163. Synthesis of Hydroxy- and Methoxy-Substituted Octahydrobenzo[*g*]isoquinolines as Potential Ligands for Serotonin Receptors

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Dedicated to Prof. *C. Benezra* on the occasion of his 50th birthday

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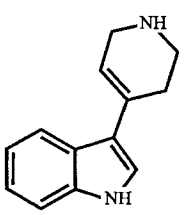
In 7 steps, 6- or 9-hydroxylated or -methoxylated *trans*-octahydrobenzo[*g*]isoquinolines were efficiently synthesized starting from dimethoxynaphthalenes *(Scheme)*, as potential new selective ligands for serotonin receptors. The 6-substituted compounds had very little affinity to common neurotransmitter receptors, with the exception of adrenergic α_2. The 9-substituted compounds, while showing interesting affinity for $5HT_{1a}$ receptors, had comparable affinities for adrenergic α_1 and α_2, and in one case for dopamine D2 receptors.

Introduction. – (Tetrahydropyridinyl)-1*H*-indoles of type **2** had been reported to have interesting and selective serotoninergic properties [1]. In analogy to a previously successful effort [2] to mimic the dopaminergic indole-containing pharmacophore of ergolines with monohydroxylated octahydrobenzo[*g*]quinolines, we accordingly chose 6- and 9-monomethoxy-substituted *trans*-octahydrobenzo[*g*]isoquinolines **1a** and **1b** as attractive targets for synthesis as putative ligands for serotonin receptors.



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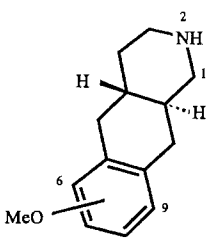
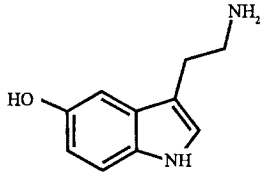


1a 6-MeO
b 9-MeO



5-HT

We argued thereby that the mean plane of the tetrahydropyridinyl moiety of **2** should be in a coplanar relationship to the indole nucleus because of the presence of the conjugated double bond. Thus, the pseudoplanar tricyclic *trans*-octahydrobenzo[*g*]isoquinolines should be able to mimic both conformationally and electronically the substituted indoles. The 6-oxy-substituted compounds of type **1a** were planned to be mimics of **2** with the O-function as a strict positional bioisostere of the indole NH group.

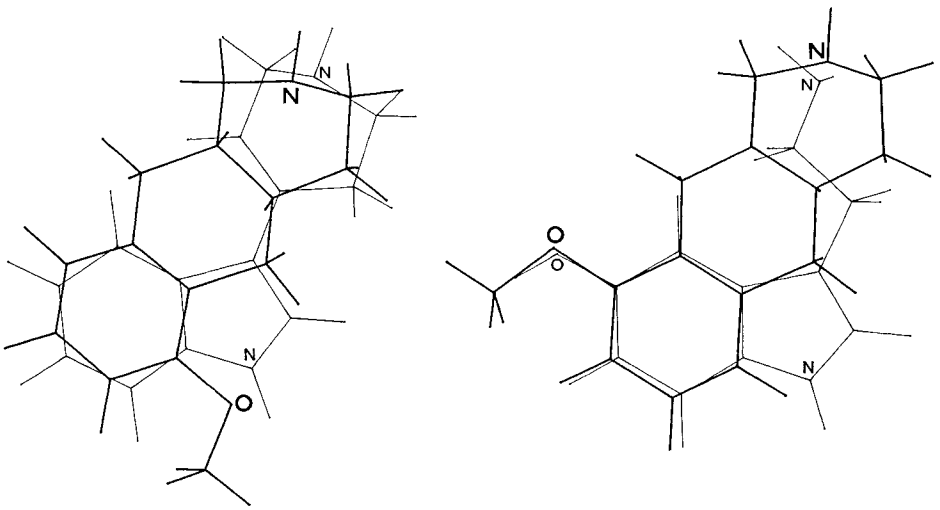
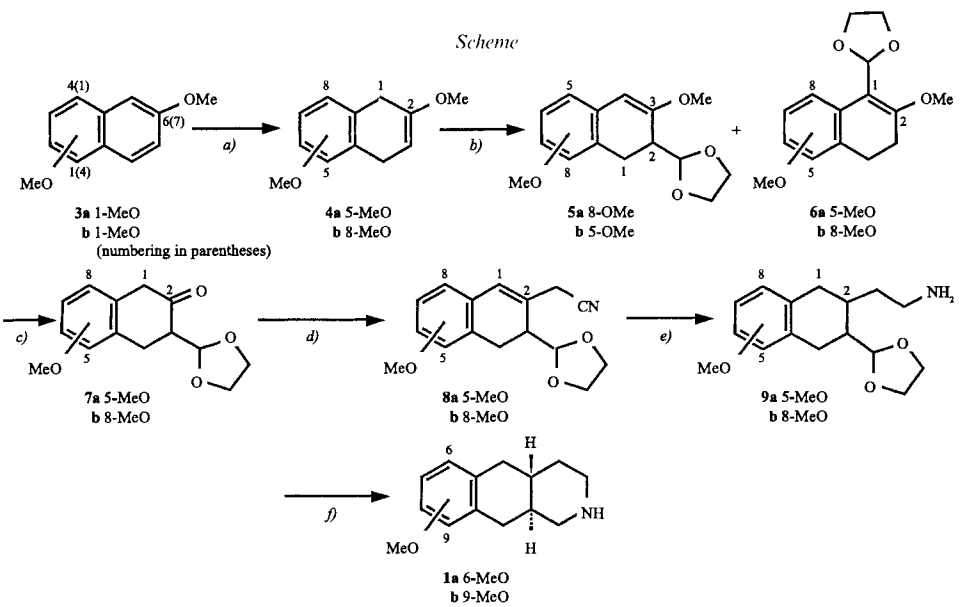


Fig. 1. *Superpositions of the 6-substituted methoxy compound* **1a** (bold lines) *on the (tetrahydropypiridinyl)-1*H*-indole* **2** *and of the corresponding 9-substituted compound* **1b** (bold lines) *on 5-HT.* The superpositions were performed with the molecular modelling program SYBIL.

The 9-oxy compounds of type **1b** could be regarded as a partial mimic of **2** with inclusion of the OH function of serotonin (5-HT) itself *(Fig. 1)*.

Chemistry. – The synthetic route to the desired octahydrobenzo[*g*]quinolines **1a** or **1b** is depicted in the *Scheme*. Our strategy is based on the formation of the piperidine ring

Scheme



a) $Na/t\text{-}BuOH/NH_3$. b) $MeOCH(OCH_2\text{-})_2/BF_3 \cdot OEt_2$. c) $AcOH/H_2O$. d) $(EtO)_2P(O)CH_2CN/NaH$. e) H_2/Pd; $LiAlH_4$. f) Conc. HCl soln./$NaBH_4$.

from suitably functionalized methoxytetralones. For this purpose, compounds **7a, b** are of capital importance, because they should allow the introduction of the ethylamino moiety *via* a *Wittig*-type reaction and make the ring closure feasible thanks to the masked aldehyde. The stereochemical outcome of the cyclisation step is predicted to be in favor of the *trans* isomers, since equilibration of the intermediate aminoaldehydes is possible under the reaction conditions. Moreover, *ab initio* force-field calculations show that the energy difference between the *trans* isomers **1a, b** and their *cis* isomers is *ca.* 8 kcal/mol.

The dioxolanylnaphthalenones **7a, b** can be derived from the corresponding enol ethers **4a, b** which have already been described [3]. The dissolved-metal reduction of dimethoxynaphthalenes **3a, b** to their nonconjugated enol ethers **4a, b** proceeds in high yield and with an isomeric purity of 80–88% [3]. By changing the reaction conditions (Na/t-$BuOH/NH_3$ instead of Na/i-PrOH), the regioselectivity was improved (> 95%) without any decrease in yield. With isomerically pure dihydrodimethoxynaphthalenes **4a** and **4b** in hand, their alkylation with 2-methoxy-1,3-dioxolane in the presence of a *Lewis* acid afforded the mixture **5a/6a** (71%) and **5b/6b** (61%), respectively, in a 7:3 ratio as determined by gas chromatography. Under these acidic conditions, the double bond has migrated in both cases to the thermodynamically preferred 1,2 position. Isomerically pure dioxolanylnaphthalenones **7a, b** were obtained *via* selective hydrolysis ($AcOH/H_2O$) of the above enol-ether mixture followed by recrystallization (62 and 57% yield, resp.).

The *Wadsworth-Emmons* reaction of **7a, b** with the anion of diethyl (cyanomethyl)phosphonate gave the thermodynamically more favored endocyclic olefinic compounds **8a, b** (56 and 58%, resp.) which were hydrogenated over Pd/C. The 1:1 diastereoisomeric mixtures of saturated nitriles thus obtained were reduced with $LiAlH_4$ to the amines **9a, b** (83 and 64%, resp.). Treatment of the latter with HCl followed by $NaBH_4$ reduction of the resulting imines afforded *trans*-octahydrobenzo[*g*]isoquinolines **1b** and **1a**, respectively, as single diastereoisomers in 82 and 61% yield. The configurational assignment of **1a, b** was based on ^{1}H-NMR data including double-resonance experiments.

The axial protons H–C(5), H–C(10), and H–C(1) gave a high field *dd* (H–C(1) appeared as a '*t*') with geminal and vicinal coupling constants of *ca.* 12 Hz. These values as well as this pattern are only explicable with a *trans* diaxial configuration of the methine protons H–C(4a) and H–C(10a). In addition, the large coupling constant (11 Hz) between them is also in favor of the *trans* configuration for **1a** or **1b** (see *Fig. 2*).

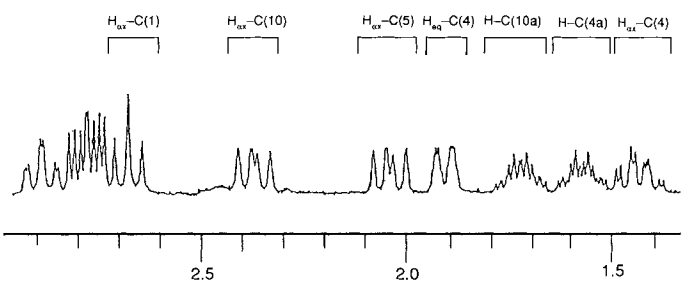


Fig. 2. *Part of the* ^{1}*H-NMR spectrum of* **1a**

The *N*-alkyl derivatives **1ac**, **1ae**, **1bc**, and **1be** (see *Table*) were obtained by allowing **1a** and **1b** to react with the suitable alkyl(Me,Pr) bromides in the presence of K_2CO_3. The MeO group of **1a**, **b** and of their *N*-alkyl derivatives was cleaved under standard conditions (BBr_3) to give *trans*-hydroxybenzo[*g*]isoquinolines **1aa**, **1ab**, **1ad**, **1ba**, **1bb**, and **1bd** (see *Table*).

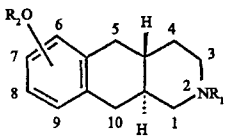


Table. *Affinity of* **1a**, **1aa-ae**, **1b**, *and* **1ba–be** *to Various Neurotransmitter Receptors*[a])

	R^1	R^2O	Binding affinities: IC_{50} [nM]						
			$5HT_{1a}$[b])	$5HT_{1c}$[c])	$5HT_2$[d])	α1[e])	α2[f])	D1[g])	D2[h])
1a	H	6-MeO	449	473	406	3150	112	*ca.* 10000	*ca.* 1000
1aa	H	6-OH	1070	2835	578	8000	175	5800	483
1ab	Me	6-OH	1575	1735	169	*ca.* 1000	152	*ca.* 10000	*ca.* 1000
1ac	Me	6-MeO	1875	275	151	595	55	> 10000	*ca.* 1000
1ad	Pr	6-OH	4030	3465	660	1683	165	4800	624
1ae	Pr	6-MeO	531	879	423	643	34	4900	155
1b	H	9-MeO	103	283	418	1207	111	> 10000	1750
1ba	H	9-OH	178	1580	3270	2600	260	5200	180
1bb	Me	9-OH	132	4700	5050	271	160	1130	174
1bc	Me	9-MeO	27	404	179	102	77	> 10000	647
1bd	Pr	9-OH	33	4270	1740	187	37	215	44
1be	Pr	9-MeO	18	922	224	68	70	3800	170

[a]) For details, see *Exper. Part.*
[b]) [^{3}H]8-OHDPAT, porcine frontal cortex.
[c]) [^{3}H]Mesulergin, porcine choroid plexus.
[d]) [^{3}H]Ketanserin, rat frontal cortex.
[e]) [^{3}H]Prazocin, calf cortex.
[f]) [^{3}H]Clonidin, calf cortex.
[g]) [^{3}H]ADTN, calf striatum.
[h]) [^{3}H]SDZ 205-501, calf striatum.

Pharmacology. – The compounds were tested in a number of radioreceptor binding assays. The results, expressed as IC_{50} (nM) are shown in the *Table*. The 6-substituted compounds **1a** and **1aa–1ae** displayed only moderate-to-weak affinity to all receptors tested, with most consistent affinity to adrenergic α_2 receptors. In this assay, the MeO compounds were consistently more potent than their OH counterparts, the order of affinity for the *N*-substituent being Pr > Me > H.

The 9-substituted series **1b** and **1ba–1be** showed higher affinity to serotonin receptor subtypes than did **1a** and **1aa–1ae** but this was frequently accompanied by similar affinity to adrenergic and even dopaminergic receptors. The differences between the OH and MeO compounds were not very significant for α_2 receptors. Increasing the size of the *N*-substituent in **1b** and **1ba–1be** resulted in higher $5HT_{1a}$, α_1, and α_2 receptor affinity, whereas the reverse was true at $5HT_{1c}$ receptors. Only the 9-hydroxy-*N*-propyl derivative **1bd** showed a moderately high affinity to D2 receptors.

Discussion. – We had hoped that the rigid tricyclic compounds **1a** and **1b** would be novel and selective serotonin-like ligands. This was not the case. Instead, the 6-substituted compounds showed very little affinity to any monoaminergic neurotransmitter receptors, with the exception of adrenergic α_2. The 9-substituted compounds which could be considered to combine structural elements of **2** and serotonin showed good affinity especially to $5HT_{1a}$ receptors, but unfortunately the most potent compounds were comparable in their affinity to adrenergic and even dopamine D2 receptors. Independently of the position of the aromatic oxy substituent, the compounds had a moderate affinity to adrenergic α_2 receptors ranging from 40 to 260 nM, for which we see no obvious structural basis.

The compounds were not considered sufficiently interesting to justify racemate resolution or detailed pharmacological characterization in animal models.

Experimental Part

General. All reactions were routinely carried out under Ar and followed by TLC (*Merck F254* silica gel plates). THF and CH_2Cl_2 were distilled immediately prior to use from sodium benzophenone ketyl and CaH, resp. Solns. were dried (Na_2SO_4) and then evaporated (*Büchi* rotary evaporator) at low pressure (water aspirator). Column chromatography: flash-chromatography technique. M.p.: *Büchi SMP-20* apparatus, not corrected. ^{1}H-NMR spectra: *Bruker Spectrospin* at 360 MHz (*WH-360*) or 90 MHz (*HX-90*), using Me_4Si as an internal standard (= 0 ppm) and $CDCl_3$ or (D_6)DMSO as solvent. MS (FAB) were determined for all compounds and were consistent with the proposed structures.

1,4-Dihydro-2,5-dimethoxynaphthalene (**4a**). To a cooled (−78°) and stirred soln. of 1,6-dimethoxynaphthalene [4] (**3a**; 70.0 g, 372 mmol) in *t*-BuOH (136 ml) and THF (105 ml) was slowly added liq. NH_3 (500 ml). The resulting dark soln. was allowed to warm to −40°, and Na (25.70 g, 1.11 mol) was added in small pieces during 45 min. The deep blue soln. was stirred for another 45 min at −40°, and then MeOH (105 ml) and H_2O (350 ml) were added. The org. solvents were evaporated (40°) and the remaining H_2O phase extracted with toluene (3 × 150 ml). The org. layer was dried and evaporated: 70.0 g (quant.) of **4a**. GC: less than 5% of conjugated isomer. The product was used in further reactions without any purification. ^{1}H-NMR: 3.38–3.41 (*m*, 4 H); 3.55 (*s*, MeO); 3.75 (*s*, MeO); 4.80 (*m*, 1 H); 6.55–7.30 (*m*, 3 H).

1,4-Dihydro-2,8-dimethoxynaphthalene (**4b**). By the above procedure, 1,7-dimethoxynaphthalene [5] (**3b**; 70 g, 372 mmol) was reduced to afford 70.0 g (quant.) of **4b** as oil. ^{1}H-NMR: 3.20–3.60 (*m*, 4 H); 3.60 (*s*, MeO); 3.80 (*s*, MeO); 4.70–4.85 (*m*, 1 H); 6.50–7.20 (*m*, 3 H).

2-(1,2-Dihydro-3,8-dimethoxynaphth-2-yl)-1,3-dioxolane (**5a**) *and 2-(3,4-Dihydro-2,5-dimethoxynaphth-1-yl)-1,3-dioxolane* (**6a**). A CH_2Cl_2 soln. (500 ml) of **4a** (118.0 g, 0.62 mol) at −25° was treated dropwise with a CH_2Cl_2 soln. (500 ml) of $BF_3 \cdot OEt_2$ (95 ml, 0.75 mol). Once the addition was completed, 2-methoxy-1,3-dioxolan (322.0 g, 3.1 mol) in CH_2Cl_2 (500 ml) was added so that the temp. did not exceed −20°. Stirring at low temp. was continued for 2.5 h. The reaction was quenched with a 10% Na_2CO_3 soln. (2 l), the org. layer separated, dried, evaporated, and distilled: 98.0 g (71%) of a brown oily mixture **5a**/**6a** (138–160°/0.05 Torr). GC (*OV 17* 9%, isotherm 265°): **5a**/**6a** 7:3. This mixture was used for the next step without further purification. ^{1}H-NMR: 2.40–3.40 (*m*, 3 H); 3.77 (*s*, MeO); 3.78–4.25 (*m*, OCH_2CH_2O); 4.85–5.00 (*m*, 1 H); 5.58 (*s*, 1 H); 6.50–7.40 (*m*, 3 H).

2-(1,2-Dihydro-3,5-dimethoxynaphth-2-yl)-1,3-dioxolan (**5b**) *and 2-(3,4-Dihydro-2,8-dimethoxynaphth-1-yl)-1,3-dioxolan* (**6b**). Compound **4b** (100 g, 0.53 mol) was subjected to the procedure described above. The dioxolan mixture obtained, after distillation at 150–155°/0.1 Torr, was crystallized from hexane: 84.2 g (61%) of **5b**/**6b** as white needles. M.p. 82–84°. ^{1}H-NMR: 2.35–3.20 (*m*, 3 H); 3.81 (*s*, MeO); 3.82–4.32 (*m*, OCH_2CH_2O); 4.80–5.05 (*m*, 1 H); 5.60 (*s*, 1 H); 6.50–7.32 (*m*, 3 H). Anal. calc. for $C_{15}H_{18}O_4$: C 68.70, H 6.81, O 24.43; found: C 68.29, H 6.90, O 24.17.

3-(1,3-Dioxolan-2-yl)-3,4-dihydro-5-methoxynaphthalen-2(1H)-one (**7a**). To an AcOH soln. (650 ml) of **5a**/**6a** (78.6 g, 0.30 mol), H_2O (72 ml) was added and the resulting soln. heated at 55° for 4 h. After evaporation, the oil was dried by coevaporation with toluene (3 × 200 ml). The crude product (95 g) was dissolved in hot (50°) i-PrOH (100 ml) and allowed slowly to cool to 0°. The crystals obtained were washed with hexane and dried under high vacuum: 46.1 g (62%) of pure **7a** as orange crystals. M.p. 87–88°. ^{1}H-NMR: 2.80–3.59 (*m*, 3 H); 3.62 (*s*, 2 H); 3.93

(*s*, MeO); 4.03–4.20 (*m*, OCH_2CH_2O); 5.42 (*d*, $J = 4$); 6.75–7.43 (*m*, 3 H). Anal. calc. for $C_{14}H_{16}O_4$: C 67.73, H 6.51, O 25.82; found: C 67.89, H 6.60, O 25.39.

3-(1,3-Dioxolan-2-yl)-3,4-dihydro-8-methoxynaphthalen-2(1H)-one (**7b**). As described above, **5b**/**6b** (70.0 g, 267 mmol) was hydrolyzed to give 38.0 g (57%) of **7b** as needles. M.p. 73–75°. ^{1}H-NMR: 2.71–2.87 (*m*, H–C(3)); 3.03–3.20 (*m*, 2 H–C(4)); 3.42, 3.76 (*AB*, $J = 21$, 2 H–C(1)); 3.81 (*s*, MeO); 3.87–4.10 (*m*, OCH_2CH_2O); 5.36 (*d*, $J = 4$); 6.77 (*d*, $J = 7$, H–C(5)); 6.85 (*d*, $J = 7$, H–C(7)); 7.19 ('*t*', $J = 7$, H–C(6)). Anal. calc. for $C_{14}H_{16}O_4$: C 67.73, H 6.51, O 25.82; found: C 67.90, H 6.53, O 25.72.

3-(1,3-Dioxolan-2-yl)-3,4-dihydro-5-methoxynaphthalene-2-acetonitrile (**8a**). NaH (55% dispersion in mineral oil; 1.40 g, 34 mmol) was placed in THF (50 ml) and cooled to 0°. Diethyl (cyanomethyl)phosphonate (5 ml, 32 mmol) in THF (20 ml) was added dropwise with stirring which was continued for 15 min at 0° (→homogeneous soln.). A soln. of **7a** (8.0 g, 32 mmol) in THF (30 ml) was added dropwise and the mixture stirred at 0° for 2 h. Then it was poured onto ice H_2O (250 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The combined extracts were dried and evaporated. The residue was chromatographed (toluene/AcOEt 9:1): 4.9 g (56%) of **8a** as white crystals. M.p. 99–100°. ^{1}H-NMR: 2.38 (*ddd*, H–C(3)); 2.74 (*dd*, $J = 6$, 7, H_{ax}–C(4)); 3.30–3.41 (*m*, H_{eq}–C(4)); 3.45–3.60 (*m*, CH_2CN); 3.82 (*s*, MeO); 3.75–4.00 (*m*, OCH_2CH_2O); 4.63 (*d*, $J = 6$, 1 H); 6.62–7.18 (*m*, 4 H). Anal. calc. for $C_{16}H_{17}NO_3$: C 70.82, H 6.31, N 5.23, O 17.73; found: C 70.77, H 6.33, N 5.30, O 17.53.

3-(1,3-Dioxolan-2-yl)-3,4-dihydro-8-methoxynaphthalene-2-acetonitrile (**8b**). In a procedure similar to that described above, **7b** (8.0 g, 32 mmol) afforded 5.0 g (58%) of **8b** as reddish oil. ^{1}H-NMR: 2.15–2.22 (*m*, H–C(3)); 2.50–3.00 (*m*, 2 H); 3.48–3.52 (*m*, CH_2CN); 3.70–4.00 (*m*, OCH_2CH_2O); 3.80 (*s*, MeO); 4.62 (*d*, $J = 7$, 1 H); 6.62–7.08 (*m*, 4 H). Anal. calc. for $C_{16}H_{17}NO_3$: C 70.82, H 6.31, N 5.23, O 17.73; found: C 70.69, H 6.30, N 5.27, O 17.91.

3-(1,3-Dioxolan-2-yl)-3,4-tetrahydro-5-methoxynaphthalene-2-ethylamine (**9a**). To a soln. of **8a** (6.0 g, 22 mmol) in THF (20 ml) and EtOH (30 ml), Pd/C (250 mg) was added and the mixture hydrogenated at r.t. until the theoretical amount of H_2 was absorbed (3 h). The catalyst was filtered off and the filtrate evaporated. The brown oily product was used for the next step without further purification. ^{1}H-NMR: 1.92–2.33 (*m*, CH_2CN); 2.47–3.07 (*m*, 6 H); 3.81 (*s*, MeO); 3.84–4.09 (*m*, OCH_2CH_2O); 4.88 ('*t*', $J = 5$, 1 H); 6.65–7.18 (*m*, 3 H).

$LiAlH_4$ (2.2 g, 58 mmol) was suspended in THF and cooled to 0°. A soln. of the saturated nitrile (5.3 g, 19 mmol) in THF (50 ml) was added dropwise during 45 min and the mixture stirred at r.t. for 4 h. It was then carefully quenched with a sat. Na_2SO_4 soln. and filtered to remove the inorg. material. The filtrate was washed with warm THF (2 × 50 ml), and the combined org. extracts were dried and evaporated. The oily residue was partitioned between AcOEt and a 10% soln. of citric acid in H_2O. The H_2O layer was separated, adjusted to pH 10 with 2N NaOH, and extracted with CH_2Cl_2 (3 × 100 ml). The org. layers were dried and evaporated: 4.7 g (83%) of **9a** as a light brown oil. ^{1}H-NMR: 1.10 (br. *s*, NH_2); 1.25–1.48 (*m*, 1 H); 1.52–1.73 (*m*, 1 H); 1.82–2.10 (*m*, 2 H); 2.47–3.00 (*m*, 6 H); 3.80, 3.82 (2*s*, MeO); 3.85–4.10 (*m*, OCH_2CH_2O); 4.88, 4.91 (2*d*, $J = 6$, 7, 1 H); 6.62–7.10 (*m*, 3 H). Anal. calc. for $C_{16}H_{23}NO$: C 69.35, H 8.31, N 5.00, O 5.83; found: C 69.17, H 8.36, N 4.96, O 5.78.

3-(1,3-Dioxolan-2-yl)-1,2,3,4-tetrahydro-8-methoxynaphthalene-2-ethylamine (**9b**). Compound **8b** (8.6 g, 32 mmol) was subjected to the above two-stage procedure to give 5.7 g (64%) of **9b** as brown oil. ^{1}H-NMR: 1.25 (br. *s*, NH_2); 1.50–1.71 (*m*, 1 H); 1.79–2.05 (*m*, 2 H); 4.45–3.05 (*m*, 6 H); 3.78, 3.80 (2*s*, MeO); 3.82–4.10 (*m*, OCH_2CH_2O); 4.78, 4.81 (2*d*, $J = 6$, 5, 1 H); 6.60–7.15 (*m*, 3 H). Anal. calc. for $C_{16}H_{23}NO$: C 69.35, H 8.31, N 5.00, O 5.83; found: C 69.80, H 8.34, N 5.01, O 5.80.

trans-*1,2,3,4,4a,5,10,10a-Octahydro-9-methoxybenzo[g]isoquinoline Hydrochloride* (**1b**·HCl). Conc. HCl (32 ml, 38 mmol) was added dropwise at r.t. to an EtOH soln. (25 ml) of **9a** (2.1 g, 7.6 mmol). The mixture was warmed at 40° for 1.5 h and then cooled to 0°. Under stirring, $NaBH_4$ (2.0 g, 53 mmol) was carefully (*caution:* foaming) added in small portions and the basic (pH 7–8) mixture stirred overnight at r.t. The pH was adjusted to 2 with 2N HCl, the EtOH evaporated, and the H_2O phase extracted with Et_2O (3 × 50 ml). The product being partially soluble in HCl, some of it crystallized and was filtered. The acidic phase and the solid were partitioned between 2N NaOH and CH_2Cl_2. The org. layer was dried and evaporated. The oily residue was treated with EtOH/HCl and the crude product recrystallized from MeOH yielding 1.5 g (82%) of **1b**·HCl. M.p. 289–291° (dec.). ^{1}H-NMR: 1.38–1.52 (*m*, H_{ax}–C(4)); 1.54–1.67 (*m*, H–C(4a)); 1.68–1.82 (*m*, H–C(10a)); 1.87–1.98 (*m*, H_{eq}–C(4)); 2.04, 2.09 (*dd*, $J = 12$, 11, H_{ax}–C(5)); 2.37, 2.41 (*dd*, $J = 12$, 12, H_{ax}–C(10)); 2.69 ('*t*', $J = 12$, H_{ax}–C(1)); 2.72–2.97 (*m*, H_{ax}–C(3), H_{eq}–C(10), H_{eq}–C(5)); 3.27–3.41 (*m*, H_{eq}–C(3), H_{eq}–C(1)); 3.77 (*s*, MeO); 6.68 (*d*, $J = 7$, H–C(8)); 6.76 (*d*, $J = 7$, H–C(6)); 7.09 ('*t*', $J = 7$, H–C(7)). Anal. calc. for $C_{14}H_{20}ClNO$: C 66.13, H 7.93, Cl 14.00, N 5.52, O 6.33; found: C 66.20, H 8.00, Cl 13.89, N 5.61, O 6.41.

trans-*1,2,3,4,4a,5,10,10a-Octahydro-6-methoxybenzo[g]isoquinoline Hydrochloride* (**1a**·HCl). Compound **9b** (5.6 g, 20 mmol) was subjected to the above procedure: 3.1 g (61%) of **1a**·HCl. M.p. 278–280°. ^{1}H-NMR: 1.27–1.63 (*m*, H_{ax}–C(4), H–C(4a), H–C(10a)); 1.75–1.90 (br. *d*, H_{eq}–C(4)); 2.11, 2.17 (*dd*, $J = 11$, 12, H_{ax}–C(5));

2.30–2.47 (*m*, H_{ax}–C(10), H_{ax}–C(1)); 2.62–2.75 (*m*, H_{eq}–C(5), H_{eq}–C(10)); 2.89, 2.92 (*dd*, *J* = 5, 6, H_{ax}–C(3)); 3.08–3.22 (*m*, H_{eq}–C(3), H_{eq}–C(1)); 3.79 (*s*, MeO); 6.65 (*d*, *J* = 7, H–C(7)); 6.69 (*d*, *J* = 7, H–C(9)); 7.50 ('*t*', *J* = 7, H–C(8)). Anal. calc. for $C_{14}H_{20}ClNO$: C 66.13, H 7.93, Cl 14.00, N 5.52, O 6.63; found: C 66.10, H 8.00, Cl 14.04, N 5.57, O 6.70.

Alkylation of **1a** *and* **1b**. *General Procedure*. To a suspension of **1a** (0.54 g of base, 2.5 mmol) and K_2CO_3 (1.0 g, 7.5 mmol) in THF (15 ml), alkyl iodide (3.7 mmol) was added and the mixture stirred at 40° overnight. It was then allowed to cool, the solvent evaporated, and the residue partitioned between CH_2Cl_2 (100 ml) and 2N NaOH (200 ml). The org. layer was dried and evaporated and the residue treated with HCl/EtOH to give the corresponding hydrochloride.

trans-*1,2,3,4,4a,5,10,10a-Octahydro-6-methoxy-2-methylbenzo[*g*]isoquinoline Hydrochloride* (**1ac**). MeI as alkylating agent (see above). The crude product was recrystallized from MeOH/Et_2O to give 490 mg (73%) of **1ac** as white crystals. M.p. 244–248° (dec.). ^{1}H-NMR: 1.50–1.67 (*m*, H–C(4a)); 1.60–1.72 (*m*, H_{ax}–C(4)); 1.82–2.06 (*m*, H–C(10a), H_{eq}–C(4), H_{ax}–C(10)); 2.37, 2.41 (*dd*, *J* = 12, 12, H_{ax}–C(5)); 2.73 (*s*, MeN); 2.75–2.86 (*m*, H_{ax}–C(1), H_{eq}–C(5), H_{eq}–C(10)); 3.40–3.56 (*m*, H_{eq}–C(1), H_{eq}–C(3)); 3.78 (*s*, MeO); 6.67 (*d*, *J* = 7, H–C(7)); 6.75 (*d*, *J* = 7, H–C(9)); 7.04 ('*t*', *J* = 7, H–C(8)). Anal. calc. for $C_{15}H_{22}ClNO$: C 67.38, H 8.32, Cl 13.21, N 5.24, O 6.08; found: C 66.98, H 8.27, Cl 13.12, N 5.30, O 5.98.

trans-*1,2,3,4,4a,5,10,10a-Octahydro-6-methoxy-2-propylbenzo[*g*]isoquinoline Hydrochloride* (**1ae**). PrI as alkylating agent (see above). Recrystallization of the crude product from MeOH/Et_2O afforded 630 mg (85%) of **1ae** as white crystals. M.p. 254–256°. ^{1}H-NMR: 0.95 (*t*, *J* = 7, $CH_3CH_2CH_2$); 1.50–1.67 (*m*, H_{ax}–C(4)); 1.73–2.20 (*m*, H–C(4a), H–C(10a), H_{eq}–C(4), $CH_3CH_2CH_2$); 2.39, 2.42 (*dd*, *J* = 12, 12, H_{ax}–C(5)); 2.62–2.78 (*m*, H_{ax}–C(10), H_{ax}–C(3), H_{ax}–C(1), H_{eq}–C(5), H_{eq}–C(10), $CH_3CH_2CH_2$); 3.38–3.50 (*m*, H_{eq}–C(3), H_{eq}–C(1)); 3.78 (*s*, MeO); 6.67 (*d*, *J* = 7, H–C(7)); 6.75 (*d*, *J* = 7, H–C(9)); 7.05 ('*t*', *J* = 7, H–C(8)). Anal. calc. for $C_{17}H_{26}ClNO$: C 69.07, H 8.93, Cl 12.02, N 4.76, O 5.41; found: C 69.11, H 9.00, Cl 11.96, N 4.79, O 5.40.

trans-*1,2,3,4,4a,5,10,10a-Octahydro-9-methoxy-2-methylbenzo[*g*]isoquinoline Hydrochloride* (**1bc**) was prepared like **1ac** using **1b** as starting material: 475 mg (70%). M.p. 250–252°. ^{1}H-NMR: 1.42–1.58 (*m*, H–C(4a)); 1.60–1.70 (*m*, H_{ax}–C(4)); 1.85–2.08 (*m*, H–C(10a), H_{eq}–C(4), H_{ax}–C(10)); 2.32, 2.38 (*dd*, *J* = 12, 12, H_{ax}–C(5)); 2.72 (*s*, MeN); 2.73–2.85 (*m*, H_{ax}–C(1), H_{eq}–C(5), H_{eq}–C(10)); 2.9–3.04 (*m*, H_{ax}–C(3)); 3.37–3.53 (*m*, H_{eq}–C(1), H_{eq}–C(3)); 3.76 (*s*, MeO); 6.68 (*d*, *J* = 7, H–C(8)); 6.76 (*d*, *J* = 7, H–C(6)); 7.09 ('*t*', *J* = 7, H–C(7)). Anal. calc. for $C_{15}H_{22}ClNO$: C 67.38, H 8.32, Cl 13.21, N 5.24, O 6.08; found: C 67.51, H 8.37, Cl 13.20, N 5.25, O 6.10.

trans-*1,2,3,4,4a,5,10,10a-Octahydro-9-methoxy-2-propylbenzo[*g*]isoquinoline Hydrochloride* (**1be**) was prepared like **1ae** using **1b** as starting material: 600 mg (80%). M.p. 268–270°. ^{1}H-NMR: 0.92 (*t*, *J* = 6, $CH_3CH_2CH_2$); 1.50–1.82 (*m*, H_{ax}–C(4), H–C(4a), $CH_3CH_2CH_2$); 1.85–2.10 (*m*, H–C(10a), H_{eq}–C(4), H_{ax}–C(10)); 2.35, 2.39 (*dd*, *J* = 12, 12, H_{ax}–C(5)); 2.69, 2.76 (*dd*, *J* = 11, 11, H_{ax}–C(1)); 2.79, 2.82 (2*d*, *J* = 6, 6, H_{eq}–C(5), H_{eq}–C(10)); 2.89–3.02 (*m*, H_{ax}–C(3), $CH_3CH_2CH_2$), 3.45–3.60 (*m*, H_{eq}–C(1), H_{eq}–C(3)); 3.77 (*s*, MeO); 6.68 (*d*, *J* = 7, H–C(8)); 6.77 (*d*, *J* = 7, H–C(6)); 7.09 ('*t*', *J* = 7, H–C(7)). Anal. calc. for $C_{17}H_{26}ClNO$: C 69.07, H 8.93, Cl 12.02, N 4.76, O 5.41; found: C 69.24, H 8.87, Cl 11.99, N 4.81, O 5.38.

trans-*1,2,3,4,4a,5,10,10a-Octahydrobenzo[*g*]isoquinolin-6-ol Hydrochloride* (**1aa**). A CH_2Cl_2 (2 ml) soln. of BBr_3 (0.67 ml, 7.0 mmol) was dropwise added to a cooled (−78°) soln. of **1a** (300 mg base, 1.4 mmol) in CH_2Cl_2 (10 ml) under stirring. The mixture was stirred at r.t. for 1 h and quenched with a sat. $NaHCO_3$ soln. (5 ml). The precipitate formed was filtered, washed with H_2O, and dried. It was then dissolved in MeOH (5 ml) and treated with MeOH/HCl to yield 150 mg **1aa** (54%) as white prisms. M.p. > 350°. ^{1}H-NMR: comparable to that of **1a**, MeO signal missing; 9.5 (br. *s*, OH). Anal. calc. for $C_{13}H_{18}ClNO$: C 65.15, H 7.62, Cl 14.81, N 5.83, O 6.74; found: C 65.09, H 7.70, Cl 14.89, N 5.87, O 6.77.

trans-*1,2,3,4,4a,5,10,10a-Octahydroybenzo[*g*]isoquinoline-6-ol Hydrochloride* (**1ba**) was obtained in 47% yield by using the above procedure with **1b** as starting material. M.p. > 350°. ^{1}H-NMR: comparable to that of **1b**, MeO signal missing; 9.2 (br. *s*, OH). Anal. calc. for $C_{13}H_{18}ClNO$: C 65.15, H 7.62, Cl 14.81, N 5.83, O 6.73; found: C 65.23, H 7.57, Cl 15.00, N 5.77, O 6.80.

Demethylation of the N*-Alkyl Derivatives. General Procedure*. The method for the demethylation of **1a** (→**1aa**) was followed with a slightly modified workup procedure: after quenching the reaction mixture with a sat. $NaHCO_3$ soln. CH_2Cl_2 was added. The org. phase was dried and evaporated, the residue dissolved in MeOH and treated with MeOH/HCl to give the hydrochloride.

trans-*1,2,3,4,4a,10,10a-Octahydro-2-methylbenzo[*g*]isoquinoline-6-ol Hydrochloride* (**1ab**). Application of the general procedure to **1ac** afforded **1ab** (74%), recrystallized from MeOH/H_2O. M.p. 352–354° (dec.). ^{1}H-NMR: comparable to that of **1ac**, MeO signal missing; 9.30 (*s*, OH). Anal. calc. for $C_{14}H_{19}ClNO$; C 66.36, H 7.94, Cl 14.00, N 5.52, O 6.31; found: C 66.17, H 8.01, Cl 13.79, N 5.60, O 6.33.

trans-*1,2,3,4,4a,10,10a-Octahydro-2-propylbenzo[g]isoquinoline-6-ol Hydrochloride* (**1ad**). Prepared from **1ae** in 82% yield. M.p. 320–322°. ^{1}H-NMR: comparable to that of **1ae**, MeO signal missing; 9.31 (*s*, OH). Anal. calc. for $C_{16}H_{24}ClNO$: C 68.21, H 8.62, Cl 12.63, N 5.08, O 5.74; found: C 68.16, H 8.59, Cl 12.39, N 4.97, O 5.80.

trans-*1,2,3,4,4a,10,10a-Octahydro-2-methylbenzo[g]isoquinoline-9-ol Hydrochloride* (**1bb**). Application of the general procedure to **1bc** afforded **1bb** (85%), recrystallized from MeOH. M.p. 329–331°. ^{1}H-NMR: comparable to that of **1bc**, MeO signal missing; 9.36 (*s*, OH). Anal. calc. for $C_{14}H_{19}ClNO$: C 66.36, H 7.94, Cl 14.00, N 5.52, O 6.31; found: C 66.51, H 8.00, Cl 13.89, N 5.61, O 6.28.

trans-*1,2,3,4,4a,10,10a-Octahydro-2-propylbenzo[g]isoquinoline-9-ol Hydrochloride* (**1bd**). Application of the general procedure to **1be** followed by a recrystallization in MeOH gave **1bd** (67%). M.p. 328° (dec.). ^{1}H-NMR: comparable to that of **1be**, MeO signal missing; 9.37 (*s*, H). Anal. calc. for $C_{16}H_{24}ClNO$: C 68.21, H 8.62, Cl 12.63, N 5.08, O 5.73; found: C 68.12, H 8.57, Cl 12.59, N 5.01, O 5.68.

Binding Studies. Displacement studies were carried out on various homogenates. Typically, 4–6 different concentrations of test compounds were incubated in triplicate, and the IC_{50} value (nM) was determined by appropriately weighted regression analysis. The ligands were as follows: for $5HT_{1a}$ receptors, [^{3}H]8-HODPAT[6] in porcine frontal cortex; for $5HT_{1c}$ receptors, [^{3}H]mesulergin[7] in porcine choroid plexus; for $5HT_2$ receptors, [^{3}H]ketanserin[8] in rat frontal cortex; for α_1-adrenoceptors, [^{3}H]prazocin[9] in calf cortex; for α_2-adrenoceptors, [^{3}H]clonidine[10] in calf cortex; for dopamine D1 and D2 receptors, [^{3}H]ADTN[11] and [^{3}H]SDZ205-501[12], resp., both in calf striatum.

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