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STEREOSELECTIVE SYNTHESIS OF METHOXY SUBSTITUTED 1,2,3,4,4a,5,10,10a-OCTAHYDROBENZO[g]QUINOLINES

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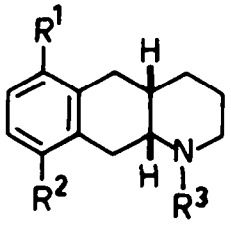
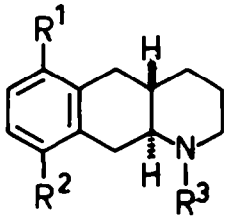
Abstract. - The preparation of the cis- and trans-isomers of 6- and 9-methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]-quinoline is reported. The syntheses involved reductions of cyclic iminium chlorides, which afforded the diastereomers conveniently and in good yields. Small cis/trans ratios were obtained with $NaCNBH_3$ as the reducing agent. Catalytic hydrogenation using PtO_2 in THF or t-BuOH gave the largest cis/trans ratios. The N-benzyl derivatives were prepared to permit determination of relative stereochemistries.

Derivatives of 1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline (OHB[g]Q) may be considered as rigid phenethylamine congeners. Such compounds frequently possess impressive biological properties and oxygenated OHB[g]Q derivatives have demonstrated dopaminergic[1,2] or analgetic and narcotic activities.[3] Previously, oxygenated OHB[g]Q derivatives have been prepared by i) cyclization of 2-(methoxybenzyl)piperidine-3-carboxylic acids,[1,2,4] ii) cyanoethylation of a 3-methoxycarbonyl-2-tetralone followed by reductive cyclization,[5] and iii) cyclization of 2-(methoxybenzyl)-α,α-dimethyl-3-piperidinemethanol.[3] In general, these reactions proceed in poor yield and/or are limited to certain substitution patterns. The present report describes a new, convenient and stereoselective synthesis of the cis- and trans-isomers of 6- and 9-methoxy-OHB[g]Q (1 and 2, respectively).





1a: R^1=OCH_3, R^2=R^3=H
b: R^2=OCH_3, R^1=R^3=H
9a: R^1=OCH_3, R^2=H, R^3=CH_2Ph
b: R^1=H, R^2=OCH_3, R^3=CH_2Ph

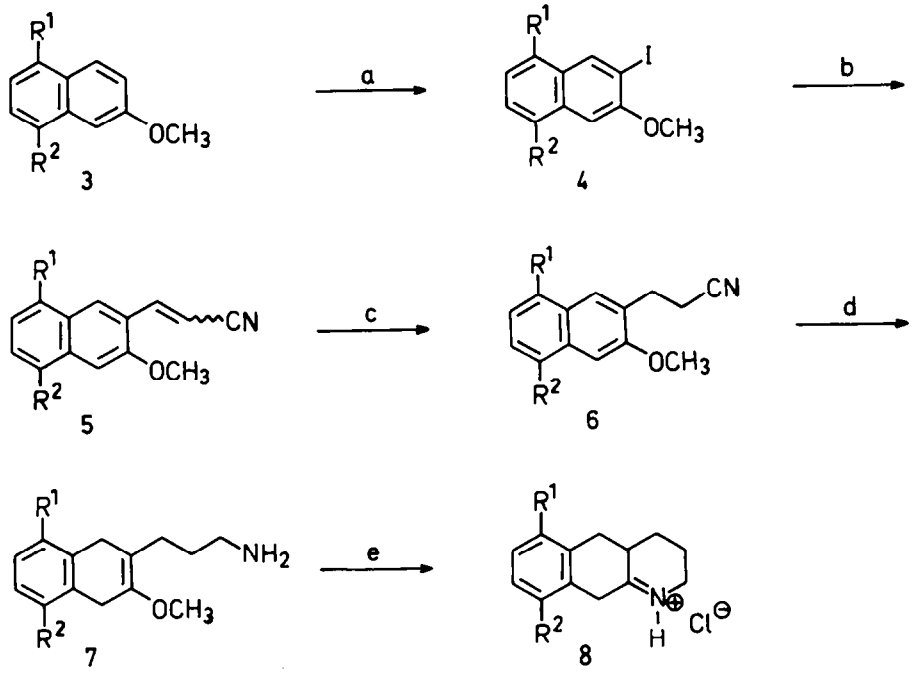
2a: R^1=OCH_3, R^2=R^3=H
b: R^2=OCH_3, R^1=R^3=H
10a: R^1=OCH_3, R^2=H, R^3=CH_2Ph
b: R^1=H, R^2=OCH_3, R^3=CH_2Ph

RESULTS AND DISCUSSION

Synthesis of iminium chlorides 8a and 8b. The synthetic sequence giving 8a and 8b is depicted below.

We have recently reported that ortho-lithiation of dimethoxynaphthalene 3a occurs regioselectively at C7 and that 3b regiospecifically gives ortho-lithiation in the C6-position.[6] Thus, lithium anions of 3a and 3b were treated with iodine to produce iodides 4a and 4b. As expected, 4b was isolated in high yield after iodination of 3b. Compound 4a, however, was obtained in only 57% yield from 3a. In methylations of ortho-lithiated 3a we observed the formation of an 8:2 mixture of 7- and 5-methylated isomers.[6] It is therefore noteworthy that attempts to detect or isolate the 5-iodo- or any other isomer of 4a failed.

Heck vinylation[7] of the iodinated isomers 4a and 4b, using acrylonitrile, triethylamine, and a catalytic amount of $Pd(OAc)_2$ in MeCN gave 4:1 mixtures (^1H NMR) of E- and Z-isomers 5 in excellent yields. The stereochemical assignments of the E- and Z-isomers were mainly based on the magnitudes of the vinylic proton proton coupling constants (E: J=16.7, 16.9 Hz; Z: J=12.2 Hz). The E-isomers could be isolated by recrystallization. However, in preparative runs, the crude E/Z mixtures were converted directly to the saturated nitriles 6a and 6b (H_2, 10% Pd(C), $MeOH/CH_2Cl_2$). Thus, pure 6a and 6b were obtained in > 92 % yield from 4a and 4b, respectively, after recrystallization.



a: $R^1 = OCH_3$, $R^2 = H$
b: $R^1 = H$, $R^2 = OCH_3$

Reagents: a) BuLi/THF, I_2; b) CH_2=CHCN, $N(Et)_3$, $Pd(OAc)_2$, MeCN; c) H_2, Pd(C), $MeOH/CH_2Cl_2$; d) Na, EtOH; e) HCl(aq)/MeOH.

In the next step, both the more substituted ring and the cyano group were reduced (Na, EtOH) to give **7a** and **7b** as the sole products. Cyano groups do not appear to be compatible with ordinary Birch conditions[8] but no reductive cleavage of the cyano group was observed under the present conditions. Solvolysis of enol ethers **7a** and **7b** furnished iminium chlorides **8a** and **8b**. We were never able to observe the intermediate ketones. Thus, the formation of the piperidine ring and the subsequent dehydration seem to occur spontaneously.

Reductions of **8a** and **8b**. The iminium chlorides **8a** and **8b** served as synthetic intermediates both for the cis- and trans-OHB[g]Q derivatives. $NaCNBH_3$ reduction of **8a** or **8b** in MeOH at pH 6 produced predominantly the trans-isomers **2a** and **2b** (cis/trans ratios = 1:9). The pure trans isomers were obtained by fractional crystallization of the hydrochlorides.

The stereochemical outcome of the catalytic hydrogenation of **8a** and **8b** varied with catalyst and solvent (**Table I**). In addition, hydrogenation of **8a** consistently gave larger cis/trans ratios than **8b**. The cis/trans product ratios shown in **Table I** increase with increasing dielectric constants of the aprotic solvents (EtOAc, THF) but decrease with increasing dielectric constants of the neutral protic solvents (t-BuOH, MeOH). Thus, the present results agree with previously observed stereochemistries of carbonyl hydrogenations.[9] Augustine *et al.*[10] have demonstrated that most of these effects can be rationalized if both steric and electronic solvent effects are considered; the ability of the solvent to compete for catalyst sites considerably affects the nature of the catalyst and thus the rate as well as the selectivity of the reduction.

The largest cis/trans ratios were obtained with PtO_2 in t-BuOH or in THF (Table I). Under these conditions, pure **1a**·HCl was obtained in 51 % yield from **8a** after recrystallization. However, pure **1b** could not be conveniently prepared from **8b** by this procedure. Instead, the mixture of **1b** and **2b** was N-benzylated and the N-benzyl derivative **9b** was then separated from **10b** by chromatography on aluminum oxide followed by fractional crystallization. Isomerically pure **1b** was finally obtained, in 31 % overall yield from **8b**, by hydrogenolysis of **9b**.

Table I. Product ratios in catalytic hydrogenations of iminium chlorides **8a** and **8b**.

		Isomeric ratio[a]	
Catalyst	Solvent	**1a** : **2a**	**1b** : **2b**
Pd(C) 10%	MeOH	29 : 71	10 : 90
Pd(C) 10%	t-BuOH	41 : 59	12 : 88
PtO_2	HOAc	48 : 52	25 : 75
PtO_2	MeOH	42 : 58	33 : 67
PtO_2	EtOAc	62 : 38	37 : 63
PtO_2	t-BuOH	75 : 25	48 : 52
PtO_2	THF	81 : 19	47 : 53

[a]Based on GC-analysis of trifluoroacetylated crude reaction products.

The consistent difference in stereoselectivity in reductions of **8a** and **8b** is probably not due to haptophilic effects[11] or to other effects related to heteroatom coordination.[12] Instead, the difference in stereoselectivities may be related to a greater tendency of **8b**, as compared to **8a**, to undergo imine/enamine isomerization; the styrenic enamine (enammonium ion) corresponding to **8b** should be more stable than that formed from **8a** due to conjugative stabilization between the 9-methoxy

group and the double bond. This interpretation is supported by the fact that Pd(C) gave smaller cis/trans ratios than PtO_2; Pd is known to isomerize double bonds to a larger extent than Pt.[13]

Structural assignments of 1 and 2. ^1H NMR spectral studies of the N-benzyl derivatives 9 and 10 made it possible to assign the stereochemistries of 1 and 2. In 90 MHz ^1H NMR spectra of $CDCl_3$ solutions of **10a** and **10b**, the α-hydrogens of the N-benzyl groups appeared as AB quartets centered at δ 3.74 and 3.77 ppm, respectively, with large chemical shift differences (0.92 and 1.11 ppm, respectively) between the A and B portions. In contrast, the corresponding hydrogens of **9a** and **9b** appeared as apparent singlets at δ 3.68 and 3.72 ppm, respectively. It has been demonstrated that the AB quartet due to the diastereotopic α-hydrogens of N-benzyl substituted trans-OHB[g]Q derivatives and related compounds have a larger chemical shift difference between the A- and B-portions than the corresponding cis-derivatives.[4] Thus, **1** and **9** were assigned the cis-stereochemistry and **2** and **10** should be trans-isomers.

NMR-Spectra of CD_3OD solutions of the hydrochlorides of **9** and **10** gave spectra similar to those of the corresponding bases in $CDCl_3$. However, in ^1H NMR spectroscopy, the benzylic protons of the hydrochlorides of **9a** and **9b** appeared as two singlets in a 7:1 ratio and in the proton decoupled ^{13}C NMR spectra of these compounds several carbons appeared as two signals exhibiting approximately the same difference in intensity (7:1), indicating the presence of two conformations in a slow (NMR-time scale) equilibrium.

Concluding remarks. The syntheses presented here are convenient to perform in multi gram-scale and the overall yields of the OHB[g]Q derivatives **1a**, **1b**, **2a** and **2b** are quite acceptable (22 %, 22 %, 27 %, and 25 %, respectively, as calculated from the easily available dimethoxynaphthalene derivatives **3a** and **3b**). A number of compounds of potential biological interest can be prepared from these new OHB[g]Q derivatives.

EXPERIMENTAL SECTION

General Comments. Dry THF was distilled from Na metal in the presence of benzophenone under dry N_2. Other chemicals were used as received. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX 90Q spectrometer at 20 °C and were referenced to internal Me_4Si. ^{13}C NMR data of the hydrochlorides of compound 1, 2, 8, 9 and 10 in CD_3OD are given in Table II. IR spectra were recorded on a Perkin-Elmer 157G spectrophotometer. Mass spectra were recorded at 70 eV on a LKB 9000 spectrometer using a direct insertion probe. GC was performed on a Varian 2700 instrument with a flame ionization detector. Thin-layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel 60 F_{254} (0.2mm), or for amines, on Al_2O_3 60 F_{245} neutral (Typ E), E. Merck. Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden.

Iodination of 3b. Preparation of 3,5-Dimethoxy-2-iodonaphthalene (4b). A solution of butyllithium in hexane (1.5 M; 177 mL, 0.27 mol) was added to a stirred solution of **3b** (50 g, 0.27 mol) in dry THF (500 mL) kept under N_2 at -78 °C. After stirring at rt over night, the reaction mixture was cooled to -78 °C and a solution of I_2 (71 g, 0.27 mol) in dry THF (100 mL) was added dropwise. When the addition was complete, a saturated aqueous solution of NH_4Cl (200 mL) was added followed by a saturated aqueous solution of $Na_2S_2O_3$ (100 mL). The volatiles were evaporated and ether was added to the residue. The ether layer was washed with water, dried ($MgSO_4$) and concentrated to afford 76.9 g (92 %) of **4b** which was pure according to NMR and GC. An analytical sample was prepared by recrystallisation from ether; mp 125-126 °C; Rf 0.77 (ether/light petroleum 1:1); ^1H NMR ($CDCl_3$) δ 8.26 (s, C4-H), 7.46 (s, C1-H), 7.28 - 7.18 (m, C6-H, C8-H), 6.90 - 6.70 (m, C7-H), 2.98 (s, OMe's); ^{13}C NMR ($CDCl_3$) δ 154.85, 154.30 (C3, C5), 138.76 (C1), 131.19 (C8a), 126.19 (C4a), 124.25 (C7), 118.84 (C8), 104.60 (C6), 100.19 (C4), 88.76 (C2), 56.36, 55.44 (OMe's); mass spectrum, m/z (relative intensity) 314 (100, M^+), 299 (42, M^+-CH_3), 127 (19, I^+). Anal. Calc for $C_{12}H_{11}O_2I$: C, 45.9 H, 3.5. Found: C, 45.9 H, 3.5.

Iodination of 3a. Preparation of 2,5-Dimethoxy-3-iodonaphthhalene (4a). Compound 4a was prepared from 3a (50 g, 0.27 mol) by the above procedure. Ether was added to the concentrated residue and pure 4a (47.6 g, 57%) crystallized on standing: mp 110.5-112 °C; Rf 0,74 (ether/ light petroleum 1:1); ^{1}H NMR ($CDCl_3$) δ 8.72 (s, C4-H), 7.45-7.28 (m, C6-H, C8-H), 7.01 (s, C1-H), 6.72-6.54 (m,C7-H), 3.95 (s, OMe's). ^{13}C NMR ($CDCl_3$) δ 155.47, 154.36 (C2, C5), 135.43 (C8a), 122.05 (C4a), 133.85 (C4), 127.18 (C7), 118.87 (C8), 105.15 (C6), 102.41 (C1), 86.75 (C3), 56.21, 55.37 (OMe's); mass spectrum, m/z (relative intensity) 314 (100, M^+), 299 (14, M^+-CH_3), 127 (21, I^+). Anal. Calc for $C_{12}H_{11}O_2I$: C, 45.9 H, 3.5. Found: C, 45.8 H, 3.5.

Heck vinylation of 4b. Preparation of (E)- and (Z)-2-(2-cyanoethenyl)-3,5-dimethoxynaphthalene (5b). A mixture of 4b (30 g, 95.5 mmol), acrylonitrile (7.6 g, 143.2 mmol), $Pd(OAc)_2$ (214 mg, 0.95 mmol), triethylamine (9.7 g, 95.5 mmol) and MeCN (40 mL) was heated in a capped Pyrex flask at 120 °C for 3 d. The cooled reaction mixture was filtered (Celite), CH_2Cl_2 was added and the solution was washed with 1 M HCl and with brine, dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in a small amount of CH_2Cl_2 and eluted through a short silica column with ether/light petroleum 1:1 as eluant yielding 21.9 g (96%) of a 4:1 mixture of (E)- and (Z)-5b. An analytical sample of (E)-11b was obtained by recrystallization twice from MeOH; (E)-5b; mp 139.5-140.5 °C; Rf 0.58 (ether/light petroleum 1:1); IR: C≡N stretch ν 2210; ^{1}H NMR ($CDCl_3$) δ 7.65 (s, C4-H), 7.60 (d, J = 16.7 Hz, Cα-H), 7.48 (s, C1-H), 7.35-6.70 (m, C6-H, C7-H, C8-H), 6.15 (d, J = 16.7 Hz, Cβ-H), 3.97, 3.93 (OMe's).[(Z)-11b: δ 5.52 (d, J = 12.2 Hz, Cβ-H)]; ^{13}C NMR ($CDCl_3$) δ 155.25, 154.11 (C3, C5), 146.76 (Cβ), 129.62 (C1), 128.91, 124.09 (C4a, C8a), 127.24 (C2), 124.43 (C7), 120.42 (C8), 118.90 (CN), 105,72 (C6), 100.74 (C4), 98.12 (Cα), 55.50 (OMe's); mass spectrum m/z (relative intensity) 239 (100, M^+), 224 (61, M^+-CH_3). Anal. Calc for $C_{15}H_{13}NO_2$: C, 75.3 H, 5.5 N, 5.9. Found: C, 75.2 H, 5.5 N, 5.9.

Heck vinylation of 4a. Preparation of (E)- and (Z)-3-(2-cyanoethenyl)-2,5-dimethoxynaphthalene (5a). This mixture was prepared from 4a (30 g, 95.5 mmol) by the above procedure. Yield 20.6 g (90%); (E)-5a: mp 98-99.5 °C; Rf 0.53 (ether/light petroleum 1:1); IR, C≡N strech ν 2210; ^{1}H NMR ($CDCl_3$) δ 8.24 (s, C4-H), 7.68 (d, J=16.8 Hz, Cα-H), 7.56-7.15 (m, 2H), 7.04 (s, C1-H), 6.72-6.60 (m, 1H), 6.20 (d, J=16.9 Hz, Cβ-H), 3.92, 3.85 (s's, OMe's); [(Z)-5a: δ 5.50 (d, J=12.2 Hz, Cα-H); ^{13}C NMR ($CDCl_3$) δ 155.96 (C2, C5), 146.91 (Cβ), 136.69 (C8a), 122.89 (C4a) 128.63 (C4), 124.52 (C7), 120.80 (C3), 118.93 (CN), 118.78 (C8), 105.68 (C6), 102.57 (C1), 97.41 (Cα), 55.41 (OMe's); mass spectrum m/z (relativ intensity) 239 (100, M^+), 196 (39). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.3 H, 5.5 N, 5.9. Found: C, 75.4 H, 5.6 N, 5.8.

2-(2-Cyanoethyl)-3,5-dimethoxynaphthalene (6b). A crude mixture of (E)- and (Z)-5b (5.0 g, 20.9 mmol) was dissolved in CH_2Cl_2 (20 mL) and MeOH (80 mL) and the mixture was hydrogenated over 10% Pd(C) at 3 atm. The reaction mixture was filtered (Celite) and concentrated. Recrystallization of the residue from MeOH afforded 4.7 g (93 %) of pure 6b; mp 79-80 °C; Rf 0.53 (ether/light petroleum 1:1); IR, C≡N stretch ν 2240; ^{1}H NMR ($CDCl_3$) δ 7.57, 7.52 (s's, C1-H, C4-H), 7.41-7.10 (m, C6-H, C8-H), 6.85-6.72 (m, C7-H), 3.99, 3.97 (s's, OMe's), 3.20-2.95, (m, 2H), 2.30-2.10 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 155.41, 154.26 (C3, C5), 129.50, (C8a), 128.75 (C1), 128.20 (C2), 125.73 (C4a), 123.78 (C7), 110.67 (C8), 119.58 (CN), 104.17 (C6), 99.88 C4), 55.37, 55.31 (OMe's), 27.42 (Cβ), 17.45 (Cα); mass spectrum m/z (relative intensity) 241 (100, M^+), 226 (39, M^+-CH_3), 201 (15, M^+-CH_2CN). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.7 H, 6.3 N, 5.8. Found: C, 74.8 H, 6.1 N, 5.8.

3-(2-Cyanoethyl)-2,5-dimethoxynaphthalene (6a). Compound 6a was prepared from 5a (5.0 g, 20.9 mmol) by the above procedure. Yield 4.9 g (97%); mp 80.5-82 C; Rf 0.51 (ether-light petroleum 1:1); IR, C≡N stretch ν 2240; ^{1}H NMR ($CDCl_3$) δ 8.02 (s, C4-H), 7.40-7.22 (m, 2H), 7.03 (s, C1-H), 6.71-6.57 (m, 1H), 3.93, 3.88, (s's, OMe's), 3.20-2.95 (m, 2H), 2.80-2.14 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 156.18, 155.28 (C2, C5), 135.24 (C8a), 126.93 (C4a), 126.56 (C4), 123.41 (C7), 120.29 (C3), 119.61 (CN), 118.84 (C8), 105.10 (C6), 102.26 (C1), 55.37, 55.22 (OMe's), 27.67 (Cβ), 17.57 (Cα); mass spectrum, m/z (relative intensity) 241 (89, M^+), 201 (100, M^+-CH_2CN). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.7 H, 6.3 N, 5.8. Found: C, 74.6 H, 6.4 N, 5.8.

Sodium reduction of 6b. Preparation of 2-(3-aminopropyl)-3,5-dimethoxy-1,4-dihydronaphthalene (7b). Slices of Na (40 g, 1.74 mol) were added during ten minutes to a boiling solution of 6b (10.0 g, 41.4 mmol) in EtOH (400 mL) under N_2. After one h the heating was interrupted and water (100 mL) and NH_4Cl (95 g) were added carefully. The mixture was filtered and the volatiles were evaporated. The residue was partitionated between water and ether. The ether layer was washed several times with water, dried (K_2CO_3) and concentrated to afford 8.8 g (86%) of almost pure 7b; ^{1}H NMR ($CDCl_3$) δ 7.25-6.58 (m, 3H), 3.82, 3.62 (s's, OMe's), 3.40 (app s, 4H), 2.80-1.20 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 156.77 (C5), 145.74 (C3), 135.21 (C8a), 122.64 (C4a), 126.47 (C7), 120.01 (C8), 113.74 (C2), 106.86 (C6), 56.24, 55.19 (OMe's), 41.66 (Cα), 33.42, 31.46, 25.76, 24.09 (C1, C4, Cβ, Cγ); mass spectrum m/z (relativ intensity) 247 (16, M^+), 232 (56, M^+-CH_3), 215 (74).

Sodium reduction of **6a**. Preparation of 3-(3-Aminopropyl)-2,5-dimethoxy-1,4-dihydronaphthalene (**7a**). Compound **7a** was prepared from **6a** (15.0 g, 62.2 mmol) by the above procedure. Yield 14.3 g (93%); ^{1}H NMR ($CDCl_3$) δ 7.25-6,97 (m, 1H), 6.85-6.52 (m, 2H), 3.81, 3.59 (s's, OMe's), 3.70-3.18 (m, 4H), 2.80-2.12 (m, 4H), 1.80-1.20 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 156.77 (C5), 145.15 (C2), 134.96, (C4a), 122.98 (C8a), 126.50 (C7), 120.38 (C8), 114.39 (C3), 106.98 (C6), 56.27, 55.19 (OMe's), 41.57 (Cα), 31.41, 29.19, 28.17, 25.94, (C1, C4, Cβ, Cγ); mass spectrum m/z (relative intensity) 247 (12, M^+), 232 (39, $M-CH_3$), 215 (63).

Solvolysis of **7b**. Preparation of 9-Methoxy-2,3,4,4a,5,10-hexahydrobenzo[g]quinolinium chloride (**8b**). A solution of **7b** (20 g, 80.9 mmol) in MeOH (400 mL) and 12 M HCl (70 mL) was heated to reflux under N_2. After four h, the solution was concentrated to dryness. The residue was recrystallized from EtOH-ether yielding 18.1 g (83%) of pure **8b**; mp 217-219 °C; ^{1}H NMR (MeOH-d_4) δ 7.35-7.12 (m, 1H), 6.95-6.75 (m, 2H), 3.84 (s, OMe), 3.85-3.65 (m, 2H), 3.35-1.50 (m, 9H); mass spectrum m/z (relative intensity), 215 (100, M^+), 200 (72, M^+-CH_3). Anal. calcd for $C_{14}H_{17}NO\cdot HCl$: C, 66.8 H, 7.2 N, 5.6. Found: C, 66.7 H, 7.0 N, 5.4.

Solvolysis of **7a**. Preparation of 6-Methoxy-2,3,4,4a,5,10-hexahydrobenzo[g]quinolinium chloride (**8a**). Compound **8a** was prepared from **7a** (6.3 g, 25.5 mmol) by the same procedure but instead of being recrystallized the hygroscopic crude **8a** was triturated with ether. Yield 6.0 g (94%); mp 189-193 °C; ^{1}H NMR (MeOH-d_4) δ 7.31-7.13 (m, 1H), 6.90-6.70 (m, 2H), 3.82 (s, OMe), 3.85-1.30 (m, 11H); mass spectrum m/z (relative intensity) 215 (100, M^+), 187 (13), 186(18). Anal. Calcd for $C_{14}H_{17}NO\cdot HCl\cdot 1/2H_2O$: C, 64.5 H, 7.3 N, 5.4. Found: C, 64.6 H, 7.7 N, 5.0.

Sodium cyanoborohydride reduction of the iminium chlorides. Preparation of trans-9-methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolinium chloride (**2b**·HCl). $NaCNBH_3$ (0.43 g, 7.8 mmol) was added in portions to a solution of **8b** (3.0 g, 11.9 mmol) in MeOH (50 mL) coloured by a small amount of methyl red. The red colour was maintained during the reaction by addition of methanolic HCl when necessary. After two h the mixture was acidified to pH 2 and concentrated. The residue was partitioned between 1M NaOH and ether. The ether layer was dried (K_2CO_3) filtered and concentrated. Etheral HCl was added to an etheral solution of the amine and the resulting hydrochloride salt was recrystallized twice from EtOH-ether affording 1.30 g (43%) of pure **2b**·HCl; mp 265.5-266.5 °C; ^{1}H NMR (MeOH-d_4) δ 7.22-7.02 (m, 1H), 6.82-6.62 (m, 2H), 3.81 (s, OMe), 3.60-1.10 (m, 12H); mass spectrum m/z (relative intensity) 217 (89, M^+), 134 (59), 82 (100). Anal. Calcd for $C_{14}H_{19}NO\cdot HCl$: C, 66.3 H, 7.9 N, 5.5. Found: C, 66.0 H, 8.1 N, 5.6.

Preparation of trans-6-methoxy-1,2,3,4,4a,5,10,10-octahydrobenzo[g]quinoline hydrochloride (**2a**·HCl). Compound **2a**·HCl was prepared from **8a** (10.0 g, 39.7 mmol) by the above procedure. Yield 6.12 g (61%); mp 276.5-278.5 °C; ^{1}H NMR (MeOH-d_4) δ 7.22-7.00 (m, 1H), 6.88-6.62 (m, 2H), 3.79 (s, OMe), 3.60-2.80 (m, 5H), 2.40-1.20 (m, 7H); mass spectrum m/z (relative intensity) 217 (66, M^+), 134 (37), 82 (100). Anal. Calcd for $C_{14}H_{19}NO\cdot HCl$: C, 66.3 H, 7.9 N, 5.5. Found: C, 66.4 H, 7.9 N, 5.5.

Catalytic hydrogenation of the iminium chlorides. Preparation of cis- and trans-1-benzyl-9-methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline (**1b** and **2b**). A suspension of **8b** (10.0 g, 39.7 mmol) in t-BuOH (400 mL) was hydrogenated over PtO_2 at atmospheric pressure. When the hydrogen uptake had ceased, the catalyst was filtered of (Celite) and the volatiles were evaporated. The resulting 1:1 mixture of the two diastereomers **1b** and **2b** was benzylated prior to separation: The crude residue was dissolved in MeCN (200 mL), K_2CO_3 (16.5 g, 130 mmol) and benzyl chloride (7.5 g, 59.2 mmol) was added, and the mixture was stirred at rt over night. After filtration (Celite) and concentration of the reaction mixture, the mixture of **9b** and **10b** was separated by chromatography on an alumina column using ether-light petroleum 1:9 as eluant. Impure fractions containing excess of the **10b** were converted to the hydrochloride salt and purified by recrystallization from EtOH. The free amine from the mother liquor containing mainly the cis-isomer was purified by column chromatography. The combined fractions of the trans-isomer were treated with etheral HCl. The resulting hydrochloride was recrystallized from EtOH-ether yielding 5.2 g (38%) of **10b**·HCl; mp 216-218 °C; R_f 0.30 (ether-light petroleum 1:9); ^{1}H NMR (MeOH-d_4) δ 7.64-7.40 (m, 5H), 7.38-7.05 (m,1H), 6.87-6.14 (m, 2H), 4.91, 4.14 (d's, J=13.2, Bz-CH_2) 3.86 (s, OMe), 3.72-1.10 (m, 12H); mass spectrum m/z (relative intensity) 307 (66,M^+), 173 (50), 172 (47). Anal.Calcd for $C_{21}H_{25}NO\cdot HCl\cdot 1/2H_2O$: C, 71.5 H, 7.9 N, 4.0. Found: C, 71.4 H, 7.9 N, 4.0. Compound **9b**·HCl could not be recrystallized and was handled as the base. Recrystallization of **9b** from ether-light petroleum yielded 5.1 g (42%) of pure **9b**; mp 100-101 °C; R_f 0.47 (ether-light petroleum 1:9). A sample of the amorphous hydrochloride salt was prepared for spectral data; ^{1}H NMR (MeOH-d_4) δ 7.80-7.38 (m, 5H), 7.22-7.00 (m, 1H), 6.85-6.58 (m, 2H),4.41 (s, Bz-CH_2), 3.87 (s, OMe), 3.40-1.25 (m, 12H). Additional peaks corresponding to the minor conformation; δ 4.65 (s, Bz-CH_2), 3.79 (s, OMe); mass spectrum m/z (relative intensity) 307 (71, M^+), 173 (50), 172 (46), 91 (100). Anal. calcd for $C_{21}H_{25}NO$: C, 82.0 H, 8.2 N, 4.6. Found: C, 82.4 H, 8.4 N, 4.6.

Debenzylation of **9b**. Preparation of cis-9-methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolinium chloride (**1b**·HCl). Etheral HCl was added to a etheral solution of **9b** (0.22 g, 0.72 mmol) and the precipitate was collected and dissolved in MeOH

Table II. ^{13}C Nuclear Magnetic Resonance Spectra of some 1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolines and Related Derivatives.[a]

Carbon	8a	8b	1a	1b	2a	2b	9a	9b	10a	10b
C2	45.92	46.11	45.71	45.55	44.38	43.64	53.18	53.15	47.07	46.85
C3	18.38[b]	19.95	23.47	23.19	19.36	19.95	23.53	23.47	22.85[b]	17.97
C4	19.80[b]	24.40[b]	30.51[b]	28.54[b]	24.27[b]	25.48[b]	30.57[b]	27.73[b]	23.75[b]	23.16[b]
C4a	29.34	38.39	36.16	35.73	30.85	31.35	37.06	37.12	29.37	33.69
C5	24.40	24.52[b]	30.67[b]	30.05[b]	27.02[b]	26.28[b]	31.47[b]	30.17[b]	23.81[b]	23.69[b]
C5a	123.84	136.66	124.37	137.12	123.50	135.86	124.21	136.72	122.70	135.02
C6	157.66	121.03	158.34	121.56	158.80	122.27	158.22	121.22	158.71	122.02
C7	109.67	129.19	108.99	128.29	108.96	128.35	109.05	128.54	108.74	128.45
C8	129.13	109.54	128.14	108.43	128.15	108.43	128.26	108.59	128.01	108.40
C9	120.91	157.91	121.77	158.22	122.11	158.71	122.08	158.50	122.30	158.50
C9a	132.24	119.30	134.25	121.74	132.28	120.11	134.41	121.65	132.74	120.05
C10	c	35.45	34.31	36.29	31.81	30.36	33.01[b]	37.12	33.45	35.15
C10a	193.61	193.86	57.97	58.19	54.36	53.98	66.46	66.86	59.36	59.57
OMe	55.93	56.05	55.78	55.78	55.78	55.78	55.87	55.87	55.63	55.81

[a] The following peaks were assigned to the N-benzyl groups: **9a**; 58.15 (Bz-CH_2), 130.70, 131.13 (C1',C4'), 132.68, 130.42 (C2',C3',C5',C6'), **9b**; 57.86 (Bz-CH_2), 130.70, 131.13 (C1',C4'), 132.58, 130.42 (C2',C3',C5',C6'), **10a**; 58.59 (Bz-CH_2), 130.67, 131.61 (C1',C4'), 132.24, 130.24 (C2',C3',C5',C6'), **10b**; 58.52 (Bz-CH_2), 130.64, 130.98 (C1',C4'), 132.31, 130.21 (C2',C3',C5',C6'). [b] Ambiguous assignment. [c] Not observed.

(200 mL). Catalyst [Pd(C); 10%] was added and the mixture was hydrogenated at atmospheric pressure. The catalyst was filtered off (Celite) and the volatiles were evaporated. The residue was partitioned between ether and 1 M NaOH. The ether layer was dried (K_2CO_3), filtered and concentrated. The secondary amine thus obtained was converted to the hydrochloride and recrystallized from MeOH-ether to give 0.16 g (88%) of pure **1b**·HCl; mp 226.5-228 °C; ^{1}H NMR (MeOH-d_4) δ 7.24-7.05 (m, 1H), 6.85-6.68 (m, 2H), 3.82 (s, OMe), 3.90-3.68 (m, C10a), 3.47-2.80 (m, 6H), 2.50-2.18 (m, C4a), 2.00-1.57 (m, 4H); mass spectrum m/z (relative intensity) 217 (99, M^+), 134 (67), 82 (100). Anal. Calcd for $C_{14}H_{19}NO$·HCl: C, 66.3 H, 7.9 N, 5.5. Found: C, 66.3 H, 8.2 N, 5.5.

Preparation of cis-6-methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline hydrochloride (**1a**·HCl). Compound **1a**·HCl was prepared from **8a** (2.0 g, 7.94 mmol) by hydrogenation in t-BuOH (80 mL) with PtO_2 as catalyst using the same procedure as described above. Recrystallization of the crude salt from EtOH-ether afforded 1.0 g (51%) of pure **1a**·HCl; mp 218-220 °C; ^{1}H NMR (MeOH-d_4) δ 7.24-7.06 (m, 1H), 6.83-6.70 (m, 2H), 3.82 (s, OMe), 3.80-3.62 (m, 1H), 3.35-3.00 (m, 4H), 2.90-2.68 (m, 2H), 2.50-2.25 (m, 1H), 2.00-1.60 (m, 4H); mass spectrum m/z (relative intensity) 217 (61, M^+), 134 (40), 104 (25), 82 (100). Anal. Calcd for $C_{14}H_{19}NO$·HCl: C, 66.3 H, 7.9 N, 5.5. Found: C, 66.2 H, 8.1 N, 5.4.

Benzylation of **1a**. Preparation of cis-1-benzyl-6-methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline (**9a**). A mixture of **1a** (6.0 g, 27.6 mmol), K_2CO_3 (14.5 g, 82.8 mmol), benzyl chloride (5.2 g, 41.4 mmol) and MeCN (80 mL) was stirred under N_2 for 8 h. The mixture was filtered and concentrated. Ether was added and the solution was washed with water, dried (K_2CO_3), filtered and concentrated. Recrystallization of the base from MeOH afforded 7.7 g (91%) of pure **9a**; mp 81.5-83 °C; Rf 0.50 (ether-light petroleum 1:9). A sample of the amorphous hydrochloride was prepared for spectroscopy; ^{1}H NMR (MeOH-d_4) δ 7.83-7.40 (m, 5H), 7.30-7.05 (m, 1H), 6.95-6.70 (m, 2H), 4.41 (s, Bz-CH_2), 3.76 (s, OMe), 4.00-2.98 (m, 5H), 2.90-2.40 (m, 3H), 2.10-1.40 (m, 4H). Additional peaks corresponding to the minor conformation; δ 4.58 (s, Bz-CH_2), 3.80 (s, OMe); mass spectrum m/z (relative intensity) 307 (68, M^+), 91 (100). Anal Calcd for $C_{21}H_{25}NO$: C, 82.0 H, 8.2 N, 4.6. Found: C, 82.5 H, 8.0 N, 4.6.

Benzylation of **2a**. Preparation of trans-1-benzyl-6-methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolinium chloride (**10a**·HCl). Compound **10a** was prepared from **2a** (7.5 g, 34.5 mmol) by the above procedure. The amine was converted to the hydrochloride and recrystallized from EtOH-ether yielding 11.2 g (94%) of pure **10a**·HCl; mp 235-237 °C; Rf 0.28 (ether-light petroleum 1:9); ^{1}H NMR (MeOH-d_4) δ 7.68-7.40 (m, 5H), 7.38-7.05 (m, 1H), 6.90-6.70 (m, 2H), 4.89, 4.15 (d's, J=13.0 Hz, Bz-CH_2), 3.80 (OMe), 3.72-2.80 (m, 5H), 2.50-1.20 (m, 7H); mass spectrum m/z (relative intensity) 307 (71, M^+) 91 (100). Anal. Calcd for $C_{21}H_{25}NO$·HCl: C, 73.4 H, 7.6 N, 4.1. Found: C, 73.2 H, 7.3 N, 4.0.

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