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-HT₃ and NK₁ receptors² 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, conformation-

ally 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 chemodifferentiated⁶ 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

^{(1) (}a) Wadsworth, H. J.; Jenkins, S. M.; Orlek, B. S.; Cassidy, F.; Clark, M. S. G.; Brown, F.; Riley, G. J.; Graves, D.; Hawkins, J.; Naylor, C. B. *J. Med. Chem.* **1992**, *35*, 1280. (b) Baker, R.; Street, L. J.; Reeve, A. J.; Saunders, J. *J. Chem. Soc., Chem. Commun.* **1991**, 760.

^{(2) (}a) Snider, R. M.; Constantine, J. W.; Lowe, J. A.; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Hess, H.-J. *Science* **1991**, *251*, 435. (b) Lowe, J. A.; Ewing, F. E.; Snider, R. M.; Longo, K. P.; Constantine, J. W.; Lebel, W. S.; Woody, H. A.; Bordner, J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 839.

^{(3) (}a) Brown, G. R.; Foubister, A. J.; Freeman, S.; McTaggart, F.; Mirrlees, D. J.; Reed, A. C.; Smith, G. J.; Taylor, M. J.; Thomason, D. A.; Whittamore, P. R. O. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 597. (b) Brown, G. R.; Clarke, D. S.; Foubister, A. J.; Freeman, S.; Harrison, P. J.; Johnson, M. C.; Mallion, K. B.; McCormick, J.; McTaggart, F.; Reid, A. C.; Smith, G. J.; Taylor, M. J. *J. Med. Chem.* **1996**, *39*, 2971.

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

⁽⁵⁾ Hoffmann, H. M. R.; Plessner, T.; von Riesen, C. Synlett 1996, 690.
(6) (a) Schrake, O.; Braje, W. M.; Hoffmann, H. M. R.; Wartchow, R. Tetrahedron: Asymmetry 1998, 9, 3715. (b) Wartchow, R.; Schrake, O.; Braje, W. M.; Hoffmann, H. M. R. Z. Kristallogr. NCS 1999, 214, 285.

⁽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.

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



^{*a*} Reagents and conditions: (a) (i) KMnO₄, H₂SO₄, H₂O, 0 °C \rightarrow 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

Table 1.	Oxidation	at C9	at 1	and 5
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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 ₂ CO ₃ /Celite ¹⁷	aldehyde	aldol-like products		
10	Ag ₂ O/Ag ₂ CO ₃ /Celite ¹⁸	acid in situ	aldol-like products		
11	mod. Kornblum/NaOCl	acid in situ	complex products		
12	KMnO4 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.

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

Table	2. Optimized	Oxidation of 1	to 2		
entry	Jones oxidation	esterification ^a in situ	[mol/L]	workup ^b	yield (%)
1	catal. Jones; H ₅ IO ₆ ²⁴	14 d, rt	0.28	рН 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 NaHCO₃ (saturated aqueous) unless otherwise stated. ^{*c*} Epimerically pure. ^{*d*} Mixture (1:1) of epimers at C2; eda = ethylenediamine.

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. Refluxing²² 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

(12) Corey, E. J.; Schmidt, G. Tetrahedron Lett. 1979, 399.

(13) Ma, Z.; Bobbitt, J. M. J. Org. Chem. 1991, 56, 6110.

^{(8) (}a) Ch'ang-pai, C.; Evstigneeva, R. P.; Preobrazhenskii, N. Z. Obshch. *Khim.* **1960**, *30*, 495. (b) Grethe, G.; Lee, H. L.; Mitt, T.; Uskokovic, M. R. J. Am. Chem. Soc. **1978**, *100*, 581.

^{(9) (}a) Woodward, R. B.; Wendler, N. L.; Brutschy, F. J. J. Am. Chem. Soc. **1945**, 67, 1425. (b) Marcó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. Science **1996**, 274, 2044.

^{(10) (}a) Fatiadi, A. J. Synthesis 1987, 85. (b) Firouzabadi, H.; Mottghinejad, E.; Seddighi, M. Synthesis 1989, 378. (c) Sala, T.; Sargent, M. V. J. Chem. Soc., Chem. Commun. 1978, 253. (d) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. Synthesis 1994, 639. (e) Urch, C. J.; Brown, S. M.; Marcó, I. E.; Giles, R. R.; Tuskazaki, M. PCT Int. Appl. WO 9851654 A1.

^{(11) (}a) Yoshimura, J.; Sato, K.; Hashimoto, H. Chem Lett. 1977, 1327.
(b) Kametani, T.; Kanaya, N.; Hino, H.; Huang, S.-P.; Ihara, M. J. Chem. Soc., Perkin Trans. 1 1981, 3168. (c) Petersen, J. S.; Fels, G.; Rapoport, H. J. Am. Chem. Soc. 1984, 106, 4539. (d) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. J. Am. Chem. Soc. 1957, 79, 6562. (e) Kornblum, N.; Jones, W. J.; Anderson, G. J. J. Am. Chem. Soc. 1959, 81, 4113.

To our surprise, KMnO₄-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

(14) Dess, D. B.; Martin, J. C. J. Org. Chem. 1983, 48, 4155.
 (15) Paterson, I.; Cowden, C. J.; Rahn, V. S.; Woodrow, M. D. Synlett
 1998, 915.

- (17) (a) Fétizon, M. In Encyclopedia of Reagents for Organic Synthesis;
- Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; Vol. 6, p 4448. (b) McKillop, A.; Young, D. W. Synthesis 1979, 401.
- (18) Grethe, G.; Lee, H. L.; Mitt, T.; Uskokovic, M. R. J. Am. Chem. Soc. 1978, 100, 581.

(19) Forst, C.; Böhringer, C. Chem. Ber. 1882, 15, 1659.

- (20) (a) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363. (b) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
- (21) Bidentate chromium complexes of quinine and quinidine are known, see: Tsangaris, J. M.; Baxevanidis, G. T. Z. Naturforsch. **1974**, 29b, 532.
- (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 ¹³C 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 ¹³C NMR and GC.

(24) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323.

(25) Goutarel, R.; Janot, M.-M.; Prelog, V.; Taylor, W. I. Helv. Chim. Acta 1950, 23, 150.

(26) (a) Nahm, S. Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685. (c) Review: Mentzel, M.; Hoffmann, H. M. R. J. Prakt. Chem. **1997**, *339*, 517.

(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 NaHCO₃ (saturated aqueous), and then ethylenediamine was added dropwise within 15 min. Thereafter Et₂O was added for liquid-liquid extraction over 2 days. The organic layer was dried (MgSO₄), 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. (15,25,45,5R)-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 (CHCl₃) v 2952, 2870, 1734, 1637, 1456, 1437, 1372, 1264, 1230, 1081, 1036, 993, 909, 834 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 173.36 (C, C-9), 141.36 (CH, C-10), 114.63 (CH₂, C-11), 58.72 (CH₃, OMe), 55.00 (CH₂, C-6), 25.23 (CH, C-2), 43.09 (CH₂, C-7), 39.30 (CH₂, C-5), 27.23 (CH₂, C-8), 27.10 (CH, C-4), 23.77 (CH₂, 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 C₁₁H₁₇N₁O₂ 195.1259, found 195.1259. General Procedure for the Synthesis of C10 Esters. A solution of KMnO₄ (2.05 equiv) in H₂O was slowly added to a vigorously stirred solution of the corresponding β -amino alcohol sulfate (1.0 equiv) in 2 N H₂SO₄ 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 NaHCO₃, the aqueous layer was extracted (CH2Cl2). 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. (1S,2S,4S,5R)-2-(Hydroxymethyl)-1-azabicyclo[2.2.2]octane-





^{*a*} Reagents and conditions: (a) MeNHOMe+HCl, Me₂AlCl, DCM, 0 °C \rightarrow room temperature; yield up to 87% (b) (i) TBDMSCl, Et₃N, DMAP, DCM, room temperature; (ii) MeNHOMe+HCl, Me₂AlCl, DCM, 0 °C \rightarrow room temperature; yield over 2 steps 57%; (c) (i) TBDPSCl, Et₃N, DMAP, DCM, room temperature; (ii) MeNHOMe+ HCl, Me₂AlCl, DCM, 0 °C \rightarrow room temperature; yield over 2 steps 62%.

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 amides²⁶ were prepared, including bis-(Weinreb amide) **11**. These amides were formed in good yield (Scheme 2) and

5-carboxylic Acid Methyl Ester (3) and (1S,2S,4S,5R)-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 (CHCl₃) v 3434, 2999, 2952, 2878, 1728, 1456, 1437, 1371, 1333, 1236, 1198, 1178, 1138, 1100, 1050, 1017, 983 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) & 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); ¹³C NMR (100 MHz, CDCl₃) δ 174.54 (C, C-10), 62.02 (CH₂, C-9), 57.47 (CH, C-2), 51.93 (CH₃, C-11), 48.76 (CH₂, C-6), 42.94 (CH₂, C-7), 41.20 (CH, C-5), 25.89 (CH₂, C-3), 25.18 (CH, C-4), 24.64 (CH₂, 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 C₁₀H₁₇NO₃ 199.1208, found 199.1208. Data for 4: IR (CHCl₃) v 3434, 2951, 2878, 1776, 1731, 1462, 1410, 1372, 1292, 1230, 1151, 1136, 1119, 1086, 1027, 996, 834 cm⁻¹;¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 174.44 (C, C-10), 173.03 (C, C-9), 58.08 (CH, C-2), 52.24 (CH₃, C-11), 51.81 (CH₃, C-12), 48.34 (CH₂, C-6), 46.01 (CH₂, C-7), 40.86 (CH, C-5), 25.82 (CH2, C-3), 25.02 (CH, C-4), 24.94 (CH2, 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 C₁₁H₁₇NO₄ 227.1157, found 227.1157.

⁽¹⁶⁾ Wie, X.; Taylor, R. J. K. Tetrahedron Lett. 1998, 39, 3815.

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 1,2amino 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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