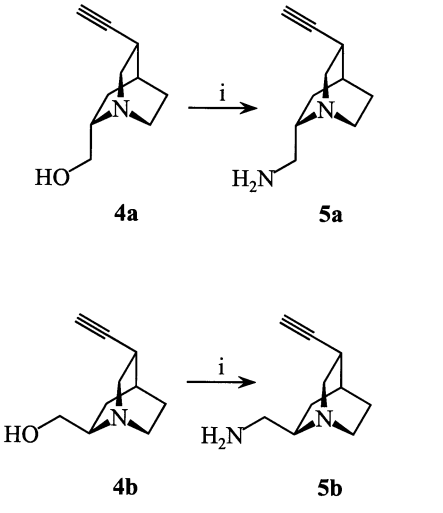
Abstract—Four new members of the family of 1,2-diamines of quincorine and quincoridine have been synthesized, being hydrogenated and didehydrogenated at the C10–C11 fragment. The alkynes, containing an additional amino group at C9, are potentially useful building blocks for cross-coupling reactions. Additional investigations concerning the chemical properties of the molecules point to a significant impact of the remote C5 substituent on the basicity of the bridgehead nitrogen.

1. Introduction

A number of reports[1] have appeared in recent years about the chemistry of quincorine (QCI) and quincoridine (QCD), two pseudo-enantiomeric 1,2-amino alcohols with four stereogenic centers each, including the (1*S*)-configured bridgehead nitrogen.[2] QCI and QCD represent chemically interesting building blocks, bearing several reactive centers, which can be utilized for the synthesis of a multitude of new compounds. The 1,2-diamines (1*S*,2*S*,4*S*,5*R*)-2-(aminomethyl)-5-vinyl-1-azabicyclo[2.2.2]octane, **2a** and (1*S*,2*R*,4*S*,5*R*)-2-(aminomethyl)-5-vinyl-1-azabicyclo[2.2.2]octane, **2b** (Schemes 1 and 2), derived from QCI and, respectively, QCD, are of special interest, because they seem to be promising building blocks as vicinal diamines in medicinal chemistry.[3]



Scheme 1. *Reagents and conditions*: (i) PPh_3, DEAD, HN_3, 0°C→reflux, 2.5 h; (ii) H_2, Pd/C 10%, THF, rt.



Scheme 2. *Reagents and conditions*: (i) PPh_3, DEAD, HN_3, THF, 0°C→reflux, 2.5 h.

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Although, research concerning the 1,2-diamines, **2a** and **2b** (Scheme 1) has been very active during the past couple of years, the existence and chemistry of saturated 5-alkyl- or unsaturated 5-alkynyl-1,2-diamines, **3a**/**b** and **5a**/**b** (Schemes 1 and 2) has not yet been described in the literature.

We herein present the synthesis of two new 1,2-diamines, derived from QCI and QCD, in two pseudo-enantiomeric forms that differ in the nature of the C10–C11 functionality, being one of the reactive centers in the molecules.

2. Results and discussion

2.1. Hydrogenated 1,2-diamines of quincorine and quincoridine

Starting from the known compounds **2a** and **2b**, we synthesized the QCI- and QCD-derivatives, **3a** and **3b**, according to the usual method (hydrogenation in the presence of Pd/C) in quantitative yield.

The same products were obtained, when the saturated derivatives[4] **1a** and **1b** were reacted with ammonia according to the method of Hoffmann.[1] Compounds **3a** and **3b** represent new derivatives of cinchona alkaloids with a saturated C10–C11 grouping. Our intention for the preparation of these derivatives was to obtain 1,2-diamines of QCI and QCD without the vinyl functionality, in order to avoid possible side reactions during the functionalization of the primary amino group. Compared to **1a**/**b**, the presence of a primary amino group instead of an alcohol function is advantageous, because these amines should allow facile syntheses of new compounds bearing the QCI or QCD moiety.

2.2. Didehydrogenated 1,2-diamines of quincorine and quincoridine

10,11-Didehydro-derivatives of quincorine and quincoridine are important precursors for the synthesis of the corresponding arylalkynes and conjugated enynes that are formed, e.g. via Pd-catalyzed cross-coupling of terminal alkynes with aryl or alkenyl halides (known as the Sonogashira Reaction).[5] They also represent important building blocks in medicinal chemistry.[6] Starting from saturated dihydro-derivatives[4] we have completed the series of 1,2-diamines of quincorine and quincoridine from the fully saturated analogs via the vinylic dehydro-derivatives[1] to alkynic didehydro-derivatives. Reaction of **4a** and **4b** with ammonia according to the usual method[4] provided the corresponding acetylenes **5a** and **5b** in moderate yields (Scheme 2).

The new alkynes **5a**/**b** proved to be more polar and more basic than the corresponding saturated and vinylic 1,2-diamines **2a**/**b** and **3a**/**b** (R_f values from TLC). Thus, the remote C5-substituent obviously has a significant impact on chemical properties, i.e. polarity and basicity. It is assumed that the distortion of the azabicyclic cage affects the basicity of the bridgehead nitrogen. By X-ray crystal structure determination it was proved that this distortion in **4a** and **4b** is less than that seen for dihydroquinine and dihydroquinidine.[7]

3. Conclusions

We have described four new members of the family of quincorine- and quincoridine-1,2-diamines **3a**, **3b**, **5a** and **5b**. The saturated 1,2-diamines, **3a** and **3b**, could be synthesized either by reacting the hydrogenated alcohols, **1a** and **1b** with ammonia, or by hydrogenating the unsaturated 1,2-diamines, **2a** and **2b**, with H_2/Pd/C. The synthesis of the didehydrogenated 1,2-diamines, **5a** and **5b** led to two new compounds with two reactive centers each, useful for either cross-coupling reactions at C11 or for derivatization at the primary nitrogen atom. These compounds have huge potential as building blocks in the development of new and effective medicinal compounds.

Investigations concerning the basicity of the bridgehead nitrogen of **5a** and **5b** suggest that the remote C5 substituent has a significant impact on the chemical properties of these derivatives.

4. Experimental

4.1. General

Experimental conditions and instruments used for the NMR spectroscopic and mass spectrometric investigations were identical to those mentioned in Ref. 1. Starting compounds **1a/b**, **2a/b** and **4a/b** were synthesized according to methods described in the literature.[1,4] ^{1}H and ^{13}C NMR resonances of compounds **3a/b** and **5a/b** were assigned using the following numbering scheme (Fig. 1):

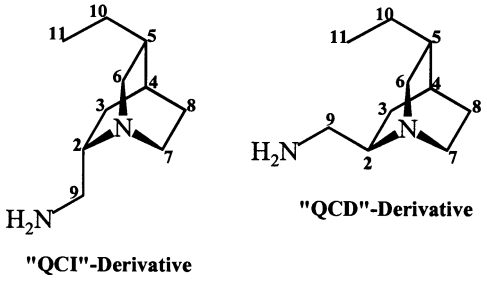

Figure 1. Numbering scheme for the assignment of the NMR resonances.

4.2. Synthesis of diamines 3a,b and 5a,b

The diamines **3a,b** and **5a,b** were prepared according to two general methods:

4.3. A: General procedure of Hoffmann:[1]

4.3.1. (1*S*,2*S*,4*S*,5*R*)-2-(Aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]octane, 3a. QCI (3.0g, 18 mmol) was allowed to react according to the reported general procedure[1] to afford the corresponding azide (4.38 g, 76%) as a yellowish solid. A portion of the product (3.0 g, 15.6 mmol) was, allowed to react according to the general procedure to afford the diamine, **3a** as a colourless oil (1.34 g, 52%); $[\alpha]_D^{20}$ −28.1 (c=1, EtOH); ^{1}H NMR (400 MHz): δ 0.75–0.85 (m, 1H, H-10$_a$), 0.88 (t, 3H, J=7.2 Hz, H-11), 1.29 (s, br, 2H, NH$_2$), 1.32–1.51 (m, 5H, H-3, H-8, H-5), 1.53–1.70 (m, 1H, H-4), 1.75–1.85 (m, 1H, H-10$_b$), 2.36–2.42 (m, 1H, H-6$_a$), 2.51–2.64 (m, 2H, H-7$_a$, H-9$_a$), 2.67–2.76 (m, 2H, H-2, H-9$_b$), 2.81–2.94 (m, 1H, H-7$_b$), 3.17 (dd, 1H, J=13.4 Hz, J=9.3 Hz, H-6$_b$); ^{13}C NMR (100 MHz): δ 58.75 (CH, C-2), 57.66 (CH$_2$, C-6), 45.60 (CH$_2$, C-9), 40.50 (CH$_2$, C-7), 37.59 (CH, C-5), 28.75 (CH$_2$, C-8), 27.51 (CH$_2$, C-3), 26.58 (CH$_2$, C-10), 25.30 (CH, C-4), 12.09 (CH$_3$, C-11); EI–MS: m/z (%): 168 (60), 152 (20), 138 (90), 110 (100), 96 (35), 82 (60), 70 (25), 55 (50), 42 (40); $C_{10}H_{20}N_2$ (168.28) Calcd.: C 71.37, H 11.98, N 16.65%; found: C 71.18, H 11.92, N 16.68%.

4.3.2. (1*S*,2*R*,4*S*,5*R*)-2-(Aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]octane, 3b. QCD (4.5g, 27 mmol) was allowed to react according to the general procedure to afford the corresponding azide (3.93g, 75%) as a yellowish solid. A portion of this product (2.5 g, 13.0 mmol) was allowed to react according to the general procedure to afford the diamine, **3b** as a colourless oil (1.16g, 54%); $[\alpha]_D^{20}$ +143.3 (c=1, EtOH); ^{1}H NMR (400 MHz): δ 0.86 (t, 3H, J=7.3 Hz, H-11), 1.13 (ddt, 1H, J=2.1 Hz, J=8.1 Hz, J=7.6 Hz, H-8$_a$), 1.32 (m, 2H, H-10), 1.35–1.40 (m, 1H, H-5), 1.45–1.52 (m, 2H, H-3$_a$, H-8$_b$), 1.58–1.65 (m, 2H, H-3$_b$, H-4), 2.39 (dd, 1H, J=13.8 Hz, J=7.3 Hz, H-9$_a$), 2.53 (dd, 1H, J=12.5 Hz, J=4.7 Hz, H-7$_a$), 2.62–2.69 (m, 1H, H-2), 2.72–2.75 (m, 1H, H-7$_b$), 2.74–2.89 (m, 3H, H-6, H-9$_b$); ^{13}C NMR (100 MHz): δ 58.84 (CH, C-2), 49.35 (CH$_2$, C-6), 48.57 (CH$_2$, C-9), 44.55 (CH$_2$, C-7), 37.75 (CH, C-5), 27.87 (CH$_2$, C-3), 25.94 (CH, C-4), 25.86 (CH$_2$, C-8), 25.57 (CH$_2$, C-10), 11.95 (CH$_3$, C-11); EI-MS: m/z (%): 168 (70), 152 (20), 138 (100), 110 (95), 96 (30), 82 (70), 70 (25), 55 (50), 42 (45); $C_{10}H_{20}N_2$ (168.28) Calcd.: C 71.37, H 11.98, N 16.65%; found: C 71.25, H 11.87, N 16.66%.

4.3.3. (1*S*,2*S*,4*S*,5*R*)-2-(Aminomethyl)-5-ethynyl-1-azabicyclo[2.2.2]octane, 5a. QCI (3.0g, 18 mmol) was allowed to react according to the general procedure to afford the corresponding azide (4.36g, 75%) as a yellowish solid. A portion of this product (3.9 g, 20.3 mmol) was allowed to react according to the general procedure to afford the diamine, **6a** as a colourless oil (1.91g, 57%); $[\alpha]_D^{20}$ +14.3 (c=1, EtOH); ^{1}H NMR (400 MHz): δ 0.78–0.84 (m, 1H, H-8$_a$), 1.29–1.47 (m, 2H, H-3), 1.65 (s, br, 2H, NH$_2$), 1.83 (sext, 1H, J= 3.0 Hz, H-4), 2.02 (d, 1H, J=2.5 Hz, H-11), 2.03–2.11 (m, 1H, H-8$_b$), 2.41–2.47 (m, 1H, H-5), 2.54 (dd, 1H, J=13.1 Hz, J=5.1 Hz, H-7$_a$), 2.51–2.55 (m, 1H, H-9$_a$), 2.66 (dd, 1H, J=13.0 Hz, J=10.3 Hz, H-9$_b$), 2.78–2.88 (m, 3H, H-2, H-6$_a$, H-7$_b$), 3.22 (dd, 1H, J=13.0 Hz, J=10.0 Hz, H-6$_b$); ^{13}C NMR (100 MHz): δ 88.16 (CH, C-11), 68.34 (C, C-11), 58.45 (CH, C-2), 57.17 (CH$_2$, C-6), 45.17 (CH$_2$, C-9), 39.89 (CH$_2$, C-7), 27.76 (CH, C-5), 26.93 (CH$_2$, C-8), 26.87 (CH, C-4), 26.49 (CH$_2$, C-3); EI-MS: m/z (%): 164 (20), 148 (10), 134 (100), 106 (30), 95 (25), 82 (17), 77 (20); $C_{10}H_{16}N_2$ (164.25) Calcd.: C 73.13, H 9.82, N 17.06%; found: C 72.27, H 9.80, N 16.71%.

4.3.4. (1*S*,2*R*,4*S*,5*R*)-2-(Aminomethyl)-5-ethynyl-1-azabicyclo[2.2.2]octane, 5b. QCD (5.0g, 30 mmol) was allowed to react according to the general procedure to afford the corresponding azide (4.49g, 77%) as a yellowish solid. From this product, 4.0g (20.8 mmol) was allowed to react according to the general procedure to afford the diamine, **6b** as a colourless oil (2.03g, 59%); $[\alpha]_D^{20}$ +168.7 (c=1, EtOH); ^{1}H NMR (400 MHz): δ 1.45–1.70 (m, 4H, H-3, H-8), 1.89 (dq, 1H, J=2.1 Hz, J=1.8 Hz, H-4), 2.09 (d, 1H, J=2.4 Hz, H-11), 2.43–2.48 (m, 1H, H-5), 2.61 (dd, 1H, J=12.8 Hz, J=4.9 Hz, H-7$_a$), 2.68-2.77 (m, 1H, H-2), 2.83–2.94 (m, 4H, H-6, H-7$_b$, H-9$_a$), 3.00 (dd, 1H, J=13.6 Hz, J=10.6 Hz, H-9$_b$); ^{13}C NMR (100 MHz): δ 87.51 (CH, C-11), 68.78 (C, C-10), 58.49 (CH, C-2), 48.72 (CH$_2$, C-6), 48.02 (CH$_2$, C-9), 44.31 (CH$_2$, C-7), 28.28 (CH, C-5), 27.50 (CH, C-4), 26.22 (CH$_2$, C-8), 25.60 (CH$_2$, C-3); EI-MS: m/z (%): 164 (50), 148 (10), 134 (100), 125 (30), 106 (60), 94 (30), 82 (40), 77 (35), 42 (40); $C_{10}H_{16}N_2$ (164.25) Calcd.: C 73.13, H 9.82, N 17.06%; found: C 72.33, H 9.83, N 16.96%.

4.4. B: Reduction of the vinylic function of 2a and 2b

A suspension of **2a** (and **2b**) (3g, 18 mmol) and Pd/C 10% in THF (100 ml) at room temperature was maintained under H_2 (1 bar) for a period of 8 h. Subsequently, the suspension was filtered through Celite and the filtrate was evaporated i.v. to give pure **3a** and **3b** in 98% yield (for characterization see method **A.**).

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