Articles

A-Ring *Ortho*-Disubstituted Aporphine Derivatives as Potential Agonists or Antagonists at Serotonergic 5-HT_{1A} Receptors

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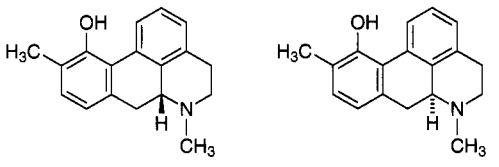
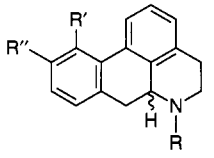
(*R*)- And (*S*)-11-hydroxy-10-methylaporphine **1** and **2** are, respectively, a potent, highly specific serotonergic (5-HT_{1A}) agonist and antagonist. In an ongoing structure–activity study, racemates of the positional isomers 8-hydroxy-9-methyl- and 8-methyl-9-hydroxyaporphine were prepared by modifications of literature methods and were resolved. The methyl ethers of the target compounds were also evaluated pharmacologically. All of the free phenolic derivatives [(+)- and (−)-**8** and **10**] were inert in an assay for 5-HT_{1A} receptor activity. All of the methyl ethers [(+)- and (−)-**9** and **11**] demonstrated quantitatively similar low potency stimulant effect at 5-HT_{1A} receptors. The agonist or antagonist activity exhibited by **1** and **2** reflects the high degree of structural specificity required of aporphine derivatives for action at 5-HT_{1A} receptors.

Previous communications from our laboratories described potent and highly specific serotonergic (5-HT_{1A}) agonist effects of (*R*)-11-hydroxy-10-methylaporphine (**1**)[1] (PM-1000) and similarly potent and specific serotonergic (5-HT_{1A}) antagonist effects of the (*S*)-enantiomer **2**.[2] Neither enantiomer demonstrated significant activity in assays for effects at dopamine receptors. Neumeyer *et al.*[3] reported that (*RS*)-(±)-11-hydroxyaporphine (**3**) and (*RS*)-(±)-11-hydroxy-N-*n*-propylnoraporphine (**4**) are potent dopaminergic agonists. Subsequently, (*R*)-(−)-**4** was shown to be a dopaminergic agonist and its (*S*)-(+)-enantiomer to be a dopaminergic antagonist.[4] Contrary to an earlier report,[5] 11-hydroxyaporphine **3** demonstrates effects at serotonin 5-HT_{1A} receptors superimposed upon its effects at dopamine receptors. The (*R*)-enantiomer is a weak agonist, and the (*S*)-enantiomer is an antagonist.[6] We recently found[5] that neither enantiomer of 10-methylaporphine (**5**) or of aporphine (**6**) demonstrates significant activity in assays for effects (agonist or antagonist) at serotonin 5-HT_{1A} receptors. Moreover, there was no indication of dopaminergic (DA_2) agonist activity for any of these nonoxygenated aporphines. (*RS*)-10-Hydroxy-11-methylaporphine (**7**) demonstrated no effects at 5-HT_{1A} receptors.[6]

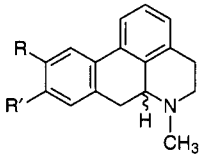


1 **2**



3: R = CH_3; R′ = OH′; R″ = H
4: R = *n*-C_3H_7; R′ = OH; R″ = H
5: R = CH_3; R′ = H; R″ = CH_3
6: R = CH_3; R′ = R″ = H
7: R = R′ = CH_3; R″ = OH

These data suggest the necessity of a combination of a methyl and a hydroxy substituent on the A ring of the aporphine system for potent interaction at the 5-HT_{1A} receptor, concomitant with absence of effects at dopamine receptors. However, it is not known whether these pharmacological effects require the 11-hydroxy-10-methyl substitution pattern. Accordingly, the present communication addresses synthesis and pharmacological evaluation of the enantiomers of aporphine A ring positional isomers of **1** and **2**: target compounds **8** and **10**. The enantiomers of the methyl ethers **9** and **11** of these compounds were also evaluated.



8: R = OH; R′ = CH_3
9: R = OCH_3; R′ = CH_3
10: R = CH_3; R′ = OH
11: R = CH_3; R′ = OCH_3

Chemistry. Preparation of (*RS*)-9-hydroxy-10-methylaporphine (**10**) (Scheme 1) began with a Gadamer condensation[10] of 2,5-dimethyl-4-nitroanisole (**12**) with *N*-methylisoquinolinium, and the aporphine ring was closed with a Pschorr cyclization (**14** → **11**). The racemic methyl ether **11** was resolved with di-*p*-toluoyl-D- and L-tartaric acids, and the resolved materials were converted into (+)- and (−)-**10**. The method outlined in Scheme 1 was equivocal for preparation of **9** in that the starting material, 2,4-dimethyl-5-nitroanisole (**15**), bears methyl groups *ortho* and *para* to the nitro function, and both would be expected to be capable of forming an

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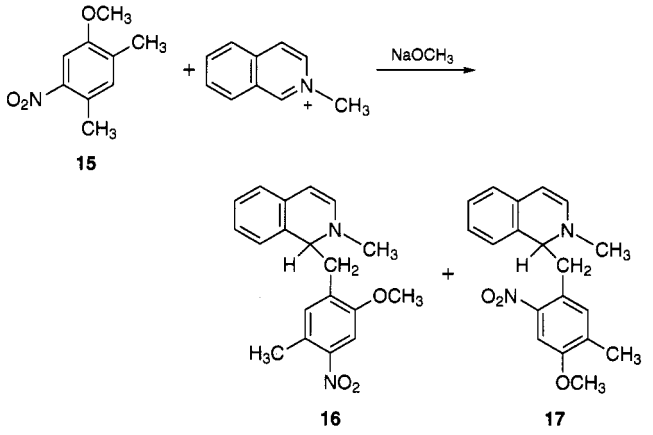
anion in the Gadamer condensation with *N*-methylisoquinolinium. Indeed, this was the case, and a mixture



of two Gadamer condensation products, **16** and **17**, was formed. Attempts to separate **16** and **17** by crystallization were unsuccessful. Chromatographic separation was likewise unsuccessful due, *inter alia*, to decomposition of the products on the column. Similarly, the reduction products **18** and **19** could not be separated nor isolated. Therefore, the mixture of **16** and **17** was utilized in the next two steps. Only the 2-aminobenzyl isomer **18** (derived from **17**) will undergo the Pschorr cyclization; the resulting aporphine product **9** was separated from other reaction products and was isolated from the cyclization mixture. Spectral (IR, NMR, and MS) data for all intermediates and final compounds were consistent with the proposed structures.

Pharmacology. Inhibition of field stimulation-induced contractions in the guinea pig ileum is a well-recognized assay for 5-HT_{1A} receptors.[13] After contractions were stabilized, compounds were tested for their ability to inhibit contractions induced by field stimulation and for their ability to antagonize contractile responses to acetylcholine. All compounds listed in Table 1 were inactive at doses up to 1 μM; they were much less potent than (*R*)-**1** (PM-1000). In higher doses, four compounds, (+)- and (−)-**9** and (+)- and (−)-**11**, produced an inhibitory effect on contraction of ileal smooth muscle produced by field stimulation. These four compounds also inhibited contractions induced by acetylcholine. Inhibition of contractions induced by field stimulation or by acetylcholine was maintained following the larger doses of the experimental compounds. These compounds did not appear to show specific activity. They may be very weak antimuscarinic agents, since both field stimulation (nerve terminal activation) and acetylcholine-induced contractions were antagonized. It is noteworthy that both enantiomers of the free phenol derivatives **8** and **10** were inactive, but both enantiomers of the methyl ethers **9** and **11** demonstrated the modest pharmacological effect. It is also noteworthy that the enantiomers of **9** and **11** did not display a significant difference in potency in the field stimulation assay. It is concluded that the pronounced 5-HT_{1A} agonism and antagonism displayed by (*R*)- and (*S*)-**1**, respectively, require both a methyl and a hydroxyl group, and moreover these effects seem to be unique to and specific for the 11-hydroxy-10-methyl substitution pattern on the aporphine ring.

Scheme 1. Preparation of (*RS*)-9-Hydroxy-10-methylaporphine

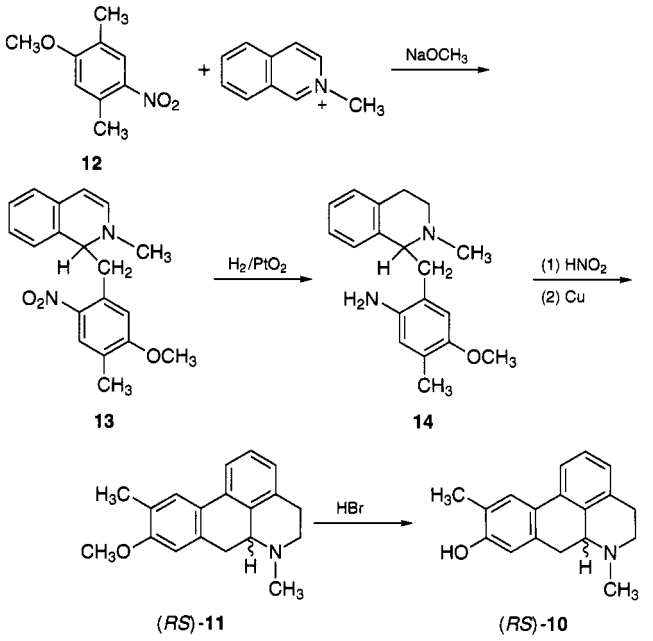


Table 1. Ability of Aporphine Derivatives To Antagonize Electrical and Acetylcholine Induced Responses in Guinea Pig Ilea

compd no.	absolute configuration	ED_{50}, μM (95% confidence limits), to inhibit contraction: field stimulation	AcCh induced
(+)-**8**	*S*	inactive[a]	inactive[a]
(−)-**8**	*R*	inactive[a]	inactive[a]
(+)-**10**	*S*	inactive[a]	inactive[a]
(−)-**10**	*R*	inactive[a]	inactive[a]
(+)-**11**	*S*	5.4 (3.9−8.5)	24.9 (11.8−154.6)
(−)-**11**	*R*	5.0 (3.4−9.3)	2.7 (2.3−3.1)
(+)-**9**	*S*	5.9 (4.1−10.7)	36.6 (12.9−2041.1)
(−)-**9**	*R*	2.6 (0.6−6.1)	11.4 (9.2−14.9)
(*R*)-**1** (PM-1000)		0.05 (0.01−0.1)	NT[b]

[a] Inactive at dose level of 1.0 μM. [b] Not tested.

Experimental Section

Pharmacology. Materials and Methods. Adult guinea pigs of either sex were sacrificed under deep ether anesthesia. Approximately 1.5 cm segments of distal ilea, 10 cm from the cecum, were mounted in a 100 mL organ bath. Tyrode's solution (37−38 °C) was saturated with 95% O_2 + 5% CO_2. Under 1 g resting tension, segments were transmurally stimulated with 120 V, 4 ms pulse duration, and frequency of 0.1 Hz rectangular pulses. Muscle contractions were recorded using a Beckman R-611 recorder via a Grass force-displacement transducer (FT 03C). Chemicals were added to the bath when the contractile responses to electrical stimulation were stabilized, usually after 30−60 min. In other preparations, contractions were induced by adding acetylcholine to the bath. Experimental compounds were added to the bath 3 min before administration of acetylcholine. ED_{50} values and their 95% confidence intervals were calculated by probit analysis.[12]

Chemistry. Melting points were determined in open glass capillaries on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Mass spectral data were obtained through chemical ionization with NH_3 on a Ribermag R 10 10C instrument unless otherwise specified. IR spectra were obtained with a Nicolet FTIR instrument, and NMR spectra were obtained with a 5 mm broadband probe in a WM 360 MHz spectrometer and processed with an Aspect 2000 processor. TMS was used as the internal standard. Optical rotations were obtained with a Perkin-Elmer Model 141 digital polarimeter. Elemental analyses were performed by Galbraith

Laboratories, Knoxville, TN. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values. Flash column chromatography was performed using 35–75 μm particle size Analtech silica with a 150 Å pore size.

(*RS*)-1-(5-Methoxy-4-methyl-2-nitrobenzyl)-2-methyl-1,2-dihydroisoquinoline (13). Na (20.0 g, 0.87 mol) was dissolved under N_2 in 500 mL of recently dried (by treatment with Mg and distillation) EtOH and then 42.74 g (0.256 mol) of 2,5-dimethyl-4-nitroanisole (**12**)[7] (dried at 9 Torr for 1 h) was added, and this mixture was warmed to 50 °C. To the resulting solution was added in one portion a warmed (50 °C) solution of 44.80 g (0.249 mol) of *N*-methylisoquinolinium chloride[8] in 100 mL of recently dried EtOH. This mixture was warmed to 80 °C and then was allowed to cool to ambient temp over 3 h with stirring. The stoppered reaction flask was maintained at −5 °C for 72 h. The resulting brick-red precipitate was collected on a filter and was triturated with five 25 mL portions of 10% HCl. The pooled acid fractions were filtered twice through Whatman GFA glass microfiber filter paper to yield a clear, bright yellow filtrate. This was basified with concentrated NH_4OH and was allowed to stand for 24 h. The dark red solid which separated was collected on a filter and was washed with 100 mL of H_2O. It was dried for 3 h at 9 Torr to yield 58.9 g (64%) of product, mp 117–119 °C. Anal. ($C_{19}H_{20}N_2O_3$) C, H, N (Karl Fischer H_2O 1.29%).

(*RS*)-1-(2-Amino-5-methoxy-4-methylbenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (14). Compound **13** (10.87 g, 0.0295 mol) in 320 mL of 99% EtOH, 640 mL of MeOH, and 40 mL of $CHCl_3$ was hydrogenated over PtO_2 at an initial pressure of 55 psig. After 2 h, 4 equiv of H_2 was absorbed, and the supernatant was clear yellow. The reduction mixture was filtered through Celite, and 300 mL of ethereal HCl was added to the filtrate. Volatiles were removed under reduced pressure to leave an off-white solid which was dried under reduced pressure for 12 h. This was recrystallized from 99% EtOH to yield 10.06 g (92%) of product: mp 244 °C; MS *m/e* 148 ((M^+ − 2HCl)/2). Anal. ($C_{19}H_{26}Cl_2N_2O$) C, H, N (Karl Fischer H_2O 0.2%).

(*RS*)-9-Methoxy-10-methylaporphine Hydrochloride (11). Cu was prepared within 4 h of starting the reaction sequence. Zn dust (1.0 g, 0.015 mol) was slowly added to a well-agitated solution of 4.0 g (0.016 mol) of $CuSO_4 \cdot 5H_2O$ in 10 mL of H_2O while the temperature was maintained at 0 °C. After precipitation of Cu was complete, the supernatant was decanted and the Cu was washed with 50 mL portions of H_2O until the washings were neutral to litmus paper. The Cu was stored under H_2O at 5 °C.

Compound **14** (1.57 g, 0.004 24 mol) in 500 mL of dilute H_2SO_4 was cooled in an ice–brine bath, and 0.586 g (0.008 49 mol) of $NaNO_2$ in 10 mL of H_2O was slowly added to the well-stirred solution through polypropylene tubing extending below the surface of the reaction mixture. The temperature of the reaction mixture was maintained at −5 °C for 15 min after all of the $NaNO_2$ was added, and then the ice–brine cooling bath was replaced with an ice–H_2O bath. After the temperature rose to 0 °C, 0.9 g (0.014 mol) of Cu was added, and the mixture was stirred for 12 h, maintaining the temperature at 0 °C. The mixture was then filtered through Celite, and the filtrate was taken to pH >10 (pH paper) with NH_4OH. EtOH (50 mL) was added to inhibit emulsion formation, and the mixture was extracted with five 75 mL portions of $CHCl_3$. The pooled extracts were dried (Na_2SO_4) and filtered through glass wool, and the solvent was removed under reduced pressure. The residue was dissolved in a minimum volume of EtOH–$CHCl_3$ (10:1), and this solution was chromatographed on a flash column (SiO_2) and eluted with EtOH–$CHCl_3$ (10:1). The fractions containing aporphine material were pooled and volatiles were removed under reduced pressure. A solution of the residual oil in 10 mL of 99% EtOH was added dropwise to excess ethereal HCl. Volatiles were removed under reduced pressure to afford an amorphous white solid which was recrystallized from 99% EtOH to yield 0.44 g (33%) of product: mp 265 °C dec; MS *m/e* 280 (M^+ + 1 − HCl). Anal. ($C_{19}H_{22}ClNO$) C, H, N (Karl Fischer H_2O 1.81%).

(*RS*)-9-Hydroxy-10-methylaporphine Hydrochloride (10). Compound **11** (300.5 mg, 0.95 mmol) in 20 mL of freshly distilled concentrated HBr was heated under N_2 at reflux temperature for 3 h. Upon cooling, the reaction mixture deposited a white solid which was collected on a filter and then dissolved in 25 mL of H_2O. This solution was basified with saturated $NaHCO_3$, and the resulting mixture was extracted with four 15 mL portions of $CHCl_3$. The pooled extracts were dried (Na_2SO_4) and filtered through glass wool, and volatiles were removed from the filtrate under reduced pressure. Absolute EtOH (10 mL) was added to the oily residue, and then excess ethereal HCl was added. Volatiles were removed under reduced pressure; traces of residual H_2O were azeotroped with 2-PrOH. The off-white solid residue was recrystallized from absolute EtOH to yield 236.6 mg (83%) of a white amorphous solid which turned green at 230 °C and melted at 284 °C dec: MS *m/e* 266 (M^+ + 1 − HCl). Anal. ($C_{18}H_{20}ClNO$) C, H, N (Karl Fischer H_2O < 0.2%).

(+)-9-Methoxy-10-methylaporphine Hydrochloride [(+)-11]. (*RS*)-**11** (0.810 g, 0.002 56 mol) in 10 mL of EtOH, 5 mL of dilute HCl, and 25 mL of H_2O was basified with saturated $NaHCO_3$, and the resulting mixture was extracted with four 20 mL portions of $CHCl_3$. The combined extracts were dried (Na_2SO_4) and filtered through glass wool, and solvents were removed under reduced pressure. A solution of the residue in 7.5 mL of EtOAc was added to a solution of 1.156 g (0.002 99 mol) of (−)-di-*p*-toluoyl-L-tartaric acid in 10 mL of EtOAc. Upon standing, a voluminous white solid separated. This was recrystallized from 4% $CHCl_3$ in absolute EtOH to constant optical rotation (six recrystallizations), $[\alpha]^{25}_D$ −27.64° (*c* = 0.0156, EtOH). The mother liquors were pooled, and upon standing, a second crop of crystals was deposited, which was recrystallized six times to constant optical rotation. The combined products were dissolved in 25 mL of EtOH, 5 mL of dilute HCl, and 25 mL of H_2O. This solution was basified with saturated $NaHCO_3$, and the resulting mixture was extracted with four 25 mL portions of $CHCl_3$. The combined extracts were dried (Na_2SO_4) and filtered through glass wool, and solvent was removed from the filtrate under reduced pressure. The residual oil in 7.5 mL of 99% EtOH was treated with excess ethereal HCl. Volatiles were removed under reduced pressure to yield 9.34 mg (11%) of a white crystalline solid: mp 260 °C dec; $[\alpha]^{25}_D$ +62.29° (*c* = 0.1, 1:1 99% EtOH/$CHCl_3$); MS *m/e* 280 (M^+ + 1 − HCl); NMR (free base) ($CDCl_3$) was identical to that of (*RS*)-**11**.

(+)-9-Hydroxy-10-methylaporphine [(+)-10]. A suspension of 65.55 mg (0.208 mmol) of (+)-**11** in 10 mL of freshly distilled concentrated HBr was stirred and heated at reflux temperature under N_2 for 3 h. The cooled reaction mixture was treated with excess saturated $NaHCO_3$, and the resulting mixture was extracted with three 15 mL portions of $CHCl_3$. The pooled extracts were evaporated under reduced pressure, and the residual oil in 3 mL of Et_2O was chromatographed on SiO_2 (60–200 mesh activated with 10% H_2O). The column was eluted first with 200 mL of Et_2O, retaining the aporphine product on the column, and then with 99% EtOH/$CHCl_3$ (1:1). Solvents were removed from the latter eluate, and a solution of the residue in dry Et_2O was treated with ethereal HCl to afford 36.5 mg (58%) of product: mp 230 °C dec; $[\alpha]^{25}_D$ +51.72° (*c* = 0.87, 1:1 99% EtOH/$CHCl_3$); MS *m/e* 266 (M^+ + 1 − HCl); NMR (free base) ($CDCl_3$) was identical to that of (*RS*)-**10**.

(−)-9-Methoxy-10-methylaporphine Hydrochloride [(−)-11]. (*RS*)-**11** (0.9 g, 0.0028 mol) was treated as described above for preparation of (+)-**11**, using 1.50 g (0.003 90 mol) of (+)-di-*p*-toluoyl-D-tartaric acid. D-Tartrate salt: $[\alpha]^{25}_D$ +25° (*c* = 0.010, EtOH); yield of HCl salt, 0.099 g (11%) of a white solid; mp 265 °C dec; $[\alpha]^{25}_D$ −57.50° (*c* = 0.93, 1:1 99% EtOH/$CHCl_3$); MS *m/e* 280 (M^+ + 1 − HCl); NMR (free base) ($CDCl_3$) was identical with that of (*RS*)-**11**.

(−)-9-Hydroxy-10-methylaporphine Hydrochloride [(−)-10]. (−)-**11** (30.65 mg, 0.097 mmol) was treated as described above for preparation of (+)-**10**: yield 19.2 mg (67%); mp 240 °C dec; $[\alpha]^{25}_D$ −53.92° (*c* = 0.65, 1:1 99% EtOH/$CHCl_3$); MS *m/e* 266 (M^+ − HCl); NMR (free base) ($CDCl_3$) was identical with that of (*RS*)-**10**.

(*RS*)-1-(4-Methoxy-5-methyl-2-nitrobenzyl)-2-methyl-1,2-dihydroisoquinoline (17) and (*RS*)-1-(2-Methoxy-5-methyl-4-nitrobenzyl)-2-methyl-1,2-dihydroisoquinoline (16). Na (10.0 g, 0.43 mol) was dissolved under N_2 in 200 mL of recently dried (by treatment with Mg and distillation) EtOH. 2,4-Dimethyl-5-nitroanisole **15**[9] (40.39 g, 0.223 mol) (dried at ambient temp at 9 Torr for 1 h) was dissolved in the NaOEt solution at 50 °C. This solution was added in one portion to 33.99 g (0.189 mol) of *N*-methylisoquinolinium chloride[8] in 50 mL of recently dried EtOH warmed to 50 °C. The resulting mixture was heated to 70 °C over 30 min and then was allowed to cool to ambient temperature over 90 min. The reaction mixture was again warmed to 50 °C for 45 min, after which the stoppered reaction flask was stored at −5 °C for 72 h. The brick-red solid which separated was collected on a filter. After trituration of this material with five 50 mL portions of dilute HCl, the combined aqueous extracts were filtered twice through Whatman GFA glass microfiber filter paper to afford a clear bright yellow filtrate. This was basified with concentrated NH_4OH and was allowed to stand for 24 h. The dark red solid which formed was collected on a filter and was washed with 100 mL of H_2O. It was dried at room temperature at 9 Torr for 3 h to afford 54.90 g (89%) of a red solid: mp 67 °C; MS *m/e* 325 (M + 1). Anal. ($C_{19}H_{20}N_2O_3$) C, H, N. This material was carried to the next step without further purification.

(*RS*)-1-(2-Amino-4-methoxy-5-methylbenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (18) and (*RS*)-1-(4-Amino-2-methoxy-5-methylbenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (19). The mixture of **16** and **17** (6.57 g, 0.0203 mol) in 200 mL of 99% EtOH, 400 mL of MeOH, and 50 mL of $CHCl_3$ was hydrogenated over PtO_2 in a Parr hydrogenation apparatus at an initial pressure of 55 psig. After 16 h 4 equiv of H_2 was absorbed, and the supernatant was clear yellow. The reduction mixture was filtered through Celite, and volatiles were removed from the filtrate under reduced pressure to give a tan solid which was dried at ambient temperature for 12 h at 9 Torr to provide 7.45 g (quant) of product: mp 186 °C; MS *m/e* 149 ((M^+ − 2HCl)/2).

(*RS*)-10-Methoxy-9-methylaporphine Hydrochloride (9). Cu was freshly prepared as described for **11**. The mixture of **18** and **19** (4.98 g, 0.013 mol) in 50 mL of H_2O was basified with 10% Na_2CO_3, and the resulting mixture was extracted with four 25 mL portions of $CHCl_3$. Volatiles were removed from the pooled extracts under reduced pressure to afford a yellow oil which dissolved in 10 mL of EtOH. This solution was added dropwise to 1.5 L of dilute H_2SO_4. The resulting solution was divided into three equal portions, each of which was placed in a separate reaction vessel, and all three portions were subsequently treated alike: The solution was cooled to −5 °C, and a 7 mL portion of a freshly prepared solution of 1.8 g (0.026 mol) of $NaNO_2$ in 21 mL of H_2O was added dropwise from a polypropylene tube extending below the surface of the liquid. The rate of addition was such that the temperature did not exceed −5 °C. The reaction mixture was stirred for an additional 15 min and was then transferred to an ice−H_2O bath. When the temperature of the reaction mixture reached 0 °C, 2.5 g (0.04 mol) of Cu was added and the resulting mixture was stirred for 12 h. The three reaction mixtures were then filtered through Celite, and the filtrates were combined. This solution was taken to pH >10 with concentrated NH_4OH. EtOH (50 mL) was added to inhibit emulsion formation, and the mixture was extracted wtih five 75 mL portions of $CHCl_3$. The combined extracts were dried (Na_2SO_4) and filtered through glass wool in a gravity funnel, and the solvent was removed from the filtrate under reduced pressure. The residue was dissolved in a minimum amount of EtOH/$CHCl_3$ (10:1), and this solution was chromatographed on a flash column (SiO_2) and eluted with EtOH/$CHCl_3$ (10:1). The fractions containing aporphine material were combined, and solvent was removed under reduced pressure. The residual oil in 25 mL of Et_2O was added dropwise with stirring to excess ethereal HCl. The solid which separated was recrystallized from 99% EtOH−Et_2O to afford 0.82 g (19%) of product: mp 220 °C dec; MS *m/e* 280 (M^+ − HCl); NMR (free base) δ 2.16 (s, 3H, arom CH_3), 2.48 (s, 3H, NCH_3), 2.52 (t, 2H, CH_2), 2.66 (dd, 1H, benzyl CH), 2.98 (dt, 2H, benzyl CH_2), 3.10 (dd, 2H, benzyl CH_2), 3.82 (s, 3H, OCH_3), 6.80 (d, 2H, arom H), 6.96 (s, 1H, arom H), 7.10 (s, 1H, arom H), 7.17 (dd, 1H, arom H), 7.45 (d, 1H, arom H); HRMS (FAB$^+$) 280.1691 (M + H^+), calcd for $C_{19}H_{22}NO$ 280.1701.

(*RS*)-10-Hydroxy-9-methylaporphine Hydrochloride (8). Compound **9** (0.46 g, 0.001 46 mol) in 40 mL of freshly distilled concentrated HBr was treated as described for (*RS*)-**10**. The crude product in a minimal volume of 1% $CHCl_3$ in EtOAc was chromatographed on SiO_2 (60−200 mesh activated with 10% H_2O) and was eluted under N_2 with 1% $CHCl_3$ in EtOAc. Volatiles were removed from the eluate under reduced pressure. The residue in 10 mL of dry Et_2O was treated with excess ethereal HCl. The white solid which separated was recryst twice from 99% EtOH−Et_2O to afford 24.0 mg (14%) of product. This solid turned green at 235 °C and melted at 256 °C dec: HRMS (FAB$^+$) 266.1548 (M + H^+), calcd for $C_{18}H_2$-ONO 266.1545.

(+)-10-Methoxy-9-methylaporphine Hydrochloride [(+)-9]. (*RS*)-**9** (1.22 g, 0.0039 mol) was treated as described above for preparation of (+)-**11**. The free base of (*RS*)-**9** in 10 mL of EtOAc was treated with 1.63 g (0.004 22 mol) of (−)-di-*p*-toluoyl-L-tartaric acid in 10 mL of EtOAc. The white solid which separated was recrystallized to constant optical rotation from 99% EtOH (four recrystallizations), $[\alpha]^{25}_D$ −37.11° (*c* = 0.001, EtOH). The product of the final recrystallization in 25 mL of EtOH, 25 mL of H_2O, and 5 mL of dilute HCl was treated with excess saturated $NaHCO_3$, and the resulting mixture was extracted with four 25 mL portions of $CHCl_3$. The combined extracts were dried (Na_2SO_4) and filtered through glass wool, and the solvent was removed under reduced pressure. The residual oil was treated with ethereal HCl to provide 80 mg (7%) of a white crystalline solid that turned green at 220 °C and melted at 239 °C dec: $[\alpha]^{25}_D$ +44.62° (*c* = 0.09, 1:1 99% EtOH/$CHCl_3$); MS *m/e* 280 (M + 1 − HCl); NMR (free base) ($CDCl_3$) was identical to that of (*RS*)-**9**.

(+)-10-Hydroxy-9-methylaporphine Hydrochloride [(+)-8]. (+)-**9** (70 mg, 0.222 mmol) was treated with 10 mL of freshly distilled concentrated HBr as described above for (*RS*)-**10**. The crude product in a minimum volume of 1% $CHCl_3$ in EtOAc was chromatographed on SiO_2 (60−200 mesh) under N_2 and was eluted with the same solvent system. Solvent was evaporated from the eluate under reduced pressure, and the residue was treated with ethereal HCl. The resulting white solid was recrystallized twice from EtOH−Et_2O to afford 47.9 mg (72%) of product which turned green at 230 °C and melted at 258 °C dec: $[\alpha]^{25}_D$ +74.45° (*c* = 0.1, 1:1 99% EtOH−$CHCl_3$); MS *m/e* 266 (M^+ + 1 − HCl); NMR (free base) ($CDCl_3$) was identical to that of (*RS*)-**8**.

(−)-10-Methoxy-9-methylaporphine Hydrochloride [(−)-9]. (*RS*)-**9** (1.22 g, 0.0039 mol) was treated as described above for (+)-**11**. The free base of (*RS*)-**9** in 10 mL of EtOAc was treated with a solution of 1.63 g (0.0042 mol) of (+)-di-*p*-toluoyl-D-tartaric acid in 10 mL of EtOAc. The resulting voluminous white precipitate was recrystallized from 99% EtOH to constant optical rotation (four recrystallizations), $[\alpha]^{25}_D$ +34.17° (*c* = 0.0011, EtOH). The solid from the final recrystallization in 25 mL of EtOH, 5 mL of dilute HCl, and 25 mL of H_2O was treated with excess saturated $NaHCO_3$ and the resulting mixture was extracted with four 25 mL portions of $CHCl_3$. The pooled extracts were dried (Na_2SO_4) and filtered through glass wool, and the solvent was removed under reduced pressure. The residual oil was treated with ethereal HCl to provide 70 mg (6%) of a white crystalline solid which turned green at 220 °C and melted at 245 °C dec: $[\alpha]^{25}_D$ −46.32° (*c* = 0.09, 1:1 99% EtOH−$CHCl_3$); MS *m/e* 280 (M + 1 − HCl); NMR (free base) ($CDCl_3$) was identical to that of (*RS*)-**9**.

(−)-10-Hydroxy-9-methylaporphine Hydrochloride [(−)-8]. (−)-**9** (50.0 mg, 0.158 mmol) was treated with 10 mL of freshly distilled concentrated HBr as described above for (*RS*)-**10**. The free base of the crude product in a minimum amount of 1% $CHCl_3$ in EtOAc was chromatographed on SiO_2 (60−200 mesh activated with 10% H_2O) and was eluted under N_2 with the same solvent system. Solvents were removed from

the eluate under reduced pressure, and the residue was treated with ethereal HCl. The resulting white solid was recrystallized twice from 99% EtOH–Et_2O to yield 45.3 mg (95%) of a white solid that turned green at 230 °C and melted at 258 °C dec: $[\alpha]^{25}_D$ −73.85° (c = 0.09, 1:1 99% EtOH–$CHCl_3$); MS m/e 266 ($M^+ + 1 - HCl$); NMR (free base) ($CDCl_3$) was identical to that of (*RS*)-**8**.

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