5-HT_{1A}-Receptor Antagonism: *N*-Alkyl Derivatives of (*R*)-(−)-8,11-Dimethoxynoraporphine

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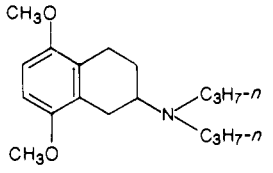
Prompted by previous findings that a *p*-dimethoxy substitution pattern on an aromatic ring permits retention of dopaminergic agonist effects in certain ring systems, catechol derivatives of which are potent dopaminergic agonists, an 8,11-dimethoxy substitution pattern was introduced into the aporphine ring in place of the 10,11-dihydroxy moiety in apomorphine. Acid-catalyzed rearrangement of an appropriate morphine derivative provided the aporphine ring system with retention of the stereochemical integrity of the 6a asymmetric center. The hydroxyl group at position 10 was removed by catalytic hydrogenolysis of its phenyltetrazolyl ether. The methyl ether of the resulting 11-hydroxyaporphine was iodinated in high yield at position 8 with trifluoroacetyl hypoiodite. This is the first account of synthesis of an iodinated aporphine derivative. The 8-iodo substituent was replaced with methoxyl by reaction with sodium methoxide and cuprous iodide. Neither the *N*-methyl target compound **7** nor the *N*-*n*-propyl derivative **8** demonstrated dopaminergic nor serotonergic agonism. However, **7** exhibited receptor-binding characteristics and other pharmacological properties suggesting that it may be a 5-HT_{1A} receptor antagonist.

The *p*-dimethoxy moiety has been incorporated into an aromatic ring in a variety of systems (structures **1**–**5**), catechol derivatives of which elicit dopaminergic agonist action. The aminotetralin derivative **1** exhibited some



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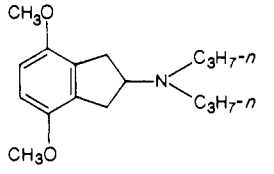

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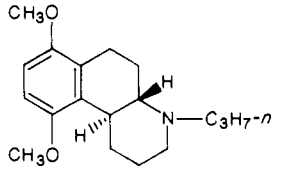

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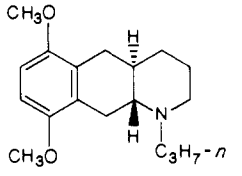

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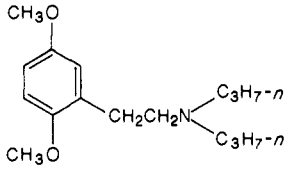

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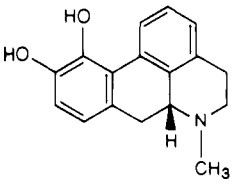
dopamine receptor agonist activity in addition to α_1-adrenoceptor effects.[1,2] The indan derivative **2** was more potent with higher dopaminergic efficacy than the aminotetralin **1**; compound **2** demonstrated equal activity with apomorphine in activation of peripheral presynaptic dopamine receptors, and central pre- and postsynaptic dopamine receptors were also activated by this compound.[3] Both the angularly and linearly annulated *trans*-octahydrobenzoquinoline derivatives **3** and **4** displayed prominent DA_2 dopaminergic effects on the peripheral sympathetic nerve terminal and displayed postjunctional dopamine receptor agonist properties on the striatum.[4] It was speculated that the angularly annulated system **3** (but not the linearly annulated system **4**) may owe its dopaminelike effects to metabolic activation phenomena. In contrast, the simple β-phenethylamine system **5** was inactive.[4] Thus, the effects of incorporating the *p*-dimethoxy moiety into a dopaminergic ring system have not been predictable. In the present study the aporphine ring system was addressed, on the basis that 10,11-dihydroxyaporphine (apomorphine, **6**) is a prototypical dopaminergic agonist.



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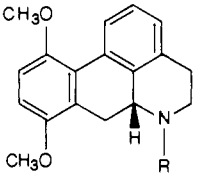

7: R = CH_3
8: R = *n*-C_3H_7

The choice of N-substituents in the target molecules **7** and **8** was based upon observations[5,6] that *N*-methyl and *N*-*n*-propyl substituents may confer qualitatively and quantitatively different effects upon a molecule.

Chemistry

The preparation of the target systems **7** and **8** is outlined in Scheme I. Etherification of the 11-hydroxy group of **10a,b** could not be accomplished with dimethyl sulfate and sodium hydride in tetrahydrofuran; only starting material was recovered. When sodium *tert*-amylate in toluene was used, etherification of the 11-hydroxy group was achieved. However, quaternization of the amino group could not be avoided as a side reaction, and the yield of the desired ethers **11a,b** was low and isolation of the product was tedious. When diazomethane was used, no quaternized product could be detected. As was described in a previous communication,[7] the hydrogenolytic removal of the (phenyltetrazolyl)oxy moiety from the aporphines **11a,b** was erratic and capricious in both catalytic hydrogenolysis reactions and in catalytic hydrogen-transfer reactions. Attempts to replace the phenyltetrazolyl moiety with other

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(2) De Marinis, R. M.; Shah, D. H.; Hall, R. F.; Hieble, J. P.; Pendleton, R. G. *J. Med. Chem.* **1982**, *25*, 136.
(3) Sindelar, R. D.; Mott, J.; Barfknecht, C. F.; Arneric, S. P.; Flynn, J. R.; Long, J. P.; Bhatnagar, R. K. *J. Med. Chem.* **1982**, *25*, 858.
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(7) Cannon, J. G.; Mohan, P.; Bojarski, J.; Long, J. P.; Bhatnagar, R. K.; Leonard, P. A.; Flynn, J. R.; Chatterjee, T. K. *J. Med. Chem.* **1988**, *31*, 313.

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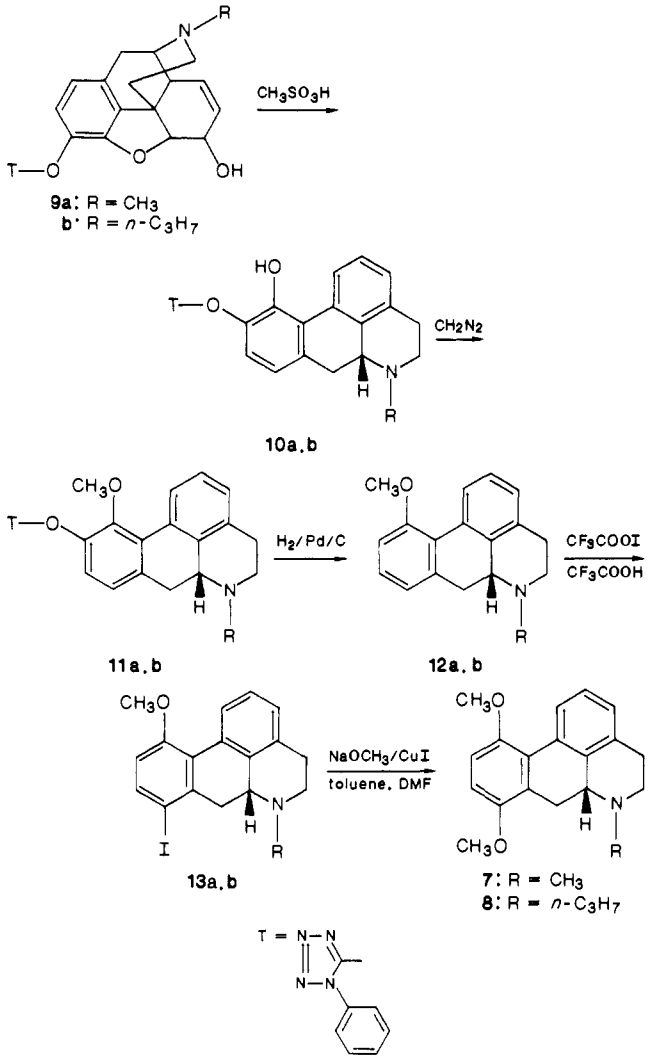
Scheme I. Preparation of 8,11-Dimethoxyaporphine Derivatives



heterocyclic rings in the reductive-deoxygenation strategy led to preparation of morphine 3-(2-pyrimidyl) ether and morphine 3-(2-benzoxazolyl) ether. Attempts to rearrange these derivatives to the aporphine ring with methanesulfonic acid led to isolation of unstable, intractable, blue-green solids. Consistent success in catalytic hydrogenolytic deoxygenation of the phenyltetrazolyl ethers **11a,b** depended upon obtaining the ethers in a high degree of chemical purity. Neumeyer and Ram[19] reported this conversion at room temperature with a reaction time of 11–19 days being required for completion. It was stated[19] that the ambient reaction temperature was necessary to avoid racemization at the chiral 6a-position of the aporphine ring. However, in the present work no racemization could be detected at 45–50 °C and the reaction time was reduced to 24 h. Iodination of 11-methoxyaporphine in yields of 90% or better was achieved by use of trifluoroacetyl hypoiodite by modifications of procedures of Barnett, Andrews, and Keefer[8] and Haszeldine and Sharpe.[9] The low yields and laborious, tedious workup resulting from application of a method of Bacon et al.,[10,11] for displacement of iodine in **13a** and **13b** with methoxyl, were obviated by replacement of the specified solvent (collidine) with *N,N*-dimethylformamide.

Table I. Cardiovascular and Behavorial Responses of Aporphines and Reference Compounds

		minimal effective dose, μg/kg		
compd	*n*	arterial pressure decrease (cat)	heart rate decrease (cat)	rate behavior
8-OH-DPAT	20	10	10	500[a]
apomorphine	>20	10	10	100[b]
7	4	>1000	>1000	5000[c]
8	4	>1000	>1000	inactive at 5000

[a] Induces 5-HT syndrome, including "piano playing" and flat body posture, which suggest involvement of 5-HT_{1A} subtype. [b] Stereotypic behavior (licking and sniffing, and high doses increase locomotion). These behaviorial responses are associated with D_1 and D_2 dopamine receptors. [c] Pretreatment (0.5 and 1 h) of 10 rats prevented most behavioral responses induced by 8-OH-DPAT. No alterations of behavior induced by apomorphine were observed.

Table II. Displacement of ^{3}H-Labeled Ligands from 5-HT_{1A} and D_2 Binding Sites by Compounds 7 and 8

compd	*n*	K_i, nM (95% CL): 5-HT_{1A} binding sites	*n*	K_i, nM (95% CL): D_2 binding sites
8-OH-DPAT[a]	5	2.1 (0.9–5.4)	2	3500
spiperone	3	30 (10–91)	5	0.045 (0.035–0.057)
7	3	8.6 (7.0–10.7)	3	210 (73–610)
8	2	240	3	770 (200–3400)

[a] Specific 5-HT_{1A}-receptor agonist.

For preparation of target compound 8, a variety of literature sequences for the synthesis of the 3-(1-phenyltetrazol-5-yl) ether of *N*-*n*-propylnormorphine (**9b**) was attempted. The most satisfactory procedure involved subjecting normorphine to a modification of the amine alkylation method of Gribble et al.[12] and subsequent conversion to the ether. Attempts to apply a method of Kim[13] for N-demethylation of apomorphine and certain phenolic ether derivatives of it to various aporphine derivatives were unsuccessful; only ring-cleavage products were isolated. Spectral (IR, NMR, MS) data for all intermediate products and for the target molecules were consistent with the proposed structures.

Pharmacology

Compounds 7 and 8 did not alter cardiac responses to neuronal stimulation to the cat heart with doses up to 1 mg/kg administered intravenously (Table I). Likewise, neither 7 nor 8 induced significant alteration in heart rate, in arterial pressure, or in cardiovascular responses due to acetylcholine or epinephrine. Thus there is no experimental evidence of 5-HT_{1A} or DA_2 receptor agonist properties.

As shown in Table I, subcutaneous pretreatment (0.5 h and 1 h) doses of 5 mg/kg of 7 significantly antagonized most behavioral components of the "serotonin syndrome" (flat body posture, forepaw extension and padding ["piano playing"], abducted hindlimbs, occasional tremor in the forebody)[14] induced by 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH-DPAT). Compound 7 was inert in a 2-h pretreatment experiment and was inactive for antagonism of apomorphine-induced behaviors. Compound 8 was inactive at all time intervals.

Results obtained with radioligand-binding assays for 5-HT_{1A} and D_2 sites are shown in Table II. Compound

(8) Barnett, J. R.; Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 6129.
(9) Haszeldine, R. N.; Sharpe, A. G. *J. Chem. Soc.* **1952**, 993.
(10) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc. C* **1969**, 312.
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8 was nearly inactive at both binding sites. Compound 7 exhibited potent activity in displacing radiolabeled 8-OH-DPAT from its binding site, but 7 appeared to be inactive at D_2 binding sites.

Further work will be required to fully define the biological properties of 7. The lack of cardiovascular responses (hypotension and bradycardia) suggest the absence of either 5-HT_{1A} or DA_2 receptor agonist activity. Since the compound is a potent agent to displace 8-OH-DPAT from its binding sites and since it also antagonizes 8-OH-DPAT-induced behavioral responses, it is concluded that 7 may be a 5-HT_{1A} receptor antagonist. Functional interactive studies involving 5-HT_{1A} receptors will be required for supporting evidence of this hypothesis.

Experimental Section

Pharmacology. Methods. Cat Cardioaccelerator Nerve Preparation. This assay was used to determine the activity of various agents at presynaptic dopamine receptors on the sympathetic nerve terminal. Cats were anesthetized with pentobarbital sodium (30 mg/kg, ip) and intubated. Respiration was maintained with a Harvard respirator. Systemic arterial pressure was monitored with a Statham P23A pressure transducer from a cannula positioned in the femoral artery. Mean heart rate was obtained from phasic arterial blood pressure pulses with a Beckman Type 9857 cardiotachometer. A femoral vein also was cannulated for drug administration. After bilateral vagotomy and systemic administration of atropine sulfate (200 μg/kg), the postganglionic right cardioaccelerator nerve trunk was exposed via a midsternal incision. The nerve trunk was placed on a bipolar electrode for stimulation. It was stimulated with a Grass 48 stimulator using the following parameters: 2 Hz, 5-ms pulse duration, 20 V. These parameters produced reproducible chronotropic responses that were sensitive to β-adrenoceptor antagonism. Blood pressure and heart rate were continuously recorded on a Beckman R511A recorder.

Behavioral Studies. The ability of the compounds (administered subcutaneously) to induce behavioral changes in rats were determined. The rats were observed for locomotor activity and induction of the "serotonin syndrome".[14] Rats were also pretreated with the subject compounds 7 and 8 15 min prior to subcutaneous administration of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), a 5-HT_{1A} agonist.

Binding Assays. Procedures used in radioligand-binding assays have been published in detail elsewhere for 5-HT_{1A} sites[7] and for D_2 sites.[15] Rat brain tissue was homogenized in ice-cold solution, centrifuged to isolate the membranes, and then washed. The solution of the radioligand and unlabeled competitor and the suspension of membranes were kept separate on ice until the moment of mixture. The mixture was vortexed and incubated for 30 min at 37 °C, and then it was vacuum filtered. The filters were washed with cold buffer, incubated for 24 h in scintillation cocktail, and counted. Data were analyzed with the LIGAND program of Munson and Rodbard[16] as modified by McPherson.[17] K_D values for the radioligands were determined by saturation curves to be 1.9 nM for [^{3}H]-8-OH-DPAT and 38 pM for [^{3}H]-spiperone.

Chemistry. Melting points were determined in open glass capillaries on Thomas-Hoover Uni-Melt or Melt-temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Where analyses were indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values. Analytical TLC was carried out on silica gel plates (Analtech, 20 × 20 cm, 2000 μm). Column chromatography was performed on silica gel (Baker, 5,3405, 60–200 mesh). Flash column chromatography was performed with a 150-Å pore size, 35–75-μm particle size silica (Analtech). Radial thin-layer chromatographic separations were carried out on a Chromatotron apparatus (Harrison Research) using Kieselgel 60 PF_{254} (EM Science) as the stationary phase. IR spectra were measured with KBr pellets with a Nicolet 5DXB FT-IR spectrometer. NMR spectra were recorded on a Varian Associates EM 360A spectrometer or a Brucker-IBM NR80 instrument using Me_4Si as the internal standard. Mass spectra were recorded with a Ribermag R10-10C mass spectrometer. Optical rotational data were obtained with a Perkin-Elmer Model 141 polarimeter.

(*R*)-10-*O*-(1-Phenyltetrazol-5-yl)apomorphine Hydrochloride (10a). A solution of 12.0 g (28.0 mmol) of 3-*O*-(1-phenyltetrazol-5-yl)morphine (**9a**)[18] in 15 mL of freshly distilled methanesulfonic acid was heated at 90–95 °C, for 1.5 h. The cooled reaction mixture was treated with excess saturated $NaHCO_3$ and was extracted with four 60-mL portions of $CHCl_3$. The pooled extracts were washed with two 50-mL portions of H_2O, dried (Na_2SO_4), and filtered, and the filtrate was taken to dryness under reduced pressure to yield 11.3 g of a green solid. This material was chromatographed on a flash column and was eluted with Me_2CO to afford (after removal of the solvent and drying under reduced pressure) 10.6 g (92%) of a yellowish crystalline solid. This material was treated with excess ethereal HCl to provide a white solid, mp 191–193 °C dec (lit.[19] mp 182–188 °C).

(*R*)-(−)-10-*O*-(1-Phenyltetrazol-5-yl)-11-methoxyaporphine (11a). A suspension of 1.0 g (2.4 mmol) of the free base of **10a** in a solution of 3 g (0.07 mol) of CH_2N_2 in 300 mL of Et_2O was stirred at room temperature for 24 h. Excess CH_2N_2 was destroyed with AcOH and the resulting mixture was filtered. The filtrate was evaporated under reduced pressure to leave a brown crystalline solid. This was chromatographed on a flash column and eluted with Me_2CO to yield a yellow crystalline solid, which was recrystallized from Me_2CO–H_2O (1:1) to afford 0.75 g (72%) of white needles: mp 153–155 °C; MS *m/e* 425 (M^+); $[\alpha]^{24.0}_{589}$ −112.2° (*c* 0.90, MeOH). Anal. ($C_{25}H_{23}N_5O_2$) C, H, N. Ram and Neumeyer[19] characterized this compound as its HCl salt.

(*R*)-(−)-11-Methoxyaporphine Hydrochloride (12a). Compound **11a** (1.0 g, 2.35 mmol) in 90 mL of AcOH was hydrogenolyzed in a Parr apparatus at 45 °C for 24 h over 1.1 g of 10% Pd/C at an initial pressure of 45 psig. The cooled reaction mixture was filtered through Celite and the filtrate was taken to near dryness under reduced pressure. The residue was diluted with 75 mL of H_2O and this mixture was basified with Na_2CO_3 and extracted with four 50-mL portions of $CHCl_3$. The pooled organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was taken to dryness under reduced pressure. The residue was subjected to chromatographic separation on a Chromatotron apparatus (hexane–EtOAc–Me_2CO 7:5:3) to afford, after removal of the solvents and drying under reduced pressure, 0.35 g (56%) of a white solid. This was converted into its salt with ethereal HCl: mp 240–243 °C (dec, (lit.[19] mp 235–242 °C); $[\alpha]^{25}_{589}$ −103° (*c* 0.50, MeOH); MS *m/e* 265 (M^+ − HCl). Anal. ($C_{18}H_{20}ClNO$) C, H, N.

(*R*)-8-Iodo-11-methoxyaporphine Hydrochloride (13a). To a solution of 1.35 g (5.1 mmol) of **12a** and 0.83 g (3.7 mmol) of silver trifluoroacetate (purified by treating its ethereal solution with activated charcoal, filtering through a thin layer of Celite, and evaporating the filtrate to dryness) in 50 mL of trifluoroacetic acid was added 0.75 g (3.0 mmol) of I_2 in 25 mL of CH_2Cl_2. The resulting solution was stirred for 1 h at room temperature and was filtered. The filtrate was washed with 10% $Na_2S_2O_3$ and was extracted with four 25-mL portions of CH_2Cl_2. The pooled extracts were washed with two 25-mL portions of H_2O, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The residue was subjected to chromatographic separation on a Chronatotron apparatus (hexane–Et_2O 8:1) to afford 1.10 g (94%) of the free base of **13a**. This material was treated with ethereal HCl to provide a white precipitate: mp 242–243 °C dec; MS *m/e* 391 (M^+ − HCl). Anal. ($C_{18}H_{19}ClINO$) C, H, N.

(*R*)-(−)-8,11-Dimethoxyaporphine Hydrochloride (7). A mixture of 0.09 g (0.23 mmol) of the free base of **13a**, 0.05 g (0.26

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(17) McPherson, G. A. *A Collection of Radioligand Binding Analysis Programs*; Elsevier Science Publishers: Amsterdam, 1985.
(18) Bognar, R.; Gal, Gy.; Kerekes, P.; Horvath, G.; Kovacs, M. T. *Org. Prep. Proced. Int.* **1974**, *6*, 305.
(19) Ram, V. J.; Meumeyer, J. L. *J. Org. Chem.* **1982**, *47*, 4372.

mmol) of CuI, and a solution of 0.11 g (4.8 mg-atom) of Na in 1 mL of MeOH in 5 mL of toluene–DMF (13:4) was heated under reflux with stirring overnight. The cooled reaction mixture was filtered through Celite. The filtrate was dissolved in 25 mL of $CHCl_3$, washed with five 15-mL portions of H_2O, dried (Na_2SO_4), and filtered. The filtrate was taken to dryness under reduced pressure. The residue was subjected to chromatographic separation on a Chromatotron apparatus (hexane–Et_2O 1:1) to afford 0.05 g (60%) of a solid. This was converted to its salt with ethereal HCl: mp 235–236 °C dec; $[\alpha]^{25}_{589}$ –98.2° (c 0.30, MeOH); MS m/e 295 (M^+ – HCl). Anal. ($C_{19}H_{22}ClNO_2$) C, H, N.

***N*-*n*-Propylnormorphine (14).** To a stirred solution of 2.0 g (7.3 mmol) of normorphine[20] in 17 mL (228 mmol) of propionic acid and 20 mL of benzene at 50–55 °C under N_2 was added over 30 min 1.2 g (31.7 mmol) of $NaBH_4$ pellets. The resulting mixture was stirred at 55 °C for 10 h, and then it was allowed to come to room temperature and 150 mL of H_2O was added. The resulting mixture was taken to pH 9 with $NaHCO_3$ and was extracted with five 25-mL portions of $CHCl_3$. The pooled extracts were dried (Na_2SO_4) and filtered, and the filtrate was taken to dryness under reduced pressure to yield a tan solid, which, after washing with Me_2CO, afforded 1.70 g (74%) of a finely divided white solid: mp 219–221 °C dec (lit.[21] mp 225–229 °C); MS m/e 313 (M^+).

3-*O*-(1-Phenyltetrazol-5-yl)-*N*-*n*-propylnormorphine (9b). A suspension of 0.10 g (0.32 mmol) of **14** in 50 mL of Me_2CO was heated under reflux for 24 h with 0.60 (0.32 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole and 2.1 g (15.3 mmol) of K_2CO_3. The reaction mixture was cooled and filtered, and the filtrate was evaporated to give a white solid, which was recrystallized from Me_2CO–H_2O (1:1) to yield 0.12 g (82%) of product: mp 122–124 °C; MS m/e 457 (M^+); $[\alpha]^{22}_{589}$ –0.20° (c 20, MeOH).

(*R*)-(+)-10-*O*-(1-Phenyltetrazol-5-yl)-*N*-*n*-propylnorapomorphine Hydrochloride (10b). A solution of 3.0 g (6.56 mmol) of **9b** in freshly distilled methanesulfonic acid was heated at 90–95 °C for 1.5 h. The cooled reaction mixture was treated with excess saturated $NaHCO_3$ solution and was then extracted with four 50-mL portions of $CHCl_3$. The pooled extracts were washed with two 50-mL portions of H_2O, dried (Na_2SO_4), and filtered, and the filtrate was taken to dryness under reduced pressure. The residual green solid was chromatographed on a flash column and was eluted with Me_2CO to afford, after removal of the solvent and drying under reduced pressure, 2.80 g (97%) of a yellowish crystalline solid. This was treated with ethereal HCl to form a white solid: mp 190–193 °C (dec (lit.[19] mp 175–178 °C); $[\alpha]^{25}_{589}$ +40.2° (c 0.20, MeOH) [lit.[19] $[\alpha]^{23}_{589}$ +30.8° (c 0.175, MeOH)]; MS m/e 349 (M^+ – HCl).

(*R*)-(–)-10-*O*-(-1-Phenyltetrazol-5-yl)-11-methoxy-*N*-*n*-propylnorapomorphine (11b). To a solution of 6.0 g (0.14 mol) of CH_2N_2 in 600 mL of Et_2O was added 9.0 g (20.5 mmol) of **10b** and the resulting suspension was stirred at room temperature for 24 h. Excess CH_2N_2 was destroyed with AcOH, and the resulting mixture was filtered. The filtrate was evaporated under reduced pressure to yield a brown crystalline solid, which was chromatographed on silica and eluted with $CHCl_3$ to provide a yellow solid, which, after crystallization from Me_2CO–H_2O (1:1), afforded 7.32 g (79%) of a yellow solid. This material was treated with ethereal HCl to form a white solid: mp 164–165 °C (lit.[19] mp 152–155 °C); $[\alpha]^{25}_{589}$ –65.0° (c 0.23, MeOH) [lit.[19] $[\alpha]^{23}_{589}$ –68.1° (c 0.163, MeOH)]; MS m/e 453 (M^+ – HCl).

(*R*)-(–)-11-Methoxy-*N*-*n*-propylnoraporphine (12b). Compound **11b** (1.0 g, 2.20 mmol) in 90 mL of AcOH was hydrogenolyzed over 1.1 g of 10% Pd/C in a Parr apparatus for 24 h at 45 °C at an initial pressure of 45 psig. The cooled reaction mixture was filtered through Celite and the filtrate was taken to near dryness under reduced pressure. The residue was diluted with 75 mL of H_2O and this mixture was basified with $NaHCO_3$ and extracted with four 50-mL portions of $CHCl_3$. The pooled organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was taken to dryness under reduced pressure. The residue was chromatographed on silica and eluted with $CHCl_3$ to afford 0.42 g (66%) of a solid. This was treated with ethereal HCl to provide a white solid: mp 228–229 °C dec (lit.[19] mp 227–229 °C); $[\alpha]^{20}_{589}$ –56.2° (c 0.06, MeOH) [lit.[19] $[\alpha]^{26}_{589}$ –69.9° (c 0.0515, MeOH)].

(*R*)-(–)-8-Iodo-11-methoxy-*N*-*n*-propylnorapomorphine Hydrochloride (13b). To a solution of 0.50 g (1.70 mmol) of **12b** and 0.26 g (1.01 mmol) of silver trifluoroacetate (purified as described for **13a**) in 25 mL of trifluoroacetic acid was added 0.28 g (1.25 mg-atom) of I_2 in 25 mL of $CHCl_3$. The resulting mixture was stirred for 1 h at room temperature and then was filtered. The filtrate was washed with 10% $Na_2S_2O_3$ solution and was then extracted with four 25-mL portions of CH_2Cl_2. The pooled extracts were washed with two 25-mL portions of H_2O, dried (Na_2SO_4), and taken to dryness under reduced pressure. The residue was subjected to chromatographic separation on a Chromatotron apparatus and was eluted with hexane–Et_2O (8:1) to afford an off-white solid. This material was treated with ethereal HCl to provide 0.34 g (49%) of a white solid: mp 250–252 °C dec; MS m/e 419 (M^+ – HCl); $[\alpha]^{25}_{589}$ –103.0° (c 0.29, $CHCl_3$).

(*R*)-(–)-8,11-Dimethoxy-*N*-*n*-propylnoraporphine Hydrochloride (8). A mixture of 0.03 g (0.07 mmol) of the free base of **13b**, 0.12 g (0.62 mmol) of CuI, and a solution of 0.05 g (2.2 mg-atom) of Na in 20 mL of MeOH in 25 mL of DMF was stirred and heated under reflux overnight. The cooled reaction mixture was filtered through Celite. The filtrate was diluted with 100 mL of H_2O and was extracted with three 25-mL portions of $CHCl_3$. The pooled extracts were dried (Na_2SO_4) and filtered, and the filtrate was taken to dryness under reduced pressure. The residue was chromatographed on silica and eluted with hexane–Et_2O (1:1) to afford a solid, which was treated with ethereal HCl to provide 0.02 g (93%) of a white solid: mp 195–196 °C dec; MS m/e 323 (M^+ – HCl); $[\alpha]^{25}_{589}$ –129.0° (c 0.29, MeOH). Anal. ($C_{21}H_{26}ClNO_2$) C, H, N.

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