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Synthesis and Biological Activity of Some Aporphine Derivatives Related to Apomorphine

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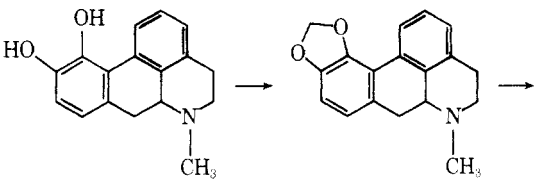
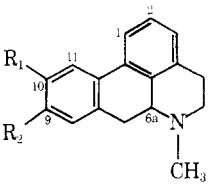
Several aporphine derivatives related to apomorphine were synthesized and evaluated for antihypertensive and central dopaminergic activity. Apocodeine (**16**) and (6a*R*)-10,11-methylenedioxyaporphine (**2**) produced apomorphine-like postural asymmetries in caudate lesioned mice but were less potent than apomorphine in this respect. Of the aporphine derivatives tested for antihypertensive activity, 11-hydroxyaporphine (**13**) proved to be the most potent upon oral administration to spontaneously hypertensive rats.

Apomorphine, (−)-**1**, has been shown to stimulate the dopaminergic system in the rat and mouse corpus striatum,[1,2] to produce a dopamine-like renal vasodilatation in dogs,[3] and to have a hypotensive effect in cats.[4] On the basis of its dopamine receptor-stimulating properties, apomorphine has been investigated recently for the treatment of Parkinson's disease.[5] We wish to report the synthesis of some aporphine derivatives related to apomorphine and their evaluation as antihypertensive and central dopaminergic agents.



1 **2**



3, R_1 = OH; R_2 = H
4, R_1 = H; R_2 = OH
5, R_1 = R_2 = OH

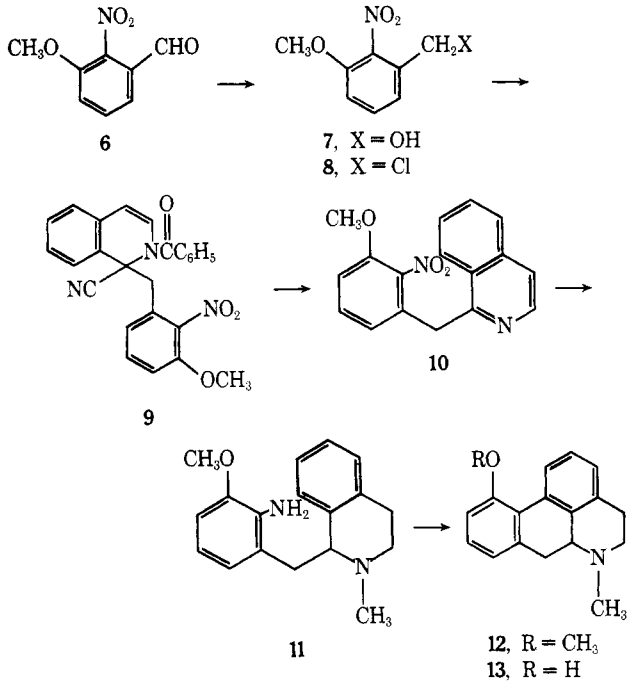
Chemistry. The disodium salt of apomorphine, (−)-**1**, was converted directly to methylene ether **2** by reaction with CH_2Br_2 in DMSO-H_2O. In accord with the nmr spectra of other aporphine alkaloids containing methylenedioxy groups,[6,7] the methylene protons of the free base of **2** were observed as a pair of doublets centered at δ 6.17 (J = 1.5 Hz, $CDCl_3$).

Cleavage of the methylenedioxy group of **2** with Na in NH_3(l) gave the expected 10-hydroxyaporphine **3** in 50% yield. The phenolic hydroxyl group in this product was assigned initially to the 10 position by analogy with the behavior of 1,2-methylenedioxyaporphines which have been found to give only 2-hydroxyaporphines under these conditions.[8] This assignment was confirmed later by nmr and tlc nonidentity with an authentic sample of the isomeric 11-hydroxy compound **13**.

Aporphines **2** and **3** were derived from apomorphine using reactions which would not lead to racemization at the chiral center 6a. Therefore, since apomorphine has been shown to possess an absolute stereochemistry designated as *R*,[8,9] **2** and **3** must also have *R* absolute configuration.

The 9-hydroxy (**4**) and the 9,10-dihydroxy (**5**)† derivatives were prepared by demethylation of the previously reported 9-methoxy[12] and 9,10-dimethoxy[13] compounds with hydrobromic acid. Synthesis of the 11-methoxy (**12**) and 11-hydroxy (**13**)‡ compounds was accomplished as outlined in Scheme I using the Reissert alkylation procedure developed by Neumeyer and coworkers.[15]

Scheme I

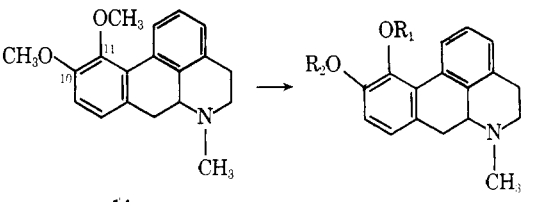


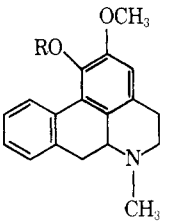
During the course of this work, selective demethylation of 10,11-dimethoxyaporphine (**14**) was studied in order to prepare **15**,§ an isomer of apocodeine (**16**). Reaction of **14** with the sodium salt of ethanethiol in DMF at 100° gave a 65% yield of apocodeine (**16**). None of the isomeric monoether **15** could be detected in the crude reaction mixture. Surprisingly, use of the more sterically hindered reagents, sodium thioisopropoxide and sodium thio-*tert*-butoxide, also gave only apocodeine, again in good yield. Although small amounts of the bis dealkylation product, apomorphine (**1**), were observed in the reactions involving sodium thioethoxide and sodium thioisopropoxide, no apomorphine was detected in the sodium thio-*tert*-butoxide reaction. Reaction of **14** with 20% hydrochloric acid at 120° also gave only apocodeine (**16**) as the monodemethylation product, but in lower yield, 35%.

†After completion of this work, two groups reported syntheses of **5**. Cannon and Aleem[10] prepared **5** beginning with the base-catalyzed condensation of 3-methyl-4-nitroveratrol with 2-methylisoquinolinium iodide by essentially the same procedure as we used. Neumeyer, *et al.*,[11] have reported synthesis of **5** *via* alkylation of an isoquinoline Reissert compound; *cf.* Scheme I.

‡Synthesis of 11-hydroxyaporphine (**13**) by the Reissert alkylation–Pschorr cyclization route has been announced[14] but experimental details have not yet been published.

§10-Hydroxy-11-methoxyaporphine (**15**) has been prepared in low yield by methylation of a monosodium salt of apomorphine (**1**) with methyl tosylate.[16]





Since increasing steric bulk of the thiol reagent, *viz.* ethyl, isopropyl, *tert*-butyl, had no effect on the course of the demethylation reaction, the 11-methoxy group of **14** cannot be sterically hindered. This methoxy group is most likely forced out of the plane of the aporphine aromatic system due to nonbonded interactions with the 10-methoxy group and the peri-1-hydrogen. This is consistent with assignment[6] of the higher field methoxy singlet, observed by us at δ 3.59 (DMSO-d_6) in the nmr spectrum of **14** to the 11-methoxy group and with the downfield shift of this methoxy singlet in **12** (which lacks the 10-methoxy group) to δ 3.82 (DMSO-d_6).

Demethylation probably occurs exclusively at the 11 position of **14** because the 11-methoxy group is relatively unhindered and demethylation of this particular methoxy group relieves some of the strain in the twisted aporphine biphenyl system. Similar steric-accelerating effects have been used by Vavrek, Cannon, and Smith[17] to account for the selective hydriodic acid demethylation of **17** to **18** and by Wilcox and Seager[18] for the selective hydrobromic acid demethylations of some trimethoxybenzene and dimethoxytetrahydroisoquinoline derivatives.

Biological Results. Compounds **2**–**5** and **16** were examined for both apomorphine-like activity and as apomorphine antagonists using the caudate brain lesioned mouse preparation described by Lotti.[2] In this preparation, apomorphine produces characteristic postural asymmetries which can be specifically blocked by apomorphine antagonists. Compounds were administered intraperitoneally at a minimum of two dose levels to groups of at least ten mice per dose. The mice were observed for postural asymmetries during the 10–60-min interval following drug administration. The highest dose of each compound tested was in excess of 25 times the dose of apomorphine (ED_{50}, 0.96 mg/kg) necessary to produce postural asymmetries in 50% of the mice.

Unlike apomorphine, **3**–**5** were ineffective in producing postural asymmetries in caudate lesioned mice (ED_{50}, >40 mg/kg). Similarly, when administered 1 hr prior to apomorphine, they were ineffective in antagonizing the response to apomorphine (4.0 mg/kg) in this preparation. Isoapomorphine (**5**) has also been reported by Pinder, Buxton, and Woodruff[19] and Neumeyer, *et al.*,[11] to have markedly reduced apomorphine-like activity in comparison with apomorphine.

The methylenedioxy ether **2** (ED_{50} 7.4 mg/kg) and apocodeine (**16**) (ED_{50} 17.0 mg/kg) produced apomorphine-

Table I. Effects of Some Aporphine Derivatives on the Mean Arterial Pressure in SH Rats

Compd no.	Dose, mg/kg[a]	Route	Anti-hypertensive act.[b]	Duration of action, hr
2	20	ip	+++	2–4
	20	po	0	
3	20	ip	+++	7–24
	5	po	0	
	20	po	+	4
5	20	ip	+++	7–24
	20	po	0	
12	20	ip	+++	2–4
	5	po	0	
	20	po	+	2–7
13	20	ip	+++	2–4
	0.31	po	0	
	1.25	po	+	4–7
	5.0	po	+++	4–7
	20	po	+++	2–7
16	20	ip	+	4–7
	20	po	0	

[a] Two rats were used at each dose of each compound. [b] The following code was used for evaluation of antihypertensive activity: 0 = no effect or mean arterial pressure change of less than 20 mm; + = lowering of mean arterial pressure of 20–29 mm; +++ = lowering of mean arterial pressure of 40 mm or more.

like postural asymmetries in caudate lesioned mice but were much less potent than apomorphine in this regard. Both **2** and **16** did not exhibit appreciable differences in onset or duration of action in comparison to apomorphine. In agreement with these results, Lal, Sourkes, Mirsala, and Belenduik[20] report that both **2** and **16** produced intermittent apomorphine-like stereotyped behavior in rats but were less effective than apomorphine.

Several of the aporphine derivatives were evaluated for antihypertensive activity in male, conscious spontaneously hypertensive (SH) rats of Wistar–Okamoto strain, 30–40 weeks of age and weighing 300–370 g. Aortic pressure was recorded continuously through indwelling catheters introduced through the caudal artery. Results are summarized in Table I. Of the compounds tested, only the 11-hydroxy derivative **13** had pronounced antihypertensive activity at 20 mg/kg po.

Compounds **2** and **13** were also tested orally in conscious, renal hypertensive dogs. Systolic arterial pressure was recorded in these animals by an indirect method using the tail artery before and at intervals up to 24 hr after drug administration. In this preparation, **2** exhibited transient antihypertensive activity at 20 mg/kg while **13** was effective in lowering arterial pressure at 10 mg/kg.

The methylenedioxy ether **2** was examined for emetic activity in dogs as defined by Lotti and Porter.[21] Apomorphine or its methylene ether **2** was administered intravenously at various dose levels to groups of at least six dogs and the number of emetic episodes was recorded during the next 30 min. The ether **2** (ED_{50} 0.12 mg/kg) was effective in producing emesis in dogs but again was much less potent than apomorphine (ED_{50} 0.006 mg/kg) in this regard. Emesis was also observed after oral administration (10 mg/kg) of the 11-hydroxy derivative **13**.

It would appear from this and other work,&[,14,16,19,20,22,23] that in the aporphine series, potent central dopaminergic-like activity is critically dependent upon a free catechol group in the proper spatial relationship to the nitrogen atom, as in apomorphine. These results do not support the hypothesis of Kier and Truitt[24] that the dopamine-like action of apomorphine results from the tetrahydroisoquinoline portion of the molecule.

& 11-Hydroxyaporphine (**13**) has been reported[14] to have similar but somewhat weaker dopamine receptor-stimulating activity compared to apomorphine.

Experimental Section

All melting points were obtained on a calibrated Thomas-Hoover Unimelt capillary melting point apparatus using open capillaries. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Nmr spectra were recorded with Varian A-60A and HA-100D spectrophotometers (Me_4Si). Tlc's were performed on fluorescent silica gel G plates, spots detected by uv or exposure to I_2 vapor. Optical rotations were determined with a Perkin-Elmer polarimeter, Model 141.

(6a*R*)-10,11-Methylenedioxyaporphine Hydrochloride (2). To a solution of 12.0 g (0.0384 mol) of apomorphine hydrochloride hemihydrate in 100 ml of DMSO under N_2 was added a solution of 4.8 g of NaOH in 50 ml of H_2O. The solution was warmed to 80° and 7.0 g of CH_2Br_2 added over 20 min. After stirring at 80° under N_2 for an additional 3 hr, the reaction mixture was cooled, poured on 400 ml of ice H_2O and filtered. The filtered solid was washed (H_2O), dried at 50° (50 mm), and dissolved in 200 ml of EtOAc. Some material which did not dissolve in EtOAc was filtered off. The solution was dried (Na_2SO_4), filtered, and concentrated to 5.8 g of an oil which was then chromatographed on 200 g of silica gel. Elution with 5% MeOH-$CHCl_3$ gave 4.1 g of crude product which was purified further by conversion to the HCl salt with EtOH–anhydrous HCl in MeOH. Precipitation with EtOAc gave the HCl: 3.7 g (30.5%); mp 273–279° dec; darkens at 253°; homogeneous on tlc (5% MeOH-$CHCl_3$) as the base. An analytical sample, same melting point, was obtained by recrystallization from MeOH-EtOAc: $[\alpha]^{24}D$ −31.6° (*c* 1.5, MeOH-H_2O). *Anal.* ($C_{18}H_{17}NO_2$·HCl) C, H, N.

(6a*R*)-10-Hydroxyaporphine Hydrochloride (3). Sodium spheres were added to a solution of 3.6 g (0.0114 mol) of (6a*R*)-10,11-methylenedioxyaporphine hydrochloride in 25 ml of THF and 200 ml of NH_3(l) until the blue color due to excess Na persisted for 2 hr. After evaporation of the NH_3, 10 ml of CH_3OH followed by H_2O was added and the crude product extracted into EtOAc. The extract was dried (Na_2SO_4), filtered, and concentrated. The residue, 2.0 g, was chromatographed on 18 g of silica gel and the product eluted with 5% CH_3OH-$CHCl_3$. The HCl, mp 252° dec, darken at 232°, 1.65 g (50.3%), was obtained by dissolving the base in MeOH, adding excess EtOAc–anhydrous HCl followed by precipitation with EtOAc, homogeneous on tlc (5% MeOH-$CHCl_3$) as the base: $[\alpha]^{24}D$ −82.3° (*c* 0.06, H_2O). *Anal.* ($C_{17}H_{17}NO$·HCl) C, H, N.

9-Hydroxyaporphine Hydrobromide (4). A solution of 450 mg (1.70 mmol) of 9-methoxyaporphine[12] in 15 ml of 48% HBr and 15 ml of HOAc was stirred at reflux under N_2 for 18 hr. The solution was concentrated under reduced pressure to dryness, redissolved in 10 ml of H_2O, and reconcentrated to dryness under vacuum. This was repeated once more with 10 ml of H_2O and then twice with 10 ml of absolute EtOH. The residue was recrystallized from MeOH-EtOAc to give 100 mg (17.7%) of 9-hydroxyaporphine hydrobromide: mp 267.9–269.9° dec; homogeneous on tlc (5% MeOH-$CHCl_3$) as the base. *Anal.* ($C_{17}H_{17}NO$·HBr) C (+0.65), H, N.

3-Hydroxy-2-nitrobenzaldehyde. A total of 200 g (1.64 mol) of *m*-hydroxybenzaldehyde was added in portions to a well-stirred mixture of 184 ml of concentrated HNO_3 and 816 ml of H_2O at a rate which maintained a reaction temperature of 50–55°. Addition usually required 1.5 hr. After addition was complete, stirring was continued until the reaction temperature dropped to 30° (about 4 hr). The reaction mixture was then poured into 500 ml of ice H_2O; the crude product was filtered, washed (H_2O), and air-dried. The crude product was stirred 30 min with 720 ml of C_6H_6 at reflux, cooled to 45°, and filtered to remove the insoluble 6-nitro derivative (57 g). After concentrating the filtrate to dryness under reduced pressure, the residue was steam distilled to remove 31 g of the 4-nitro derivative in 10 l. of distillate. Filtration of the steam distillation residue gave the crude desired 2-nitro derivative which was purified best by silica gel chromatography. An 8-cm o.d. column containing 2 kg of silica gel was charged with 75 g of crude 2-nitro derivative and eluted with C_6H_6 until tlc ($CHCl_3$) showed that only the desired 2-nitro derivative was being eluted. The elution solvent was then changed to $CHCl_3$ to elute a total of 17.5 g of pure 2-nitro derivative; mp 152.5–155.0°

(lit.[25] 157°); homogeneous by tlc ($CHCl_3$) and nmr ($CDCl_3$).

3-Methoxy-2-nitrobenzaldehyde (6). A solution of 7.0 g (0.042 mol) of 3-hydroxy-2-nitrobenzaldehyde, 1.68 g of NaOH, and 6 ml of dimethyl sulfate in 50 ml of H_2O and 50 ml of THF was stirred at room temperature. Additional 10% NaOH solution was added when necessary to maintain basic conditions. After 2 hr, more dimethyl sulfate (2 ml) was added and the mixture stirred an additional 4 hr. After concentrating the reaction mixture under reduced pressure at 25° to remove most of the THF, the precipitated solid was removed by filtration. Recrystallization from HOAc gave 5.1 g (67.0%) of product: mp 94–98° (lit.[26] mp 102°); homogeneous on tlc (50% C_6H_6–$CHCl_3$) and nmr ($CDCl_3$).

3-Methoxy-2-nitrobenzyl Alcohol (7). $NaBH_4$, 7.0 g, was added over 10 min to a stirred solution of 26.0 g (0.144 mol) of 3-methoxy-2-nitrobenzaldehyde in 200 ml of THF and 50 ml of H_2O. Occasional cooling was necessary to keep the reaction temperature below 35°. After 1 hr, 2.0 g of $NaBH_4$ was added and stirring continued for another 2 hr. The reaction mixture was then diluted with H_2O and concentrated under reduced pressure to remove most of the THF. The crude product was extracted into Et_2O, washed (H_2O), dried (Na_2SO_4), filtered, and concentrated to give the alcohol: 25.8 g (97.8%); mp 64.4–68.4°; soften at 55°. An analytical sample, mp 66.0–68.4°, homogeneous on tlc (50% C_6H_6–$CHCl_3$), was obtained by recrystallization from C_6H_6–hexane. *Anal.* ($C_8H_9NO_4$) C, H, N.

3-Methoxy-2-nitrobenzyl Chloride (8). A solution of 25.8 g (0.14 mol) of the alcohol and 40.7 g of $(C_6H_5)_3P$ in 600 ml of CCl_4 was stirred at reflux for 12 hr. After filtering and washing the precipitate with C_6H_6, organic solvents were removed under reduced pressure. The residue was dissolved in a minimum amount of C_6H_6 and chromatographed on 500 g of silica gel. Elution with 3.4 l. of C_6H_6 gave 25.0 g (87.9%) of the benzyl chloride: mp 73.5–75.5°; homogeneous on tlc (50% C_6H_6–$CHCl_3$). An analytical sample, same melting point, was obtained by recrystallization from C_6H_6–hexane. *Anal.* ($C_8H_8ClNO_3$) C, H, N.

2-Benzoyl-1-cyano-1-(3-methoxy-2-nitrobenzyl)-1,2-dihydroisoquinoline (9). To a solution of 4.76 g (0.0236 mol) of 3-methoxy-2-nitrobenzyl chloride and 6.15 g (0.0236 mol) of the Reissert compound, 2-benzoyl-1-cyano-1,2-dihydroisoquinoline, in 40 ml of dry DMF under N_2 at ice bath temperature was added, in one portion, 1.2 g of a 51% dispersion of sodium hydride in mineral oil. After stirring at 0–5° for 30 min, the reaction mixture was allowed to stir at room temperature for 18 hr. H_2O was added to precipitate the product which was filtered, washed (Et_2O), and dried to give 8.1 g (80.7%) of alkylated Reissert compound, mp 169.7–173.2°. An analytical sample, mp 172.7–174.7°, was obtained by recrystallization from EtOAc–hexane. *Anal.* ($C_{25}H_{19}N_3O_4$) C, H, N.

1-(3-Methoxy-2-nitrobenzyl)isoquinoline (10). To a rapidly stirred mixture of 24.5 g (0.0576 mol) of **9** and 245 ml of dry DMF under N_2 at room temperature, 45 ml of Triton B was added in a stream. After stirring for 30 min, the reaction mixture was poured on ice. The product was filtered and dried to give 16.8 g (99.1%) of the isoquinoline **10**: mp 120.5–124.5°; softens at 115.5°. An analytical sample, mp 127.5–130.0°, softens at 124.5°, homogeneous on tlc (2% MeOH–$CHCl_3$), was obtained after two recrystallizations from C_6H_6–hexane. *Anal* ($C_{17}H_{14}N_2O_3$) C, H, N.

The quarternary methiodide of **10**, mp 198.5–201.5° dec, was obtained by heating a solution of 17.5 g (0.0595 mol) of **10** and 35 ml of CH_3I in 100 ml of Me_2CO at reflux for 20 hr. After cooling, the quarternary salt was precipitated by the addition of Et_2O.

11-Methoxyaporphine Hydrochloride (12). A total of 24.0 g (0.055 mol) of 1-(3-methoxy-2-nitrobenzyl)-2-methylisoquinolinium iodide was reduced to the tetrahydroisoquinoline in four batches of 6 g each. A solution of 6.0 g of the quarternary methiodide in 130 ml of MeOH and 90 ml of H_2O was hydrogenated with 0.4 g of PtO_2 catalyst at an initial pressure of 40 lb/in.^{2} until H_2 uptake was complete. Catalyst was removed by filtration and the filtrate concentrated to dryness under reduced pressure. The residue was dissolved in a minimum amount of absolute EtOH, excess EtOH–anhydrous HCl solution was added, and the mixed HI–HCl salt precipitated with EtOAc.

The mixed salt, 15.9 g, was dissolved in 100 ml of HOAc and cooled in an ice bath and 9.0 ml of concentrated H_2SO_4 was added. A solution of 3.45 g of $NaNO_2$ in 20 ml of H_2O was added over 0.5 hr to the tetrahydroisoquinoline compound while the temperature was maintained at 5–10°. After addition was complete, the reaction mixture was stirred at 0° for an additional 0.5 hr. Sulfamic acid, 0.5 g, and 150 ml of cold 3 *N* H_2SO_4 were added and the mixture was allowed to warm to room temperature over 20 min and then warmed on the steam bath for 0.5 hr. Zinc dust, 10 g, was added portionwise and after stirring at steam bath temperature for 0.5 hr, the reaction mixture was cooled and filtered. Concentrated NH_4OH was added to make the reaction mixture basic and the crude product extracted with three 150-ml portions of Et_2O. After drying ($MgSO_4$), filtering, and concentrating under reduced pressure, the residue was taken up in absolute EtOH and acidified with excess EtOH–anhydrous HCl solution, and the product precipitated with EtOAc to give 2.91 g (17.5%) of 11-methoxyaporphine hydrochloride: mp 249–251° dec; darkens at 242°; homogeneous on tlc (5% MeOH–$CHCl_3$) as the base. *Anal.* ($C_{18}H_{19}NO$·HCl) C, H, N.

11-Hydroxyaporphine Hydrobromide (13). The methyl ether hydrochloride **12**, 1.0 g (3.31 mmol), was converted to free base with 10% NaOH and extraction with Et_2O. After removal of Et_2O under reduced pressure, the residue was dissolved in 50 ml of 48% HBr and heated at reflux under N_2 for 6 hr. The solution was then concentrated under reduced pressure to dryness, redissolved in 40 ml of H_2O, and reconcentrated to dryness. This was repeated once more with 40 ml of H_2O and then twice with 40 ml of absolute EtOH. The residue was recrystallized from MeOH–EtOAc to give 0.78 g (70.9%) of the phenol hydrobromide **13**: mp 288–296° dec; homogeneous on tlc (5% MeOH–$CHCl_3$) as the base. *Anal.* ($C_{17}H_{17}NO$·HBr) C, H, N.

Demethylation of (6a*R*)-10,11-Dimethoxyaporphine (14) to Apocodeine (16). A. Sodium Thioethoxide. To a solution of 100 mg (0.34 mmol) of the free base of **14** in 3 ml of dry DMF under N_2 was added 0.1 ml (80 mg, 1.3 mmol) of EtSH followed by 32 mg (0.71 mmol) of a 53% dispersion of NaH in mineral oil. After the NaH had all reacted, the reaction mixture was immersed in an oil bath maintained at 100–110° and stirred under N_2. After 4 hr, tlc (5% MeOH–$CHCl_3$) of a basified reaction mixture aliquot showed no dimethyl ether **14** remaining, a major product with the same R_f as apocodeine, and a small amount of apomorphine. The reaction mixture was then cooled, acidified with 2 *N* HCl, and made basic with excess saturated $NaHCO_3$ solution and the product was extracted into EtOAc. After drying (Na_2SO_4), filtering, and concentrating, the residue was chromatographed on a 2000-μ silica gel GF preparative plate (Analtech) with 5% MeOH–$CHCl_3$. The band at R_f 0.4–0.5 was removed with 20% MeOH–$CHCl_3$ and concentrated. The residue was dissolved in MeOH and treated with excess anhydrous HCl–EtOH solution. EtOAc was added and the solution concentrated under reduced pressure at 50° until solid began to form. After cooling, filtering, and drying, 70 mg (65%) of apocodeine hydrochloride, mp 255–259° dec, was obtained. This sample was identical with an authentic sample of apocodeine hydrochloride as determined by tlc, mixture melting point, ir (KBr pellet), and nmr (D_2O).

B. Sodium Thioisopropoxide. Substitution of 0.1 ml (80 mg, 1.05 mmol) of isopropyl mercaptan for EtSH in procedure A gave, after 3 hr of reaction, 56 mg (52%) of apocodeine hydrochloride, mp 257–262° dec.

C. Sodium Thio-*tert*-butoxide. Substitution of 0.1 ml (80 mg, 0.89 mmol) of *tert*-butyl mercaptan for EtSH in procedure A gave, after 3.5 hr of reaction, 69 mg (64%) of apocodeine hydrochloride, mp 258–262° dec.

D. 20% Hydrochloric Acid. A solution of 100 mg (0.34 mmol) of the dimethyl ether base in 5 ml of 20% HCl was heated in an oil bath at 120° for 12 hr. After concentration under reduced pressure, 3 ml of H_2O was added and the solution reconcentrated. Excess saturated $NaHCO_3$ solution was added to the residue and the product extracted into EtOAc. After chromatography on a preparative silica plate and conversion to the HCl as described in procedure A, 38 mg (35%) of apocodeine hydrochloride, mp 260–264° dec, was obtained.

9,10-Dihydroxyaporphine Hydrobromide (5). A solution of 400 mg (1.20 mmol) of 9,10-dimethoxyaporphine hydrochloride[13] in 20 ml of 48% HBr and 20 ml of HOAc was stirred at reflux under N_2 for 18 hr. The solution was concentrated under reduced pressure to dryness, redissolved in 10 ml of H_2O, and reconcentrated to dryness under vacuum. This was repeated twice more with 10 ml of absolute EtOH. The residue was recrystallized from EtOH to give 9,10-dihydroxyaporphine hydrobromide, decomposed at 297° with prior darkening at 250°. *Anal.* ($C_{17}H_{17}NO_2$·HBr) C (−0.45), H, N.

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Aporphines. 11. Synthesis and Dopaminergic Activity of Monohydroxyaporphines. Total Synthesis of (±)-11-Hydroxyaporphine, (±)-11-Hydroxynoraporphine, and (±)-11-Hydroxy-*N*-*n*-propylnoraporphine†

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The synthesis of a series of racemic aporphines functionally substituted on the 11 position with either OH or OCH_3 and on the nitrogen atom with H, CH_3, n-C_3H_7, or $CH_2C_6H_5$ (**3a–h**) is described. The method used for the synthesis of (±)-**3** involved a Reissert alkylation–Pschorr cyclization route. The synthesis of the noraporphine **3d** and **3h** involved the catalytic dealkylation of the *N*-benzylaporphine **3b**. The dopaminergic activity of the 11-substituted aporphines **3d–f,h**, the 10 substituted aporphines **5a,b**, and the 7-hydroxyaporphine **4a** and 7-hydroxynoraporphine **4b** was evaluated in comparison with (−)-apomorphine and (−)-apocodeine by measuring the rotational behavior of rats with unilateral lesions produced by the intracerebral injection of 6-hydroxydopamine. The pharmacological results showed that dopaminergic activity can reside in monohydroxyaporphines substituted in the 11 position and in the 10 position provided the *N*-*n*-propyl group is present. The finding that (+)-**3e** and -**5b** are active is an indication that a catechol system is not an absolute requirement for dopaminergic activity in such aporphines as apomorphine. In agreement with previous work, *N*-*n*-propyl derivatives of the hydroxylated aporphines were more active than the corresponding parent compounds.

The interest in apomorphine [(−)-**1**] as a potentially useful drug for the treatment of Parkinson's disease and related neurologic diseases is due to its tremor inhibitory effects, its ability to stimulate central dopamine (DA) receptors, and its structural relationship to dopamine.[2]

In our previous studies involving functionally substituted aporphines, we described the successful total synthesis of (±)-apomorphine [(±)-**1**], (±)-apocodeine [(±)-**2**], (±)-*N*-*n*-propylnorapomorphine, and (±)-*N*-*n*-propylnorapocodeine.[3a] These aporphines were substituted on the nitrogen atom and on the 10 and 11 position. The procedure was applicable to the synthesis of aporphines not derivable from the naturally occurring opium alkaloids (*i.e.*, morphine and codeine). In continuing these studies[3b] we investigated the structure–activity relationship of such aporphine derivatives as 9,10-dihydroxyaporphines (isoapomorphine), 1,2-dihydroxyaporphines, and 1,2,9,10-tetrahydroxyaporphines. It was of interest to determine the effects produced when the phenolic function in the 10 position of apomorphine was eliminated while varying the substituent on the nitrogen. The synthesis of the 11-hy-

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