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Novel Bridged Bicyclic α-Amino Acid Esters and Key Derivatives from Quincorine and Quincoridine

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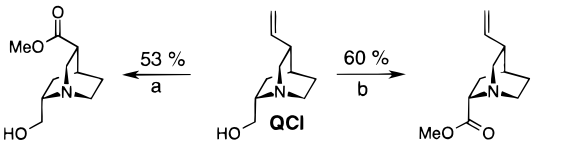
ABSTRACT



Oxidation of Quincorine (QCI) and Quincoridine (QCD) has been investigated, giving bicyclic α-amino acids and dicarboxylic acid derivatives, which are epimerically and also enantiomerically pure. Acidic Cr(VI)-mediated oxidation (Jones oxidation) has been optimized with respect to reaction conduct and work up (addition of ethylenediamine).

Monosubstituted quinuclidines play an important role in medicinal chemistry as the quinuclidine nucleus has been found to be a good mimic for the quaternary nitrogen in acetylcholine. However, unlike acetylcholine, the unprotonated form is able to cross the blood−brain barrier.[1] Quinuclidine derivatives are able to block 5-HT_3 and NK_1 receptors[2] and to act as squalene synthase inhibitors.[3] Quincorine (QCI, **1**) and pseudoenantiomeric Quincoridine (QCD, **5**) are homochiral 1,2-amino alcohols containing four stereogenic centers each, including the chiral 1*S*-configured bridgehead nitrogen.[4,5] The quinuclidine derivatives described herein represent a novel class of seminatural, conformationally constrained amino acid esters and dicarboxylic esters, which are also bicyclic. In contrast to the traditional quinuclidines frequently used in pharmacology, the QCI- and QCD-based title compounds contain two side chains at C2 and C5. These side chains have now been further chemodifferentiated[6] without recourse to protecting groups.

Results and Discussion. Oxidation of 1,2-amino alcohols to α-amino acids is well-known to be difficult and remains a challenging task especially if the basic amino nitrogen is not masked or protected.[7] To our knowledge, a readily accessible route to quinuclidine-2-carboxylic acids has not been described in the literature. A few de novo syntheses and semisynthetic routes provide the desired target molecules (acids, esters, aldehydes, etc.) only in poor yields and as epimeric mixtures.[8] During studies on the oxidative functionalization of carbon C9 of QCI **1** and of QCD **5** we have

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(4) QCI and QCD are derived from the *Cinchona* alkaloids quinine and quinidine. They are commercially available from Aldrich.

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(7) Little information on the oxidation of hydroxymethyl-quinuclidine is available in the literature. See, however: Prelog, V.; Cerkovnikov, E. *Liebigs Ann.* **1940**, *545*, 229, 262.

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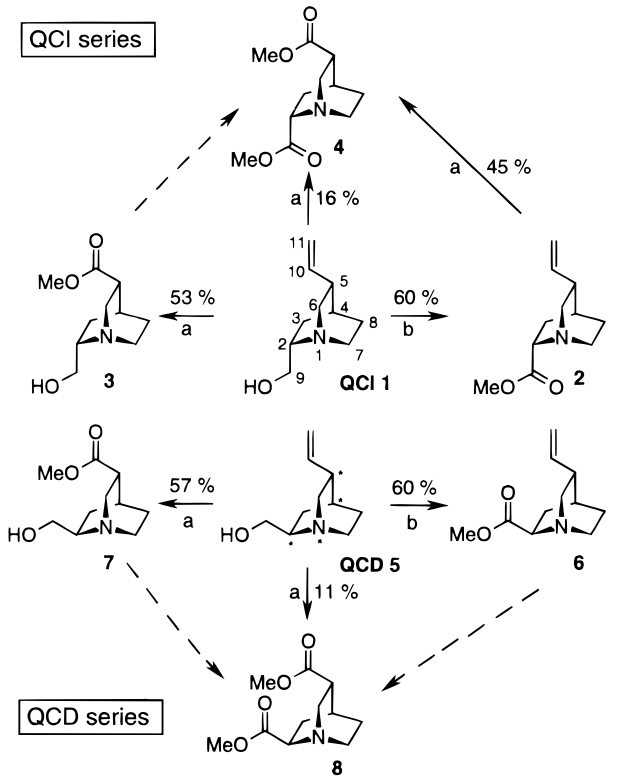
found Jones oxidation combined with subsequent esterification to be the only suitable method (Scheme 1, Table 1).

Scheme 1. Oxidation of **1** and **5**[a]



[a] Reagents and conditions: (a) (i) $KMnO_4$, H_2SO_4, H_2O, 0 °C → room temperature; (ii) MeOH, catal. HCl, room temperature; (b) (i) see Table 2; (ii) MeOH, catal. HCl, reflux.

All other standard oxidation methods failed to give the desired compounds. In some cases *N*-oxides (entries 2 and 5) and aldol-like coupling products (entries 9 and 10) were obtained. The aldehyde itself proved to be extremely unstable. Therefore, further investigations toward a stepwise oxidation were abandoned in favor of the direct route.

To optimize the Jones oxidation, we carried out the reaction under a variety of conditions (Table 2). Slow and careful addition of Jones reagent was crucial for obtaining the epimerically pure α-amino acid esters **2** and **6**. The formation of the carboxylic acid is assumed to proceed via a stable chromium chelate, which precludes epimerization at carbon C2. However, this chelate is believed to make aqueous workup also more difficult. Addition of ethylenediamine during workup facilitates isolation of the desired product, whereas the presence of ethylenediamine in the preceding oxidation reaction led to complete epimerization at carbon C2 and reduced the yield to 17% (entry 5).[21] Intermolecular hydrogen bonding of the 1,2-amino alcohol is believed to be another reason for the sluggish and incomplete oxidation process. To minimize intermolecular hydrogen-bond formation the molarity of the solution was decreased. Refluxing[22] the reaction mixture and also refluxing on subsequent esterification improved the yield of epimerically and enantiomerically pure α-amino acid ester **2** to 60%.[23]

Table 1. Oxidation at C9 at **1** and **5**

entry	reagent	target	result
1	β-hydride acceptors[9]	aldehyde	–
2	HOTMC[a,10]	aldehyde	–/*N*-oxide
3	DMSO methods[11]	aldehyde	–/18%
4	PDC-DCM[12]	aldehyde	–
5	TEMPO[13]	aldehyde	*N*-oxide
6	Dess–Martin[14]	aldehyde	–
7	DDQ[15]	aldehyde	–
8	Activated MnO_2[16]	aldehyde	-
9	Ag_2CO_3/Celite[17]	aldehyde	aldol-like products
10	Ag_2O/Ag_2CO_3/Celite[18]	acid in situ	aldol-like products
11	mod. Kornblum/NaOCl	acid in situ	complex products
12	$KMnO_4$[19]	acid	**3**,[c] 53%[d]
13	Cr reagents[20]	acid	–
14	PDC-DMF[12]	acid	–
15	Jones oxidation[b]	acid	**2**,[c] 60%[d]

[a] Highly oxidized transition metal compounds. [b] See Table 2. [c] Diastereomerically pure. [d] After esterification.

Table 2. Optimized Oxidation of **1** to **2**

entry	Jones oxidation	esterification[a] in situ	[mol/L]	workup[b]	yield (%)
1	catal. Jones; H_5IO_6[24]	14 d, rt	0.28	pH 5	0
2	3 d, rt; $Ba(OH)_2$, $CuSO_4$[25]	3 d, rt	0.28	pH 5, eda	0
3	5 d, rt, ultrasound	5 d, rt, ultrasound	0.24	pH 5, eda	0
4	2 d, rt	2 d, rt	0.24	KOH, pH 9, eda	9[c]
5	12 h, rt, eda	14 d, rt, eda	0.40	pH 5, eda	17[d]
6	7 d, rt	7 d, rt	0.24	pH 5, eda	26[c]
7	14 d, rt	14 d, rt	0.24	pH 5, eda	28[c]
8	3 d, reflux	3 d, reflux	0.125	pH 8, eda, 7 d	54[c]
9	3 d, reflux	3 d, reflux	0.10	pH 8, eda, 5 d	60[c]

[a] MeOH, HCl (catal.). [b] With $NaHCO_3$ (saturated aqueous) unless otherwise stated. [c] Epimerically pure. [d] Mixture (1:1) of epimers at C2; eda = ethylenediamine.

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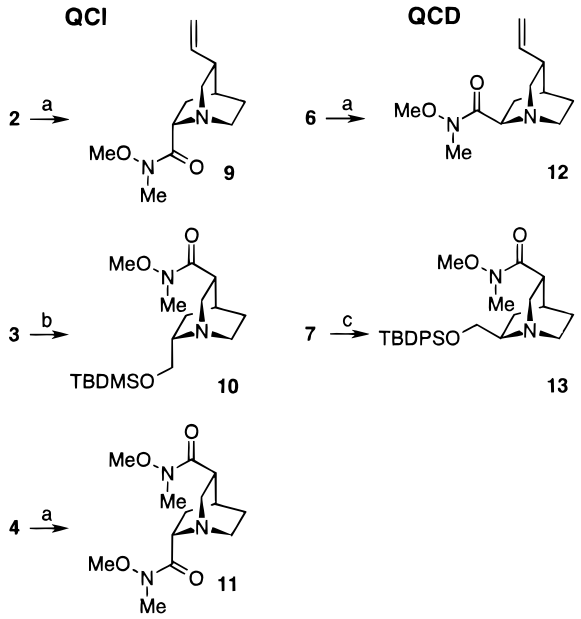
To our surprise, $KMnO_4$-mediated oxidation cleaved the vinylic side chain of **1** and **5** in the presence of the unprotected primary C9 alcohol function.[27] The configuration at carbon C5 was preserved and isolation of the ϵ-hydroxy monoesters **3** and **7** was possible upon esterification. The 1,6-dicarboxylic acid esters **4** and **8** were formed as side products in changing yield (10−20%). In general, the hydroxymethyl side chain of both QCI and QCD is very unreactive toward oxidation even when using powerful HOTMCs (Table 1, entry 2).

Because of their utility in organic synthesis, Weinreb amides[26] were prepared, including bis-(Weinreb amide) **11**. These amides were formed in good yield (Scheme 2) and

Scheme 2. Synthesis of *N*-Methoxy-*N*-methylamides[a]



[a] Reagents and conditions: (a) MeNHOMe·HCl, Me_2AlCl, DCM, 0 °C → room temperature; yield up to 87% (b) (i) TBDMSCl, Et_3N, DMAP, DCM, room temperature; (ii) MeNHOMe·HCl, Me_2AlCl, DCM, 0 °C → room temperature; yield over 2 steps 57%; (c) (i) TBDPSCl, Et_3N, DMAP, DCM, room temperature; (ii) MeNHOMe·HCl, Me_2AlCl, DCM, 0 °C → room temperature; yield over 2 steps 62%.

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(22) High-temperature favors epimerization. We believe the chelated chromium prevents epimerization from taking place.
(23) The configuration at C2 and C5 can easily be deduced by ^1H and ^{13}C NMR, especially NOESY [cross-peak for H2 and H3-*endo* in QCI (none) and QCD (present)]. All compounds of Scheme 1 are also epimers. Epimeric purity has been determined by ^{13}C NMR and GC.
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(27) **Selected Experimental Procedures and Spectroscopic Data. General Procedure for the Synthesis of C9 Esters.** A solution of Quincorine **1** or Quincoridine **5** (1 equiv) in acetone was cooled to 0 °C and treated dropwise with Jones reagent (2.67 M solution, 3.6 equiv). The mixture was refluxed for 3 days, followed by addition of 2-propanol at room temperature and stirred for 30 min. The solvent was removed and the residue was dried for 3 days in vacuo. The solid was dissolved in absolute MeOH under argon at room temperature, catalytic amounts of hydrochloric acid (concentrated) were added, and the reaction mixture was refluxed for 3 days. Two-thirds of the solvent was removed. The solution was cooled to 0 °C, and the pH was adjusted to 7−8 by adding $NaHCO_3$ (saturated aqueous), and then ethylenediamine was added dropwise within 15 min. Thereafter Et_2O was added for liquid−liquid extraction over 2 days. The organic layer was dried ($MgSO_4$), the solvent was evaporated in vacuo, and the crude product was purified by column chromatography (EtOAc/MeOH 10:1) to provide the desired esters as pale yellow oils. **(1*S*,2*S*,4*S*,5*R*)-5-Vinyl-1-azabicyclo[2.2.2]octane-2-carboxylic Acid Methyl Ester (2).** Quincorine **1** (840 mg, 5.00 mmol, 1.0 equiv) was allowed to react according to the general procedure to yield C9 ester **2** (60%, 586 mg, 3.00 mmol): IR ($CHCl_3$) ν 2952, 2870, 1734, 1637, 1456, 1437, 1372, 1264, 1230, 1081, 1036, 993, 909, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddd, 1H, *J* 17.8, 10.5 and 7.3 Hz, H-10), 5.10−5.04 (m, 2H, H-11), 3.76 (s, 3H, OMe), 3.56−3.49 (m, 1H, H-2), 3.19 (dd, 1H, *J* 14.4 and 10.0 Hz, H-6), 2.95−2.85 (m, 1H, H-7), 2.83−2.70 (m, 2H, H-6, H-7), 2.35−2.26 (m, 1H, H-5), 2.01−1.92 (m, 1H, H-4), 1.86−1.78 (m, 2H, H-8), 1.66−1.46 (m, 2H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.36 (C, C-9), 141.36 (CH, C-10), 114.63 (CH_2, C-11), 58.72 (CH_3, OMe), 55.00 (CH_2, C-6), 52.23 (CH, C-2), 43.09 (CH_2, C-7), 39.30 (CH_2, C-5), 27.23 (CH_2, C-8), 27.10 (CH, C-4), 23.77 (CH_2, C-3); MS *m*/*z* 195 (M^+, 15.02), 180 (4.77), 154 (2.92), 137 (11.98), 136 (100.00), 122 (2.57), 108 (5.47), 100 (5.86), 95 (4.59), 81 (12.45), 77 (3.28), 67 (5.01); HRMS calcd for $C_{11}H_{17}N_1O_2$ 195.1259, found 195.1259. **General Procedure for the Synthesis of C10 Esters.** A solution of $KMnO_4$ (2.05 equiv) in H_2O was slowly added to a vigorously stirred solution of the corresponding β-amino alcohol sulfate (1.0 equiv) in 2 N H_2SO_4 at 0 °C under argon. After beeing stirred at room temperature for 5 h, the reaction mixture was concentrated and dried under reduced pressure. The residue was dissolved in absolute MeOH, concentrated HCl (catal.) was added, and the reaction mixture was stirred at room temperature for 5 days. After neutralization with saturated aqueous $NaHCO_3$, the aqueous layer was extracted (CH_2Cl_2). The organic layer was dried, the solvent was evaporated, and the crude product was purified by column chromatography (EtOAc/MeOH 6:1) to afford the C10 ester including C9, C10 diesters. **(1*S*,2*S*,4*S*,5*R*)-2-(Hydroxymethyl)-1-azabicyclo[2.2.2]octane-5-carboxylic Acid Methyl Ester (3) and (1*S*,2*S*,4*S*,5*R*)-1-Azabicyclo-[2.2.2]octane-2,5-dicarboxylic Acid Dimethyl Ester (4).** Quincorine sulfate (7.93 g, 30.0 mmol, 1.0 equiv) was allowed to react according to the general procedure to yield C10 ester **3** (53%, 3.16 g, 15.9 mmol) as the main product and C9, C10 diester **4** (16%, 1.087 g, 4.79 mmol) as a side product. Data for **3**: IR ($CHCl_3$) ν 3434, 2999, 2952, 2878, 1728, 1456, 1437, 1371, 1333, 1236, 1198, 1178, 1138, 1100, 1050, 1017, 983 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72−3.68 (m, 1H, H-9), 3.69 (s, 3H, OMe), 3.62 (dd, 1H, *J* 11.5 and 10.4 Hz, H-9), 3.44−3.36 (m, 2H, H-2, H-6), 3.02−2.92 (m, 2H, H-7, H-7), 2.87 (dd, 1H, J 13.3 and 8.9 Hz, H-6), 2.57−2.51 (m, 1H, H-5), 2.23−2.19 (m, 1H, H-4), 1.70−1.64 (m, 2H, H-3, H-8), 1.57−1.49 (m, 1H, H-8), 1.10−1.03 (m, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.54 (C, C-10), 62.02 (CH_2, C-9), 57.47 (CH, C-2), 51.93 (CH_3, C-11), 48.76 (CH_2, C-6), 42.94 (CH_2, C-7), 41.20 (CH, C-5), 25.89 (CH_2, C-3), 25.18 (CH, C-4), 24.64 (CH_2, C-8); MS *m*/*z* 199 (M^+, 71.00), 197 (22.27), 182 (36.77), 168 (100.00), 158 (64.92), 140 (75.08), 126 (18.40), 112 (25.66), 96 (17.63), 82 (65.44); HRMS calcd. for $C_{10}H_{17}NO_3$ 199.1208, found 199.1208. Data for **4**: IR ($CHCl_3$) ν 3434, 2951, 2878, 1776, 1731, 1462, 1410, 1372, 1292, 1230, 1151, 1136, 1119, 1086, 1027, 996, 834 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.53−3.45 (m, 1H, H-2), 3.36 (ddd, 1H, *J* 14.5, 7.5, and 2.4 Hz, H-6), 3.05−2.97 (m, 2H, H-7, H-7), 2.91−2.82 (m, 1H, H-6), 2.54−2.48 (m, 1H, H-5), 2.30−2.26 (m, 1H, H-4), 2.02−1.96 (m, 1H, H-3), 1.79−1.71 (m, 1H, H-8), 1.65−1.59 (m, 2H, H-8, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.44 (C, C-10), 173.03 (C, C-9), 58.08 (CH, C-2), 52.24 (CH_3, C-11), 51.81 (CH_3, C-12), 48.34 (CH_2, C-6), 46.01 (CH_2, C-7), 40.86 (CH, C-5), 25.82 (CH_2, C-3), 25.02 (CH, C-4), 24.94 (CH_2, C-8); MS *m*/*z* 227 (M^+, 44.95), 212 (22.55), 196 (16.75), 186 (2.84), 168 (100.00), 155 (10.13), 140 (53.19), 126 (3.99), 113 (13.81), 100 (14.87), 82 (47.16); HRMS calcd for $C_{11}H_{17}NO_4$ 227.1157, found 227.1157.

widen the scope of application of **1** and **5** toward the synthesis of pharmacologically important and interesting compounds with additional heterocyclic and aromatic ring systems.

Conclusion. Although there are potentially many methods for the difficult oxidation of protected and unprotected 1,2-amino alcohols the acidic Cr(VI)-mediated procedure has proven to be the only feasible oxidation method for the demanding 2-(hydroxymethyl)-5-vinylquinuclidine system. Moreover, after optimization all desired products were isolated in epimerically pure form and also enantiopure. The various reactions are all one-pot methods. Due to their low molecular weight, their compact and rigid [2.2.2]azabicyclic structure, and their chemodifferentiated sidearms, the new azabicyclic carboxylic acids and dicarboxylic acids are versatile homochiral building blocks for organic synthesis. The 2-amino hexanedioic esters **4** and **8** are one-carbon homologues and mimics of 2-amino pentanedioic acid (glutamic acid) and like the other azabicyclics (Scheme 1) of interest in medicinal chemistry and combinatorial chemistry.

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Supporting Information Available: Experimental procedures and complete spectroscopic data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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