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Aporphines. 14.[1] Dopaminergic and Antinociceptive Activity of Aporphine Derivatives. Synthesis of 10-Hydroxyaporphines and 10-Hydroxy-*N*-*n*-propylnoraporphine[†,2]

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The synthesis of racemic 10-hydroxyaporphine [(±)-**2a**] and 10-hydroxy-*N*-*n*-propylnoraporphine [(±)-**2b**] is described. The method involved a Reissert alkylation–Pschorr cyclization route. The dopaminergic activity of (±)-**2b** was evaluated in comparison with L-Dopa, (−)-apomorphine (**1a**), (±)-*N*-*n*-propylnorapomorphine (NPA) (**1b**), and (±)-11-hydroxy-*N*-*n*-propylnoraporphine [(±)-11-OH-PNA] by the behavioral model of rotational behavior in animals after unilateral lesion of the ascending DA pathways. The dopaminergic activity of NPA and 11-OH-PNA is essentially equivalent to L-Dopa and (−)-apomorphine, and both are more active than (±)-**2b**. Furthermore, (±)-NPA (threshold dose, 5 μg/kg) appears to be even more potent than (−)-apomorphine (threshold dose, 25 μg/kg). The duration of action of NPA and 11-OH-PNA is considerably longer than that obtained with L-Dopa. The antinociceptive activity of (±)-**2b** was evaluated by the tail-flick procedure and compared with **1a**, **2b**, morphine, and L-Dopa. Weak but significant antinociceptive activity was shown by (±)-**2b** and by (±)-**1b** but not by (−)-apomorphine. This effect was not antagonized by naloxone. The finding that (±)-**2b** and particularly (±)-11-OH-PNA are active in doses from 500 to 50 μg/kg, respectively, in causing rotational behavior further supports previous studies indicating that *N*-*n*-propyl derivatives of monohydroxylated aporphines were more active than the corresponding parent *N*-methyl derivatives as DA receptor agonists and that a catechol system is not an absolute requirement for dopaminergic activity in such aporphines.

In continuing our studies involving the design of dopamine agonists related to apomorphine (**1a**), structures which can be considered as conformationally rigid forms of dopamine, we wished to synthesize and evaluate the monohydroxyaporphines, 10-hydroxyaporphine **2a**, and its *N*-propyl homolog (10-OH-PNA) **2b**.

In our previous studies involving functionally substituted aporphines we indicated that dopaminergic activity can reside in monohydroxyaporphines substituted in the 11 position and that the *N*-*n*-propyl derivatives of the hydroxylated aporphines were more active than the corresponding parent compounds. The evidence that such monohydroxyaporphines were direct-acting dopamine agonists was supported by the behavioral model of rotational behavior in animals after unilateral lesion of the nigrostriatal pathway[3a] and the ability of such compounds to produce stereotyped behavioral syndrome in the rat similar to apomorphine.[3b] These studies[1,3b] confirmed that (−)-*N*-*n*-propylnorapomorphine [(−)-NPA] (**1b**) first described by Koch et al.[4] was considerably more potent than (−)-apomorphine [(−)-APO] (**1a**) and that differences in stereotypic activity of APO and NPA may be related to

† This manuscript is dedicated to Professor E. E. Smissman, who as a teacher, friend, and advisor provided a constant source of inspiration to his students and to medicinal chemistry.

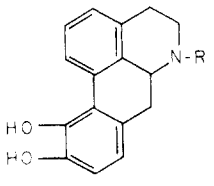
Table I. Effect of Dopa and DA Receptor Agonists on Turning Behavior in Rats[a]

Compound	Dose, mg/kg	No. of rats	Mean total time (min), means ± SEM	Mean peak act., means ± SEM	Overall mean act., means ± SEM	Total act., means ± SEM
L-Dopa	5	4	35 ± 7.5	2.9 ± 2.7	1.3 ± 0.5	52 ± 35
L-Dopa	15	8	90 ± 8	13.3 ± 0.2	5.0 ± 0.5	464 ± 85
L-Dopa	25	4	127 ± 13	8.8 ± 3.6	3.7 ± 0.5	470 ± 206
(−)-Apomorphine	0.01	8	33 ± 5	2.6 ± 1.5	1.0 ± 0.6	28 ± 14
(−)-Apomorphine	0.025	4	55 ± 5	7.4 ± 5.7	1.8 ± 0.8	102 ± 50
(−)-Apomorphine	0.05	16	63 ± 4	14.1 ± 0.9	5.4 ± 0.5	351 ± 50
(−)-Apomorphine	0.5	4	144 ± 13	10.8 ± 1.4	5.2 ± 0.8	753 ± 417
(−)-Apomorphine	1	4	153 ± 20	11.4 ± 0.6	3.7 ± 0.6	567 ± 380
(−)-Apomorphine	2	3	238 ± 15	18.4 ± 1.6	7.4 ± 1.0	1764 ± 978
(±)-10-Hydroxy-*N*-propylnoraporphine	0.25	8	0	0	0	19 ± 2
(±)-10-Hydroxy-*N*-propylnoraporphine	0.5	4	105 ± 3	4.8 ± 0.5	1.3 ± 0.3	158 ± 81
(±)-10-Hydroxy-*N*-propylnoraporphine	1	8	177 ± 16	9.8 ± 3.2	2.6 ± 0.4	515 ± 132
(±)-10-Hydroxy-*N*-propylnoraporphine	2.5	4	174 ± 25	7.8 ± 3.2	2.7 ± 0.3	477 ± 243
(±)-11-Hydroxy-*N*-propylnoraporphine	0.01	4	0	0	0	22 ± 5
(±)-11-Hydroxy-*N*-propylnoraporphine	0.05	4	195 ± 23	13.7 ± 1.6	3.7 ± 0.6	764 ± 61
(±)-11-Hydroxy-*N*-propylnoraporphine	0.1	4	200 ± 0	11.1 ± 4.2	5.4 ± 0.4	1119 ± 329
(±)-11-Hydroxy-*N*-propylnoraporphine	0.25	4	580 ± 23	14.3 ± 0.5	3.4 ± 0.3	2038 ± 402
(±)-11-Hydroxy-*N*-propylnoraporphine	1	4	725 ± 5	15 ± 1.5	6.1 ± 0.3	4764 ± 204
(±)-*N*-Propylnorapomorphine	0.005	4	205 ± 65	2.6 ± 2.3	0.8 ± 0.13	179 ± 122
(±)-*N*-Propylnorapomorphine	0.01	4	200 ± 48	12.1 ± 1.1	3.5 ± 0.6	726 ± 219
(±)-*N*-Propylnorapomorphine	0.025	4	185 ± 10	10.9 ± 1.4	4.6 ± 0.5	972 ± 172
(±)-*N*-Propylnorapomorphine	0.05	4	305 ± 23	11.0 ± 4.7	4.6 ± 0.3	1455 ± 425
(±)-*N*-Propylnorapomorphine	0.1	4	360 ± 15	12.7 ± 0.9	4.3 ± 0.4	1620 ± 215
(−)-Apocodeine	1	8	40 ± 3	7.0 ± 1.8	2.8 ± 0.35	126 ± 78
(−)-Apocodeine	5	4	200 ± 17	13.0 ± 2.0	5.7 ± 0.61	1144 ± 555

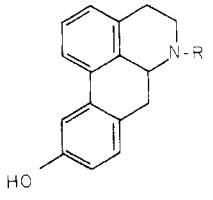
[a] Male specific pathogen-free Sprague–Dawley rats (350–450 g body weight) have been used. 6-OH-DA (8 μg/4 μl) was injected stereotaxically into the left substantia nigra 2 months before the experiment as described by Ungerstedt (1968). Most of the testing was made in the same group of four rats. As seen in the table, an additional group of four rats was used in some experiments. The testing of the various compounds took place over a period of several months with the injections being 3 days apart or more. All drugs were injected ip.

a difference in their site of action. Both these studies[1,3b] indicated that the levo isomer of such apomorphine derivatives is the more active enantiomer as a dopaminergic agonist and supported previous findings from this[5] and other laboratories[6] that the optical antipode of **1a** [viz. (+)-APO] is not an effective dopamine agonist.

In the present study we wish to report the total synthesis of the 10-hydroxyaporphines **2a,b**, their evaluation as central dopaminergic agents, and their antinociceptive properties in comparison with (−)-APO (**1a**) and (±)-NPA (**1b**) and other known dopamine agonists such as L-Dopa.



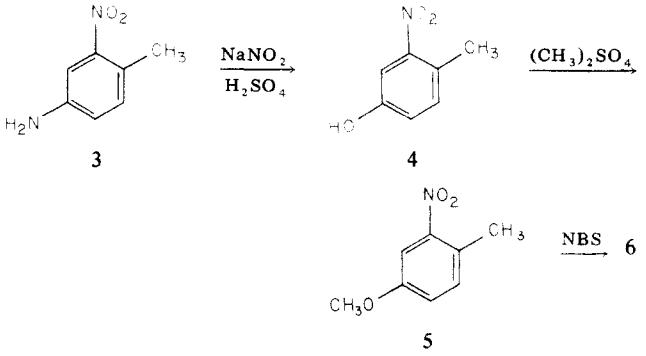
1a, R = CH_3 (APO)
b, R = C_3H_7 (NPA)



2a, R = CH_3
b, R = C_3H_7
(10-OH-PNA)

Chemistry. The synthesis of **2a,b** involved the alkylation of the isoquinaldonitrite **7** with an appropriately substituted nitrobenzyl halide (**6**) by the so-called Reissert alkylation procedure[7] used to advantage for the synthesis of related aporphines (See ref 5 and references cited therein). It was thus necessary to prepare the previously unreported α-bromo-2-nitro-4-methoxytoluene (**6**) from 2-nitro-4-aminotoluene (**3**) (Scheme I). Alkylation of the Reissert compound (**7**) with **6** followed by alkaline (KOH) hydrolysis gave a 97% yield of the isoquinoline **9**. Quaternization with an appropriate alkyl halide and careful KBH_4 reduction (room temperature, 2.5 hr) gave the tetrahydroisoquinolines **11**. Should a large excess of KBH_4 be used, or the mixture allowed to reflux, the expected C–C cleavage occurs.[8] Reduction of the nitro group to the amine, followed by Pschorr type cyclization, results in the isolation of the 10-methoxyaporphines **13**. Demethylation with HI–Ac_2O gave the aporphines **2a,b** which were isolated and characterized as the hydroiodide or the hydrobromide salts (Scheme II).

Scheme I. Synthesis of α-Bromo-4-methoxy-2-nitrotoluene



Pharmacological Data. Compounds **2a,b** were examined as dopamine (DA) agonists by evaluating the rotational behavior of 6-hydroxydopamine (6-OHDA) lesioned rats by the procedure previously described.[3a,9] We have reported[3a] that 11-hydroxyaporphine showed activity in a dose of 10 mg/kg, but 10-hydroxyaporphine **2a** lacked effect in this dose, and that **2a** became active when an *n*-propyl group replaced the methyl group on the nitrogen. In the present study we have shown that (±)-NPA (**1b**) is five to seven times more potent than apomorphine and that (±)-11-OH-PNA is about ten times more potent than (±)-10-OH-PNA (**2b**) when evaluated as a direct-acting DA agonist in this test system. The results of these experiments are summarized in Table I, in comparison with other direct-acting DA agonists.

The experimental procedures for evaluating the analgesic effects of biogenic amines are based principally on altering the threshold response latency to various forms of a nociceptive stimuli. We chose the tail-flick method

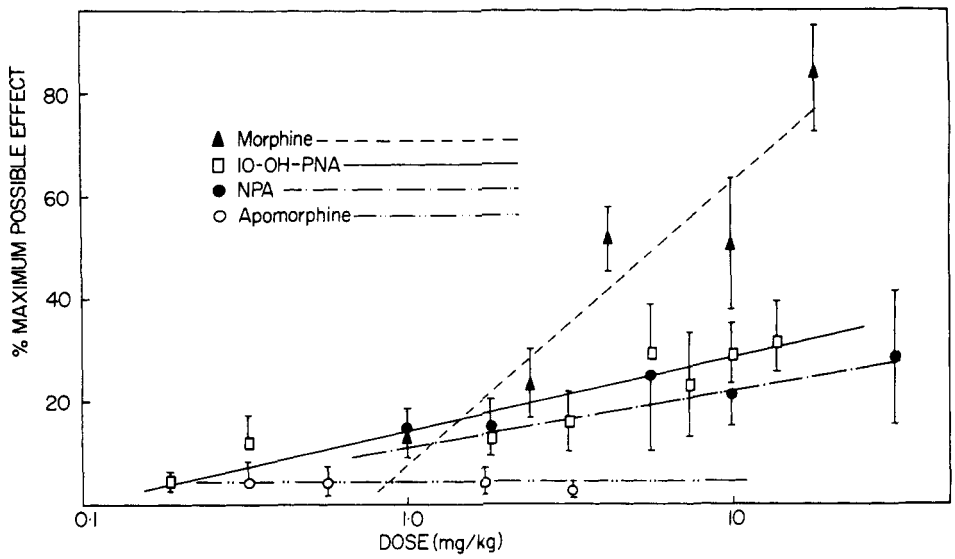
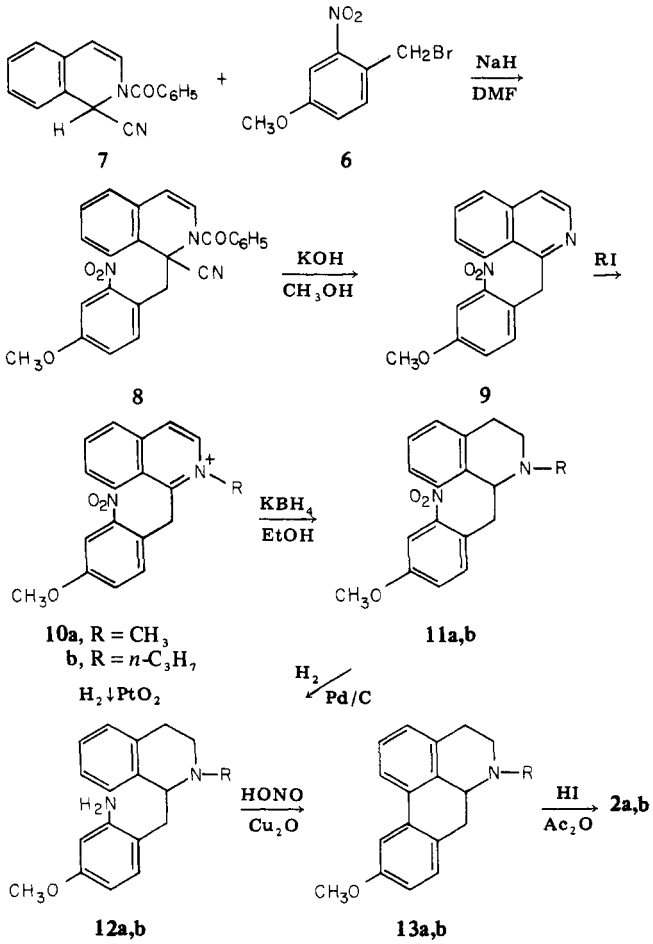


Figure 1. Comparative antinociceptive activity of morphine and aporphine derivatives in the mouse. Each point represents the percent maximum possible effect ± the standard error of the mean for groups of ten animals. Determinations of activity were made at the time of peak effect following drug administration (morphine, apomorphine, 10-OH-PNA = 60 min; NPA = 10 min).

Scheme II. Synthesis of (±)-10-Hydroxyaporphines



for the direct comparison of the antinociceptive activity of morphine and the aporphine derivatives in the mouse.

The antinociceptive properties of the aporphine derivatives were determined using a modification of the tail-flick procedure of D'Amour and Smith.[10,11] All compounds were suspended in 0.5% methylcellulose and administered intraperitoneally. Male albino mice (Charles River, CD-1) weighing 18–24 g, were divided into groups of ten animals.

A rheostat, incorporated into the apparatus, was adjusted so that the intensity of light focused on the ventral surface of each animal's tail produced a normal tail-flick reaction time of 2–4 sec. Animals with a control reaction time outside this range were eliminated from the study. Two control reaction times, 30 min apart, were determined for each group of animals prior to drug treatment. The mean value of these determinations constituted the control reaction time. Following drug treatment, subsequent reaction times were determined at 30-min intervals over a 2-hr period. A 10-sec cutoff time was employed.

Antinociceptive activity was calculated as the percentage of the maximum possible increase in response time using the following formula, percent maximum possible effect = $[(T_r - T_c/10 - T_c)] \times 100$, where T_r is the mean test reaction time and T_c is the mean control reaction time.[11]

The comparative antinociceptive efficacy of 10-OH-PNA, NPA, apomorphine, and morphine in increasing the threshold response latency to a heat stimulus at the time of peak drug effect is shown in Figure 1. Both 10-OH-PNA and NPA produced similar but weak antinociceptive activity in comparison to morphine. In contrast, apomorphine was essentially devoid of antinociceptive activity at all dose levels tested. L-Dopa (1–10 mg/kg ip) also failed to produce analgesic effects in mice. The marked difference between the slopes of the dose–response curves for 10-OH-PNA and NPA and the slope of the morphine dose–response curve would suggest that the antinociceptive mechanism for these aporphine derivatives is different from morphine. This suggestion is further strengthened by the observation in other experiments that pretreatment with naloxone hydrochloride (10 mg/kg ip), a potent opioid antagonist, completely reversed the antinociceptive activity of morphine but had essentially no effect on the antinociceptive activity produced by the aporphine derivatives.

Discussion and Conclusions

The evidence that such monohydroxyaporphines as 10-OH-PNA and 11-OH-PNA are dopamine agonists is supported by the behavioral model of rotational behavior toward the innervated side in animals with unilateral lesions of the ascending DA neurons as reported in this and previous studies[3a] and the ability of such compounds to produce stereotyped behavioral syndromes in the rat.[3b] However, 10-OH-PNA was ineffective in stimulating the striatal adenylated cyclase from rat brain[12] under con-

ditions which both dopamine and apomorphine are known to be effective. The data suggest that the monohydroxylated *N*-*n*-propylaporphines may be metabolically converted to the catechols in vivo by aromatic hydroxylase. If so, these catechols must be formed rapidly at least within the first minute after injection. Studies currently in progress have failed to reveal any catechol metabolites after the in vivo or in vitro incubation of 10-OH-PNA in rats or rat liver slices.[13] In other studies[21] 10-OH-PNA reduced the depletion of DA but not NE in the striatum produced by AMT, suggesting that like NPA, 10-OH-PNA decreases DA turnover. The weak but definite antinociceptive activity of these aporphines, which was not antagonized by naloxone, might suggest a relationship between dopaminergic and analgesic activity. However, the available information is still insufficient and may be circumstantial. Thus, apomorphine was inactive and 10-OH-PNA, which appears to be 100 times less active as a DA receptor agonist when compared with NPA, showed an antinociceptive activity similar to that obtained with NPA. In order to permit a more precise assignment of the structural requirements of the dopamine receptor and the relationship of dopamine agonists to analgesic activity, additional studies will be required.

Experimental Section

Melting points were determined on a Thomas-Hoover (Unimelt) apparatus and are uncorrected. The microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. Where analyses are indicated by symbols of elements, the analytical results are within ±0.4% of the theoretical values. Infrared spectra were recorded on a Perkin-Elmer 700 spectrophotometer. Mass spectra were recorded on a Nuclide mass spectrometer 12-90-G. NMR spectra were recorded on a Varian T-60 spectrometer, with Me_4Si as the internal standard.

4-Hydroxy-2-nitrotoluene (4). 4-Amino-2-nitrotoluene (**3**, 120 g, 0.79 mol) was converted to **4** according to an "Organic Syntheses"[14] procedure. The crude product (92.7 g) was used directly for the preparation of the methyl ether of **4**. A small sample recrystallized twice from benzene had mp 76–77° (lit.[15] mp 78°).

4-Methoxy-2-nitrotoluene (5). Methylation of **4** (80 g, 0.52 mol) yielded after distillation [bp 120–122° (6 mm)] 65.9 g (75.6%) of **5** [lit.[15] bp 266–267° (760 mm)]. The compound crystallized upon standing at room temperature (lit.[16] mp 17°).

α-Bromo-4-methoxy-2-nitrotoluene (6). A mixture of 10.9 g (65 mmol) of freshly distilled 4-methoxy-2-nitrotoluene (**5**), 11.6 g (65 mmol) of recrystallized *N*-bromosuccinimide, and 100 mg of benzoyl peroxide was refluxed for 2 hr in 75 ml of dry CCl_4 under illumination. The mixture was filtered, and the mother liquid was concentrated under reduced pressure yielding 16 g (99%) of a lightly yellow crystalline solid, which was recrystallized from benzene–ether, mp 63–64°. Anal. ($C_8H_8BrNO_3$) C, H, N.

2-Benzoyl-1,2-dihydroisoquinaldonitrile (7). This compound was prepared by a modified procedure of Weinstock and Boekelheide:[17] mp 125–126° (67%) (lit.[17] mp 125–126°).

2-Benzoyl-1-(2-nitro-4-methoxylbenzyl)-1,2-dihydroquinaldonitrile (8). A solution of 2.62 g (10 mmol) of **7** in 40 ml of dry dimethylformamide was cooled to −15° and equimolar amounts of **6** and sodium hydride (50% mineral oil suspension) were added. The mixture was stirred for 2 hr and at room temperature for an additional 2.5 hr. Addition of 250 ml of crushed ice and stirring produced a yellow precipitate, which was immediately filtered and washed alkali-free with water. After trituration with ethanol the compound was dried to yield 4.0 g (93%) of crude **8**, mp 133–137°. A small portion of this precipitate was recrystallized from 80% ethanol to give pure **8**: mp 133–135°. Anal. ($C_{25}H_{19}N_3O_4$) C, H, N.

1-(4-Methoxy-2-nitrobenzyl)isoquinoline (9). A mixture of 5.0 g (11.75 mmol) of crude **8** in 100 ml of dry methanol and 4.0 g (71.5 mmol) of finely powdered potassium hydroxide was allowed to reflux for 5 min with vigorous stirring. Addition of 300 ml of crushed ice produced a beige precipitate which was filtered, washed with water, and dried to give 3.35 g (97%) of **9**, mp 155–159°. Recrystallization from acetonitrile gave mp 164–165°. The hydroiodide salt of **9** was prepared and recrystallized from methanol: mp 214–215° dec. Anal. ($C_{17}H_{15}IN_2O_3$) C, H, N.

1-(4-Methoxy-2-nitrobenzyl)isoquinoline Methiodide (10a). A solution of 12.75 g (43.4 mmol) of **9** in 100 ml of methyl iodide was refluxed for 24 hr. The mixture was cooled in ice, and the resulting yellow crystals were collected and washed with ether to give after drying 16.9 g (89%) of the methiodide, mp 151–154° dec. An analytical sample was obtained from methanol–ether: mp 171–173° dec. Anal. ($C_{18}H_{17}IN_2O_3$) C, H, N.

Similarly prepared from **9** and 1-iodopropane was **1-(4-methoxy-2-nitrobenzyl)isoquinoline propiodide (10b).** Thus, a mixture of 9.65 g (32.7 mmol) of **9** in 100 g of 1-iodopropane yielded 11.75 g (77%) of **10b**, mp 178–185°. Recrystallization from methanol gave yellow needles, mp 208–211° dec. Anal. ($C_{20}H_{21}IN_2O_3$) C, H, N.

1-(4-Methoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (11a). To a suspension of 436 mg (1 mmol) of **10a** in 5 ml of ethanol was added under vigorous stirring 26 mg (0.5 mmol) of potassium borohydride. On 0.5-hr intervals 13 mg (0.25 mmol) of potassium borohydride was added and after three additions 0.25 ml of water was introduced. After 0.5 hr the mixture was filtered, 10 ml of H_2O was added to the filtrate, and an extraction with 2 × 20 ml of chloroform followed. The organic layer was washed with H_2O and dried, and the solvent was removed under reduced pressure. A brown syrup was obtained, which was taken up in 1 ml of methanol and cooled in ice. The yellow crystals were filtered, washed with a few drops of methanol, and dried to give 200 mg (64%) of **11a** in analytically pure form: mp 79–80°. Anal. ($C_{18}H_{20}N_2O_3$) C, H, N.

1-(4-Methoxy-2-nitrobenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (11b). Reduction of the propiodide **10b** (11.75 g, 25.4 mmol) with potassium borohydride was carried out as described for the methiodide to yield 5.1 g (59%) of **11b**, mp 78–79°. A small sample was recrystallized from EtOH for analytical purposes; the melting point was unchanged. Anal. ($C_{20}H_{24}N_2O_3$) C, H, N.

1-(2-Amino-4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (12a). A. By Reduction of 1-(4-Methoxy-2-nitrobenzyl)isoquinoline Methiodide (10a). A mixture of 700 mg (1.6 mmol) of the quaternary iodide salt **10a**, 50 ml of methanol, and 100 mg of PtO_2 was prepared and hydrogenated at room temperature and 55 psi. Absorption of hydrogen was complete after 36 hr. The catalyst was filtered and the filtrate evaporated to dryness under reduced pressure. The residue dissolved in 50 ml of chloroform was washed with 2 × 20 ml of 2 *N* NaOH and 2 × 20 ml of H_2O and dried. Evaporation of the solvent yielded 450 mg (99%) of a brown oil, which was used directly for the subsequent Pschorr cyclization.

A dihydrochloride of **10a** was prepared in CH_3OH: mp 246–247° (lit.[18] mp 228–230°).

B. By Reduction of 1-(4-Methoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (11a). A solution of 5.35 g (17.2 mmol) of the nitro compound **11a** in 200 ml of absolute EtOH was hydrogenated with 1.0 g of 10% Pd/C at 55 psi for 48 hr. The mixture was filtered and the solvent removed under reduced pressure to yield 4.8 g (99%) of an oil. Without further purification the amino derivative **12a** was used for the Pschorr cyclization.

1-(2-Amino-4-methoxybenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (12b). Method A. The quaternary iodide salt **10b** was reduced over PtO_2 in the same way as the methiodide **10a**. Thus, 3.1 g (6.7 mmol) of the propiodide **10b** in 100 ml of methanol and 0.5 g of PtO_2 yielded 1.9 g (91%) of **12b** as an oil.

Method B. The catalytic reduction of 4.5 g (13.2 mmol) of **11b** in 300 ml of ethanol was carried out as described for **11a** and yielded 4.1 g (100%) of the amine **12b** as a clear oil.

(±)-10-Methoxyaporphine Hydroiodide (13a). To a solution of 4.8 g (17 mmol) of the amine **12a** in 38 ml of 10% H_2SO_4 was added dropwise under stirring 18.8 ml of 2 *N* sodium nitrite at −5 to 0°. The mixture was stirred for an additional 20 min and the excess nitrous acid was decomposed with a small quantity of sulfamic acid. The brown solution was added dropwise to a vigorously stirred suspension of 15.9 g of Cu_2O in 298 ml of 10% H_2SO_4 at −5°. After 40 min the mixture was filtered (Celite), the

green filtrate was made basic with concentrated ammonium hydroxide, and the blue solution was extracted with 3 × 100 ml of chloroform. The brown extract was washed with H_2O, dried, and evaporated. The residue was dissolved in ether, the insoluble material was filtered, and the filtrate was concentrated under reduced pressure to yield a brown syrup. The residue was dissolved in 20 ml of acetone, made acidic with several drops of 57% hydriodic acid, and cooled in ice to give a total of 1.23 g (19.3%) of **13a**, mp 228–230° dec. (The hydrochloride salt of **13a** (mp 256°) was reported by Weisbach et al.[18]) Anal. ($C_{18}H_{20}INO$) C, H, N.

(±)-10-Methoxy-*N*-*n*-propylnoraporphine Hydroiodide (13b). Cyclization of 4.1 g (13.2 mmol) of the amine **11b** was carried out as described for **11a** and yielded 1.95 g (35%) of **13b**: mp 240–243° dec; ν_{max} (KBr) 3370, 2870, 2650, 2570, 1600, 1570, 1470, 1290, 1230, 1040 cm^{-1}; NMR (Me_2SO-d_6) δ 1.05 (t, 3), 1.8 (q, 2), 2.8–3.8 (m, 8), 3.85 (s, 3), 4.5 (br, 1), 6.95 (dd, 1), 7.1–7.65 (m, 4), 7.85 (dd, 1). Anal. ($C_{20}H_{24}INO$) C, H, N.

(±)-10-Hydroxyaporphine Hydroiodide (2a). A suspension of 400 mg (1.05 mmol) of **13a** in 2 ml of 57% hydriodic acid was carefully treated with 2 ml of acetic anhydride. The mixture was heated at 135° for 1.5 hr, and the off-white crystals were filtered, washed with acetone, and dried to give 230 mg (59%) of **2a**, mp 256–258° dec. (After completion of this investigation the synthesis of (6a*R*)-10-hydroxyaporphine hydrochloride (mp 252° dec) from (−)-apomorphine was reported.[19])

(±)-10-Hydroxy-*N*-*n*-propylnoraporphine Hydroiodide (2b). Under identical conditions as above, 400 mg (0.95 mmol) of **13b** was O-demethylated to give a total of 265 mg (69%) of **2b**: mp 260–262° dec; ν_{max} (KBr) 3260, 2900, 2730, 1620, 1580, 1510, 1470, 1320, 1220, 980, 840 cm^{-1}; NMR (Me_2SO-d_6) δ 1.0 (t, 3), 1.7 (q, 2), 2.7–4.1 (m, 8), 4.5 (br, 1), 6.75 (dd, 1), 7.05–7.5 (m, 4), 7.65 (dd, 1), 9.35 (br, 1). Anal. ($C_{19}H_{22}INO$) C, H, N.

The hydrobromide salt of **13b** was also prepared (mp 259° dec) and demethylation with 48% hydrobromic acid was carried out as described by Cannon et al.[20] Thus, 600 mg (1.6 mmol) of **13b**·HBr gave 500 mg (87%) of **2b**·HBr: mp 281–282° dec; ν_{max} (KBr) 3200, 2900, 2700, 1610, 1580, 1500, 1460, 1310, 1210, 980, 840 cm^{-1}; mass spectrum (70 eV) *m/e* 279 (M^+, 62, free base), 278 (72), 250 (92), 248 (56), 233 (33), 221 (100), 208 (56). Anal. ($C_{19}H_{22}BrNO$) C, H, N.

The free base was liberated from **2b**·HBr in an aqueous suspension with $NaHCO_3$, followed by extraction with ether.[5] The off-white crystalline residue (mp 170–171°) was immediately converted to the corresponding trimethylsilyl derivative by treatment with trimethylsilylimidazole in acetonitrile at 90° for 2 hr. The mass spectrum (70 eV) of the Me_4Si derivative exhibited *m/e* 351 (M^+, 58), 350 (75), 349 (75), 322 (98), 320 (100), 293 (73), 280 (33), 153.5 (20).

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