Aporphines. 8. Total Synthesis and Pharmacological Evaluation of (±)-Apomorphine, (±)-Apocodeine, (±)-*N*-*n*-Propylnorapomorphine, and (±)-*N*-*n*-Propylnorapocodeine†

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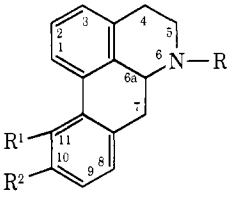
The first total synthesis and preliminary pharmacological evaluation of the title compounds (±)-2–5 are described. The method involved the alkylation of the Reissert compound **6** with nitroveratryl chloride (**7**) followed by base hydrolysis to yield 90% of the isoquinoline **9**. Quaternization (90–100%) with the appropriate alkyl halide and reduction under a variety of conditions gave the tetrahydroisoquinolines **11–13**. The selective 0-demethylation of **11** to **12** under acidic conditions led to the synthesis of apocodeine **3** and its *N*-propyl analog **5** from **12a** or **b** under Pschorr-type cyclization conditions. Similarly, **13** was converted to the (±)-dimethoxyaporphine (±)-**14** *via* Pschorr cyclization. **14a** and **b** were converted (93%) to (±)-**2** and (±)-**4** with HI-Ac_2O. (−)-Apocodeine was also prepared *via* a selective monomethylation of (−)-apomorphine with CH_2N_2 in Et_2O. The conversion of both (−)- and (±)-**2** and -**4** to **14a** and **b** with CH_2N_2 in Et_2O was also accomplished. The synthetic racemic aporphines had pharmacological activity qualitatively similar to that of their levo isomers derived from morphine. The test results suggested that potent pharmacological activity may reside in the levo isomer and that the dextro isomer is relatively inactive. Replacing the *N*-methyl substituent of apomorphine with an *n*-propyl group enhanced potency. Etherification of the 10,11-hydroxyl groups or the 11-hydroxyl group reduced potency.

(−)-Apomorphine [(−)-**2**], the semisynthetic alkaloid obtained by vigorous treatment of morphine with strong mineral acids, has for years found medicinal application as a powerful centrally acting emetic[2] and more recently has been found useful in the treatment of Parkinson's disease.[3,4] (−)-Apomorphine hydrochloride [(−)-**2**·HCl] was first prepared by Matthieson and Wright by the acid-catalyzed rearrangement of morphine.[5] Pure apocodeine [(−)-**3**] was first described by Folkers,[6] although this compound had been prepared earlier by Knorr,[7] albeit in impure form, by fusing codeine with oxalic acid. Apocodeine has also been used therapeutically, as an expectorant, emetic, hypnotic, and cathartic.[8] The preparation of apomorphine and apocodeine by the acid-catalyzed rearrangement of morphine and codeine results in the retention of the configuration at the C_{6a} chiral center leading to the corresponding levo (−) isomers. A number of investigators have since these earlier studies utilized the acid-catalyzed rearrangement of morphine and *N*-alkylnormorphine derivatives for the synthesis of apomorphine and *N*-alkylnorapomorphine derivatives.[9]



1 (aporphine), R = CH_3; R^1, R^2 = H
2 (apomorphine), R = CH_3; R^1, R^2 = OH
3 (apocodeine), R = CH_3; R^1 = OH; R^2 = OCH_3
4 (*N*-*n*-propylnorapomorphine), R = *n*-C_3H_7; R^1, R^2 = OH
5 (*N*-*n*-propylnorapocodeine), R = *n*-C_3H_7; R^1 = OH; R^2 = OCH_3

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† Presented in part at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, MEDI 37. For the previous paper in this series, see ref 1.

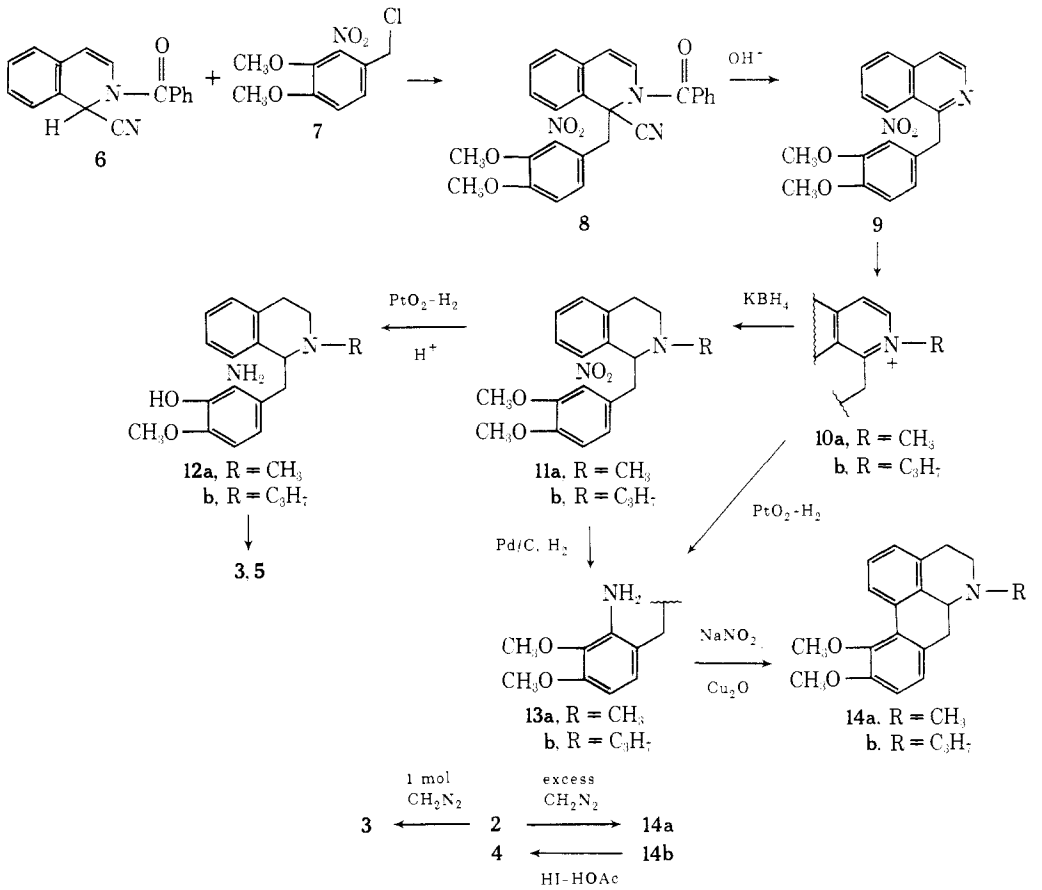
In this paper we wish to describe the first total synthesis of the racemic aporphines **2–5** and **14**. We shall also report the preliminary pharmacological evaluation of these aporphines and their comparison with the levorotatory isomers, obtained by the rearrangement of the naturally occurring alkaloids.

The initial efforts in these laboratories were directed toward the development of a general synthetic pathway which would be applicable to the synthesis of aporphines not derivable from morphine or from the aporphine alkaloids. Although the acid-catalyzed rearrangement of morphine or codeine serves as a useful method for the generation of apomorphine and apocodeine, it became necessary to develop a general method applicable to the synthesis of sufficient quantities of these and related aporphines for pharmacological evaluation.

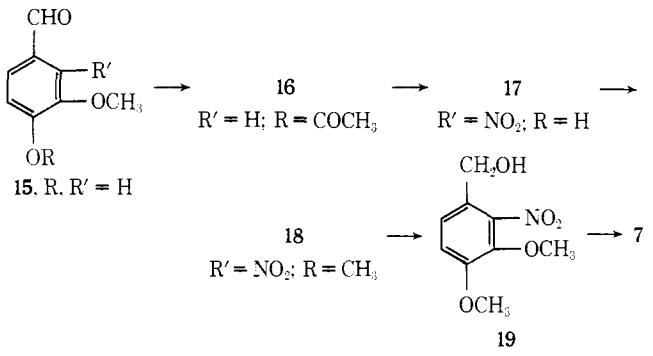
In our preliminary communications we have reported the synthesis of aporphine (**1**)[10,11] and apomorphine (**2**)[12] *via* the Reissert alkylation and Pschorr cyclization route. The present approach follows this general synthetic sequence and will be discussed as it applies to the synthesis of the subject compounds. The advantage of this route over other sequences has been discussed in our previous publications.[11,13]

The synthetic route used for the preparation of **2–5** is shown in Scheme I and the synthesis of the reagent **7**[14] is shown in Scheme II. Our initial studies involved the alkylation of the anion of the Reissert compound **6** by **7** to give the alkylated Reissert compound **8** in 35% yield. In this procedure phenyllithium was used to generate the anion in Et_2O at −20°.[15] A procedure for the generation of the anion of **6** employing sodium hydride in DMF at room temperature was found to be superior and resulted in our obtaining excellent yields of the desired isoquinoline **9** without the isolation of **8**. The crude product **8** was hydrolyzed to furnish 90% of **9** (from **6**). The base **9** was then converted to the appropriate quaternary salts **10** and reduced with KBH_4 to the tetrahydroisoquinolines **11** in better than 80% yield. The anomalous carbon–carbon bond cleavage which occurs in a number of isomeric 1-benzylisoquinolinium salts when treated with KBH_4 was rationalized by the mechanism proposed in our previous publication.[13]

Scheme I



Scheme II



Our original study of the reduction of 11a,b to 13a,b in 10% H_2SO_4 over 10% Pd/C had apparently given 13a,b in acceptable yield; the amine 13 was found to be rather sensitive to air. Subsequently, we found that under these conditions the product 13b so obtained was contaminated with 10–15% of the ether cleavage product 12b and that the observed air sensitivity of the mixture was caused by this component. We now know that 13b was not particularly sensitive to air and that even 12b, which was an *o*-aminophenol, was quite stable as a crystalline solid.

The catalytic hydrogenation of 11b to 13b was studied in order to learn how to avoid the concurrent formation of 12b. We found that hydrogenation over 10% Pd/C under neutral conditions in a mixture of equal parts of MeOH and THF gave 89–98% yields of 13b when carried out on a scale of 0.02–0.1 mol. 13b was obtained as an oil that contained only traces of impurity on tlc.

The reduction of 11b over 10% Pd/C in a mixture of 1 part of 10% aqueous H_2SO_4 and 10 parts of absolute EtOH gave a 20% yield of 12b, along with 13b. Reduction over rhodium in 10% aqueous H_2SO_4 gave higher yields of 12b than did reduction over Pd/C under the same conditions. Both 13b and 12b were badly contaminated with several other uncharacterized products. When 11b was hydrogenated over Adams platinum oxide in 10% aqueous sulfuric acid, 12b was obtained in 66% yield.

Some attention was also given to the reduction of the isoquinolinium salt 10b directly to 13b, rather than proceding by way of 11b. When 10b was hydrogenated over PtO_2 in either MeOH or in a mixture of equal parts of MeOH and THF, 13b was obtained in 87% yield, provided that the solution of 10b was used promptly and that the presence of water or acid was avoided. The amine 13a was converted to (±)-apomorphine dimethyl ether (14a) by modification of the Pschorr cyclization procedure of Späth and Hromatka.[16] Considerable efforts were made in improving this procedure for carrying out the cyclization of 13 to 14 by way of the intermediate diazo compound. Optimum yields of 53% were obtained in the conversion of 13b to 14b. A detailed description of this modified procedure is given in the Experimental Section.

The spectral properties of (±)-apomorphine dimethyl ether [(±)-14a] were identical with those of a sample of (−)-apomorphine dimethyl ether [(−)-14a] prepared in 74% yield from (−)-apomorphine hydrochloride [(−)-2·HCl] and diazomethane. The oily (±)-14a was converted into a crystalline picrate, mp 187–189° dec, and a crystalline perchlorate, mp 263° dec. Both these derivatives melted considerably higher than the corresponding derivatives obtained from (−)-14a. The two preparations of apomorphine dimethyl ether, (−)-14a and (±)-14a, showed identical ir (film), uv, and nmr spectra. (±)-Apomorphine dimethyl ether [(±)-14a] was converted to a colorless hydroiodide [(±)-14a·HI], mp 279° dec, and this compound was in turn converted to (±)-apomorphine hydroiodide

Table I. Comparison of Activity of Racemic and Levo Aporphines

Compd	Feature	Mouse screen: ED_{50} (95% confidence limits), mg/kg iv	Mouse screen: Observed effect at ED_{50}	Overt behavior min effective dose, mg/kg iv: Monkey[b]	Overt behavior min effective dose, mg/kg iv: Cat[c]	Dog emesis min effective dose, mg/kg iv
(−)-**2**·HCl	N-Me, 10,11-OH	0.032 (0.016–0.61)	Decr. general activity	0.05	0.05	0.012
(±)-**2**·HI	N-Me, 10, 11-OH	0.056 (0.025–0.13)	Decr. general activity	0.05	0.2	0.025
(−)-**4**·HCl[a]	N-Pr, 10,11-OH	0.0024 (0.0013–0.0042)	Decr. general activity	0.00075	0.00025	0.0005
(±)-**4**·HI	N-Pr, 10,11-OH	0.0056 (0.0034–0.0094)	Decr. general activity, incr. sensitivity to touch	0.0005	0.001	0.0012
(±)-**5**·HI	N-Pr, 10-OCH_3, 11-OH	5.6 (1.8–18.0)	Decr. general activity			1.0
(−)-**14a**·$HClO_4$	N-Me, 10,11-OCH_3	18.0 (5.6–56.0)	Decr. general activity, decr. sensitivity to touch, motor deficits	>0.1	>1.0	>0.1
(±)-**14a**·HI	N-Me, 10,11-OCH_3	5.6 (1.8–18.0)	Decr. general activity, decr. sensitivity to touch			>0.1
(−)-**14b**·HI	N-Pr, 10,11-OCH_3	5.6 (1.8–18.0)	Decr. general activity	>0.1	>0.1	>0.1
(±)-**14b**·HI	N-Pr, 10,11-OCH_3	5.6 (1.8–18.0)	Decr general activity, decr. sensitivity to touch			>0.1

[a] See Archer, ref 9. [b] Observed effect: abnormal mouth movements, yawning. [c] Observed effect: relaxed nictitating membrane.

[(±)-**2**·HI] by dissolving it in an equivalent mixture of 57% HI and Ac_2O and refluxing the solution for 1 hr. The product was isolated by adding Et_2O to the reaction mixture and was obtained in 93% yield as a colorless crystalline powder, mp 282° dec. The substance discolored slowly when stored at 0° under nitrogen. In a similar reaction (±)-**14b** was converted to (±)-*N*-*n*-propylnorapomorphine hydroiodide [(±)-**4**·HI] in 93% yield.

Advantage was taken of the selective demethylation of (±)-**11** to (±)-**12** under acidic conditions for the synthesis of the apocodeines (±)-**3** and (±)-**5**. **12a** and **b** were converted by a similar Pschorr-type cyclization and isolated as hydroiodide salts of **3** and **5** in 25 and 35% yield. Apocodeine [(−)-**3**] was also prepared *via* a selective monomethylation of apomorphine [(−)-**2**] in 20% yield using CH_2N_2 in Et_2O.

Pharmacological Data. As our first objective it was desired to learn how the activity of totally synthetic (±)-aporphines compared with the activity of aporphines derived from natural products (*i.e.*, the levo isomers), to determine the effect of replacing the methyl substituent on the nitrogen with a larger group, and to determine if etherification of the hydroxyl groups of apomorphine affected activity. For these studies we compared two sets of compounds, one derived from apomorphine itself (*N*-methyl) and the other from the *N*-propyl analog. The activity of these compounds was evaluated in a mouse screen,[17] in a dog emesis screen,[18] and for overt behavior effects in the cat and the monkey. All drugs were medicated intravenously. In the mouse screen, ED_{50} values and fiducial limits were calculated. For the emesis and overt behavior tests, the lowest tested dose able to elicit an effect in any of the animals tested at that dose was recorded as the minimal effective dose. The minimum effective dose thus was an observed value, not a statistically derived value. For potency comparisons, minimum effective dose values serve to show the existence of large potency differences.

The synthetic racemic aporphines (±)-**2** and (±)-**4** each had activity similar in kind and potency to that of its respective levo isomer derived from naturally occurring precursors, in all four tests (Table I). In three of the four tests—the mouse screen, dog emesis, and cat overt behavior—each racemate had a higher test value than its (−) isomer. Although only the cat overt behavior test differences were large enough to be significant, the consistent and similar relationship seen with both compound pairs suggests that the racemates may be approximately half as potent as their (−) isomers. This would support the hypothesis that potent pharmacological activity resides in the (−) isomer and that the (+) isomer is relatively inactive. To confirm this hypothesis, the corresponding (+) isomers should be prepared and evaluated. Such studies are currently underway in our laboratories.‡

Pharmacological activity was a function both of the substituent group on the nitrogen and of the 10,11-phenolic hydroxyl groups. Replacing the *N*-methyl substituent of apomorphine (**2**) with a propyl group (**4**) enhanced potency in all four tests by 1-2 orders of magnitude (Table I). For both apomorphine and *N*-*n*-propylnorapomorphine, etherification of the hydroxyl groups greatly reduced potency in all of the tests used. Similarly, the potency was reduced by monoetherification of the 10-hydroxy group as in *N*-*n*-propylnorapocodeine [(±)-**5**].

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected or in a Du Pont 900 thermal analyzer (dta) under nitrogen. The microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The ir spectra were recorded on a Perkin-Elmer grating spectrophotometer, Model 521; uv spectra were recorded with a Beckman Model DK-1A; and the nmr spectra were determined on a Varian A-60 spectrophotometer with TMS as the internal standard. Where analyses are indicated by symbols of elements, the analytical results were within ±0.4% of the theoretical values.

2-Nitrovanillin (17). Vanillin (**15**, 304 g, 2 mol) was converted to **17** *via* **16** by the procedure described by Slotta.[14] The wet product was used directly for the preparation of the methyl ether of 2-nitrovanillin (**18**). A small sample of 2-nitrovanillin when dried had mp 135.5–137° (lit.[14] mp 137°).

2-Nitroveratraldehyde (18). 2-Nitrovanillin was converted into **18** by the procedure described by Slotta.[14] The overall yield from

‡ After completion of our studies, Saari, King, and Lotti[19] reported the preparation of (+)-apomorphine *via* resolution of (±)-**14a**. Their results also suggest that the optical antipode of apomorphine (+)-**2**, its dimethyl ether (+)-**14a**, and (−)-**14a** do not possess significant apomorphine-like activity nor are they effective apomorphine antagonists. These studies support the results reported herein.

15 was 37%; mp 58–61° (lit.[14] mp 63–64°). Unconverted 2-nitrovanillin was recovered from the reaction mixture.

2-Nitroveratryl Alcohol (19). A solution of 11 g (0.29 mol) of $NaBH_4$ in 200 ml of 40% EtOH was added slowly at room temperature to a solution of 100 g (0.473 mol) of 18 in 3 l. of EtOH. The reaction mixture was heated slowly to boiling and allowed to reflux overnight; 75 ml of 10% HCl was added, and the solution was concentrated to about 500 ml and poured into 3 l. of ice water. The resulting precipitate was filtered, washed with water, and dried *in vacuo* to yield 100 g of the crude alcohol 19, mp 61–63°. Recrystallization from C_6H_6 yielded 79.6 g (79%) of 19, mp 62–64° (lit.[14] mp 68–69°).

α-Chloro-3,4-dimethoxy-2-nitrotoluene (7). 19 (70 g, 0.33 mol) was converted into the corresponding benzyl chloride by reaction with 700 ml of concentrated HCl during 2.5 hr. The reaction mixture was poured into 700 ml of ice water, and the precipitated product was recrystallized from Et_2O–n-C_6H_{14} to yield 62.5 g (81%) of 7, mp 53–56° (lit.[14] mp 57–58°). *Anal.* ($C_9H_{10}ClNO_4$) C, H.

2-Benzoyl-1-(3,4-dimethoxy-2-nitrobenzyl)-1,2-dihydroisoquinaldonitrile (8). A mixture of 7.80 g (30 mmol) of 2-benzoyl-1,2-dihydroisoquinaldonitrile (6) and 7.65 g (33 mmol) of α-chloro-3,4-dimethoxy-2-nitrotoluene (7) in a flame-dried round-bottom flask equipped with magnetic stirrer and nitrogen inlet was dissolved in 75 ml of spectro-quality DMF. A dispersion of 54% NaH in mineral oil (1.9 g, 43 mmol of NaH) was added to the stirred reaction mixture. After 1.5 hr of stirring at room temperature, the reaction mixture was poured into 250 ml of $CHCl_3$, and 250 ml of water was added cautiously. The layers were separated, and the $CHCl_3$ layer was extracted with 2 × 250 ml of water. The three aqueous layers were combined and extracted with 50 ml of $CHCl_3$, which was added to the principal extract. The $CHCl_3$ solution was evaporated under reduced pressure almost to dryness and 350 ml of absolute ethanol was added to complete the precipitation of a yellow crystalline solid. A small portion of this was filtered off and the balance of the suspension was used directly for hydrolysis to 9.

The sample of yellow solid that had been filtered off was dried to give the isoquinaldonitrile 8 as pale yellow flakes, mp 208–209°. *Anal.* ($C_{26}H_{21}N_3O_5$) C, H, N.

1-(3,4-Dimethoxy-2-nitrobenzyl)isoquinoline (9). The EtOH suspension of 8 was heated to reflux and a solution of 5 g (75 mmol) of KOH in 35 ml of water was added. In a few minutes a clear solution was formed. After 0.5 hr of reflux, solvent was removed under reduced pressure and the residue was dissolved in 150 ml of $CHCl_3$ and 100 ml of water. The layers were separated, and the $CHCl_3$ layer was extracted with 2 × 100 ml of water. The water layers were combined and extracted with 25 ml of $CHCl_3$ which was added to the original $CHCl_3$ solution. The combined $CHCl_3$ solution was dried over Na_2SO_4 and was then concentrated under reduced pressure to about 50 ml. EtOH (50 ml) was added and the solution was reconcentrated; this procedure was repeated once again. The solution was cooled to 0° and the solid that separated was collected and washed with cold EtOH. The product was 8.92 g (90% from 6) of the isoquinoline 9 as a yellow powder, mp 124–126°.

A portion of the product, recrystallized from $CHCl_3$–Et_2O, was obtained as almost colorless needles, mp 129–130°. *Anal.* ($C_{18}H_{16}N_2O_4$) C, H, N.

The picrate salt of 9 was prepared, mp 175–177° dec (sealed tube under nitrogen).

1-(3,4-Dimethoxy-2-nitrobenzyl)isoquinoline Methiodide (10a). 1-(3,4-Dimethoxy-2-nitrobenzyl)isoquinoline (9) was converted quantitatively into the quaternary salt 10a by refluxing with a 20–30-fold excess of MeI for 15–20 hr. The product, mp 190–193°, could be recrystallized from water and from EtOH, but the mp was unchanged. *Anal.* ($C_{19}H_{19}IN_2O_4$) C, H, I, N.

Similarly prepared from 9 and 1-iodopropane was 1-(3,4-dimethoxy-2-nitrobenzyl)isoquinoline propiodide (10b), mp 184–186°. *Anal.* ($C_{21}H_{23}IN_2O_4$) C, H, N.

1-(3,4-Dimethoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (11a). The procedure of Torossian[20] for the reduction of isoquinoline was modified for this reaction. An aqueous solution of 550 mg (10 mol) of KBH_4 was added to a solution of 1.7 g (3.65 mmol) of the methiodide **10a** in a mixture of 150 ml of EtOH and 100 ml of water, and the mixture was stirred for 45 min at 30°. The mixture was slowly heated and finally allowed to reflux for 1 hr. Solid KBH_4 was added in small portions to the boiling reaction mixture. The solution was refluxed for an additional 1 hr and allowed to stand at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in water. The solution was brought to pH 9 by addition of 20% NaOH and extracted with Et_2O. The combined Et_2O extracts were dried over $MgSO_4$ in the presence of a little charcoal. The Et_2O was removed under pressure to yield 1.0 g (80%) of the tetrahydroisoquinoline 11a as a nearly colorless solid, mp 90–93°. A portion was recrystallized from n-hexane and then from petroleum ether–EtOH (25:0.3) to give yellow-green crystals, mp 97–98.5°. *Anal.* ($C_{19}H_{22}N_2O_4$) C, H, N.

1-(3,4-Dimethoxy-2-nitrobenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinoline (11b). The reduction of the propiodide **10b** (3.7 g) by KBH_4 was carried out by using the procedure described above for the methiodide 11a. The oily product was recrystallized from petroleum ether to yield 2 g (72%) of 11b as a slightly yellow powder, mp 74–76°. A small amount, recrystallized again from petroleum ether, had mp 75.5–76°. *Anal.* ($C_{21}H_{26}N_2O_4$) C, H, N.

1-(2-Amino-3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (13a). A sample of 1.5 g (4.4 mmol) of 1-(3,4-dimethoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (11a) was dissolved in 50 ml of MeOH and hydrogenated in a Parr apparatus, using 350 mg of 5% Pd/C. Hydrogenation was complete after 1 hr. The oily residue from evaporation of the solvent was recrystallized from 25 ml of petroleum ether to yield 1.1 g (80%) of the amine 13a as yellow crystals, mp 84–85°. The nmr spectrum was consistent with the assigned structure. The ir spectrum showed absorption at 3440 (aromatic NH_2) and 1280 cm^{-1} (C–N stretching); no nitro group absorption was found. The uv absorption spectrum showed λ_{max} (MeOH) 212 mμ (ε 39,000), 265 (11,000), 272 (1400), and 285 (1600). *Anal.* ($C_{19}H_{24}N_2O_2$) C, H, N.

A dipicrolonate salt was prepared and recrystallized from EtOH: mp 191–192° dec, not depressed by admixture with an authentic sample.[21] The infrared spectra of both dipicrolonate salts were identical.

1-(2-Amino-3,4-dimethoxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinoline (13b). a. By Reduction of 1-(3,4-Dimethoxy-2-nitrobenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinoline (11b). In a typical run a solution of 20 g (0.053 mol) of 11b in a mixture of 35 ml of MeOH and 35 ml of THF was hydrogenated at room temperature and 45–50 psi over 2.5 g of 10% Pd/C. Absorption of hydrogen was complete after about 4 hr. The catalyst was filtered off, and the filtrate was evaporated to dryness under vacuum. The residual yellow oil was dissolved in petroleum ether (bp 30–60°); the solution was washed with water, dried over $MgSO_4$, and evaporated to dryness under vacuum to give 17.8 g (98%) of **13b** as a yellow oil which could be used in the next step without purification. The compound could be further purified by distillation: bp 182° (0.1 mm); $n^{25}D$ 1.5761. *Anal.* ($C_{21}H_{28}N_2O_2$) C, H, N.

An orange monopicrolonate salt, mp 134.5–136°, was prepared and recrystallized from ethanol. *Anal.* ($C_{31}H_{36}N_6O_7$) C, H, N.

b. By Reduction of 1-(3,4-Dimethoxy-2-nitrobenzyl)isoquinoline Propiodide (10b). A mixture of 10 g (0.02 mol) of the quaternary iodide salt 10b, 50 ml of MeOH, and 0.5 g of PtO_2 was prepared and immediately hydrogenated at room temperature and 60 psi. Absorption of hydrogen was complete after 2 days. The catalyst was filtered off, and the filtrate was evaporated to dryness under vacuum. The residue was dissolved in petroleum ether (bp 30–60°) and the solution was washed with 10% NaOH. The aqueous phase was extracted twice with petroleum ether, the organic phases were combined and dried over $MgSO_4$, and then they were evaporated to dryness to give 6 g (87%) of **13b** that was identical with **13b** prepared by the reduction of **11b**, as described above.

(±)-10,11-Dimethoxy-*N*-*n*-propylnoraporphine Hydroiodide [(±)-14b·HI]. (±)-*N*-*n*-Propylnorapomorphine Dimethyl Ether Hydroiodide. A solution of 8.9 g (0.026 mol) of the amine **13b** in 50 ml of 10% aqueous sulfuric acid was stirred at 0–3° and 18 ml of 2 *M* $NaNO_2$ (0.036 mol) was added during 5 min. Stirring of the cold deep red solution was continued for an additional 20 min; then excess nitrous acid was destroyed by the addition of sulfamic acid until a starch–iodide test was negative. The diazo solution was added dropwise under nitrogen during 10 min to a stirred mixture of 10 g of cuprous oxide and 400 ml of 10% sulfuric acid; the reaction mixture was not cooled. The mixture was stirred at room temperature for about 15 hr and then was filtered to give a pale green solution whose pH was adjusted to about 6 with concentrated NH_4OH. The cloudy mixture was stirred vigorously for 30 min and then was made strongly basic by the addition of more concentrated NH_4OH; the total volume of base used

was about 200 ml. The now deep blue solution was extracted with 50 ml of $CHCl_3$ by stirring the mixture for 20 min. The aqueous phase was extracted further with 3 × 40 ml of $CHCl_3$. The combined $CHCl_3$ extracts were washed with 75 ml of water, were dried over $MgSO_4$, and were evaporated to dryness under vacuum to give 9 g of a dark brown residue. The residue was stirred with about 70 ml of Et_2O and some Et_2O-insoluble material was filtered off. The Et_2O solution was evaporated under vacuum to give 8.55 g of a brown oily residue. The residue was dissolved in 15 ml of Me_2CO and to the solution there was added dropwise 57% HI until a pH 2 was reached. A yellow crystalline salt separated and was filtered off after standing first at room temperature and then at 0°. The salt was washed on the filter with Me_2CO and with relatively large amounts of Et_2O and then was dried to give 6.1 g of the hydroiodide of **14b**. By working up the filtrate and washings, an additional 0.15 g of salt was obtained. The combined weights represented a 53% yield in the Pschorr cyclization step. A small amount of the oily free base liberated from the hydroiodide by neutralization became crystalline on standing. The pale yellow solid had mp 132–133°.

The hydroiodide could be recrystallized from 90% EtOH–Et_2O; the colorless crystalline solid had mp 245° dec (dta). The uv spectrum showed λ_{max} (MeOH) 216 mμ (ε 49,000), 269 (18,000), and 306 sh (2200). *Anal.* ($C_{21}H_{26}INO_2$) C, H, I, N.

The hydrochloride was also prepared: mp 243.5–244° (MeOH). *Anal.* ($C_{21}H_{25}NO_2 \cdot HCl \cdot H_2O$) C, H, N.

(±)-10,11-Dimethoxyaporphine Hydroiodide [(±)-14a·HI]. (±)-Apomorphine Dimethyl Ether Hydroiodide. The procedure described above was repeated using 4.68 g of the amine **13a** to obtain 1.83 g (41%) of the pure ether **14a** as a brown oil which yielded a picrate, mp 187–189° dec, and a perchlorate, mp 263°. The brown oil was dissolved in a small amount of absolute EtOH, and 57% HI was added. When crystallization began several volumes of Et_2O were added, the mixture was cooled, and the solid was filtered off. Recrystallization from Me_2CO–H_2O gave the hydroiodide of **14a** as colorless plates, mp 279° dec (dta). The uv spectrum showed λ_{max} (MeOH) 216 mμ (ε 47,000), 269 (19,000), and 306 sh (2300). *Anal.* ($C_{19}H_{22}INO_2$) C, H, N.

(±)-Apomorphine Hydroiodide [(±)-2·HI]. The reaction was carried out under nitrogen in a flame-dried flask equipped with magnetic stirrer, septum cap adapter, and nitrogen bubbler. Ac_2O (2.9 ml, 31 mmol) was added from a syringe during 5 min to a stirred mixture of 1.04 g (2.5 mmol) of **(±)-14a·HI** partly dissolved in 4.0 ml (30 mmol) of 57% HI. The reaction mixture was heated at reflux in an oil bath for 1 hr and then allowed to cool under nitrogen. Then 15 ml of Et_2O was added, and the precipitated solid was filtered off and washed copiously with Et_2O. When dry, the white, crystalline powder weighed 0.90 g (93%). An analytical sample was prepared by recrystallization from 90% EtOH upon addition of Et_2O. The fine white crystals had mp 282° dec (dta); λ_{max} (MeOH) 217 mμ (ε 41,000), 273 (17,000), and 309 (3300). *Anal.* ($C_{17}H_{17}NO_2 \cdot HI$) C, H, N.

(±)-*N*-*n*-Propylnorapomorphine Hydroiodide [(±)-4·HI]. This compound was prepared in a 95% yield by the manner as described for **(±)-2·HI**. The white, crystalline material was recrystallized from 90% EtOH by the addition of Et_2O. It had mp 278° dec (dta); λ_{max} (MeOH) 215 mμ (ε 43,000), 273 (17,000), and 307 (3100). *Anal.* ($C_{19}H_{22}NO_2I$) C, H, N, I.

1-(2-Amino-3-hydroxy-4-methoxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinoline (12b). A mixture of 10 g (30.6 mmol) of **11b**, 50 ml of 10% H_2SO_4, and 0.5 g of PtO_2 was hydrogenated at room temperature and 60 psi for 25 hr; 90 mmol of hydrogen was absorbed. The catalyst was filtered off; the filtrate was made basic with concentrated NH_4OH and then was extracted with Et_2O. The dry $(MgSO)_4$ extract was evaporated to dryness. The oily residue was crystallized from boiling *n*-hexane to give 6.3 g (66%) of **12b** as colorless crystals, mp 133.5–134°. The uv spectrum showed λ_{max} (EtOH) 264 mμ (ε 1521) and 271 (1617); the maxima were shifted to 271 and 290 mμ when the solution was made basic with NaOH. *Anal.* ($C_{20}H_{26}N_2O_2$) C, H, N.

Similarly prepared from **11a** was **1-(2-amino-3-hydroxy-4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (12a)** in 59% yield, mp 121–122.5°. *Anal.* ($C_{18}H_{22}N_2O_2$) C, H, N.

(±)-11-Hydroxy-10-methoxy-*N*-*n*-propylnoraporphine Hydroiodide [(±)-5·HI]. (±)-*N*-*n*-Propylnorapocodeine Hydroiodide. The amine **12b** (10 g, 20.3 mmol) was converted by the Pschorr reaction to 4.73 g (35%) of the hydroiodide of **5**, mp 269° dec. The procedure was identical with that described for the conversion of 13b to **14b·HI**. *Anal.* ($C_{20}H_{23}NO_2HI$) C, H, N.

(±)-11-Hydroxy-10-methoxyaporphine Hydroiodide [(±)-3·HI]. (±)-Apocodeine Hydroiodide. The amine **12a** (1.1 g) was converted to 0.37 g (25%) of the hydroiodide of **3**, mp 272° dec, by the procedure described above for the conversion of **13b** to **14b·HI**: uv λ_{max} (MeOH) 270 mμ (ε 16,700) and 306 (4020). *Anal.* ($C_{18}H_{20}NO_2HI$) C, H, N.

Conversion of (−)-Apomorphine [(−)-2] to (−)-Apomorphine Dimethyl Ether (14a). Apomorphine hydrochloride (−)-**2** (Penick, N. F.) (6.34 g, 20 mmol) was partially dissolved in 250 ml of H_2O, to which 40 ml of 1.0 *M* $NaHCO_3$ solution was added (under a CO_2 atmosphere). The precipitate was dissolved by extraction with two 200-ml portions of Et_2O, and the Et_2O extract was dried over K_2CO_3. The Et_2O solution was freed of solvent under reduced pressure and the crystalline residue dissolved in 200 ml of MeOH (under nitrogen). To the MeOH solution was added an ethereal solution of diazomethane (~3 g) prepared from 21.5 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide. The reaction mixture was protected from the atmosphere. After 20 hr of standing at room temperature (shielded from light) the solution was freed of Et_2O under reduced pressure. To the MeOH solution was added ethereal diazomethane (the same amount as before), and after another 20 hr of standing the solvent was removed under reduced pressure. The residue was taken up in 150 ml of 1 *N* HCl. The acid solution was extracted with three 75-ml portions of Et_2O. It was made basic with 20% NaOH and extracted with four 50-ml portions of Et_2O. The ether extracts were combined, extracted with three 50-ml portions of 5% NaOH, and washed with 50 ml of saturated NaCl solution. The Et_2O solution was treated with charcoal and dried over Na_2SO_4. The solvent was removed under vacuum to leave 4.46 g of an orange oil (74%) which became a glass when it was cooled to 0°. This showed on tlc (silica, 10% MeOH–$CHCl_3$) only small amounts of impurity.

This material yielded a *d*-bitartrate, mp 183° dec (lit.[16] mp 177–178°), as well as a picrate, mp 148–150°, and a colorless perchlorate, mp 216° dec.

The free base was liberated from the bitartrate by dissolving the salt in 1 *N* HCl, making the solution basic with 20% NaOH, and extracting with Et_2O. The Et_2O solution was washed with 5% NaOH and dried over Na_2SO_4. Removal of solvent left a yellow glass, which slowly crystallized as pale yellow crystals on standing in the refrigerator, mp 68–70°.

Spectra were taken of the purified material: uv λ_{max} (MeOH) 215 mμ (ε 37,000), 269 (18,000), and 316 s (2300); nmr ($CDCl_3$) δ 2.57 (3 H, singlet), 3.03 (7 H, multiplet), 3.73 (3 H, singlet), 3.91 (3 H, singlet), 6.91 and 7.18 (3 H, multiplet), 8.22 (1 H, doublet, J = 2.0 Hz), 8.35 (1 H, doublet, J = 2.0 Hz).

The hydroiodide salt of **(−)-14a** was prepared in absolute EtOH with excess 57% HI. Upon the addition of several volumes of Et_2O and cooling, crystallization occurred. After recrystallization from EtOH–Et_2O, the white crystals had mp 205° dec (sealed tube under nitrogen). *Anal.* ($C_{19}H_{22}NO_2I$) C, H, N, I.

(−)-*N*-*n*-Propylnorapomorphine Dimethyl Ether Hydroiodide [(−)-14b·HI]. This compound was prepared in the same manner as **(−)-14a**. Thus, from 1.67 g of **(−)-14b·HCl**, 1.07 g (66%) of a brown oil was obtained. Part of this product was converted to the hydroiodide by the procedure described above for the preparation of **(±)-14a·HI**. After recrystallization from EtOH–Et_2O, the pale yellow crystalline material had mp 240° dec (dta): λ_{max} (MeOH) 216 mμ (ε 49,000), 269 (18,000), and 3065 (2200). *Anal.* ($C_{21}H_{25}NO_2I$) C, H, N, I.

Apocodeine [(−)-3] by Monomethylation of Apomorphine [(−)-2]. Apomorphine base was liberated from its hydrochloride as described above. To the Et_2O solution of **(−)-3** was added an ethereal solution of CH_2N_2 (containing about 0.075 mol of diazomethane). The reaction solution was kept under nitrogen and in the dark. After 5 hr, tlc (silica, 10% MeOH–$CHCl_3$) showed that apocodeine was the only substance present.§ The wine-red solution was filtered to remove a suspension of polymeric material, and the filtrate was treated with glacial AcOH dropwise until gas evolution ceased. The solution was washed with aqueous $NaHCO_3$ and then with saturated NaCl solution and dried over $MgSO_4$. The dried Et_2O solution was treated with charcoal, which removed all but a trace of the red color. Evaporation to dryness under vacuum gave 2.3 g of pale orange oil, which was taken up in hot methanol. The solution was cooled and seeded with

§When the reaction mixture was allowed to stand after all the apomorphine had been consumed, thin-layer chromatography showed the formation of the dimethyl ether.

apocodeine to give 0.89 g (20%) of off-white waxy prisms, homogeneous in tlc. Concentration of the mother liquors caused severe discoloration and no additional apocodeine could be recovered.

The waxy solid was recrystallized from MeOH containing a little CH_2Cl_2 to give colorless prisms, which were crushed and stored under high vacuum to remove what was apparently solvent of crystallization. The colorless powder had mp 122–124° (softening above 100°) and was identical with that obtained by rearrangement of codeine (lit.[6] mp 122.5–124.5°).

Tlc indicated that the yield in this methylation reaction was essentially quantitative. Because the product is very sensitive to light and to air, the yield is controlled by the sophistication of the work-up procedure.

Acknowledgments. We wish to thank Dr. E. R. Atkinson for helpful discussions, Dr. G. R. Handrick for the preparation of a number of compounds, and Dr. F. C. Nachod for assistance in the preparation of the manuscript.

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Aporphines. 9.[1] Synthesis and Pharmacological Evaluation of (±)-9,10-Dihydroxyaporphine [(±)-Isoapomorphine], (+)-, (−)-, and (±)-1,2-Dihydroxyaporphine, and (+)-1,2,9,10-Tetrahydroxyaporphine†

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The synthesis and preliminary pharmacological evaluation of the title compounds **2–4** are described and compared with those of (−)-nuciferine and (−)-apomorphine [(−)-**1**]. The method used for the synthesis of (±)-**2** involved modifications of the Reissert alkylation–Pschorr cyclization route previously employed for the synthesis of apomorphine and apocodeine. Two alternative sequences of reactions (**9a** → **10a** → **13a** → **13b** → **13c** or **9a** → **9b** → **10b** → **13c**) were investigated for the preparation of the Pschorr precursor **13c**. O-Demethylation of (±)-**6**, nuciferine, and glaucine was accomplished with 57% HI in Ac_2O to give the desired hydroxyaporphines **2–4**. The pharmacological results indicated that emetic and CNS activity resides principally in those aporphines that are substituted with phenolic hydroxyl groups in the 10 and 11 positions. Shifting the hydroxyl groups to positions 9,10 or to positions 1,2 markedly reduced pharmacological potency. Similarly, the tetrahydroxyaporphine substituted in the 1,2,9,10 positions also markedly reduced the activity in comparison with apomorphine.

In our previous study[1] we described the successful total synthesis of five racemic aporphines functionally substituted on the nitrogen atom and on the 10 and 11 positions. The procedure was applicable to the synthesis of aporphines not derivable from the naturally occurring opium alkaloids (*i.e.*, morphine and codeine). Preliminary pharmacological evaluation of (−)-apomorphine and (±)-apomorphine and their corresponding *N*-propyl homologs indicated that they were qualitatively similar in their pharmacological effects but that the racemic compounds were approximately half as potent in their emetic effects in dogs as their respective levo isomers.[1] In a continuing study of the structure-activity relationships of aporphine derivatives, we undertook the synthesis of (±)-9,10-dihydroxyaporphine [isoapomorphine (±)-**2**] and the preparation of (−)-, (+)-, and (±)-1,2-dihydroxyaporphine [(−)-**3**, (+)-**3**, and (±)-**3**] and (+)-1,2,9,10-tetrahydroxyaporphine [(+)-**4**].‡

† Presented in part at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, MEDI 37.

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‡ These nuciferine isomers were supplied through the courtesy of Dr. Bryce Douglas, Smith Kline and French Laboratories. Glaucine is commercially available.