chemistry and Lani Russell and Nicole Grinder for preparing the manuscript.

Registry No. **5a**, 110706-41-7; **5a**·2HCl, 123621-18-1; **5b**, 123593-76-0; **5b**·2HCl, 123594-09-2; **5c**, 123593-77-1; **5c**·2HCl, 123594-10-5; **5d**, 123593-78-2; **5d**·2HCl, 123594-11-6; **5e**, 123593-79-3; **5e**·2HCl, 123594-12-7; **5f**, 123593-80-6; **5f**·2HCl, 123594-13-8; **5g**, 123593-81-7; **5g**·2HCl, 123594-14-9; **5h**, 123593-82-8; **5h**·2HCl, 123594-15-0; **5i**, 123593-83-9; **5i**·2HCl, 123594-16-1; **5j**, 123593-84-0; **5j**·2HCl, 123594-17-2; **5k**, 123593-85-1; **5k**·2HCl, 123594-18-3; **5l**, 123593-86-2; **5l**·2HCl, 123594-19-4; **5m**, 123593-87-3; **5m**·2HCl, 123594-20-7; **5n**, 123593-88-4; **5n**·2HCl, 123594-21-8; **5o**, 123593-89-5; **5o**·2HCl, 123594-22-9; **5p**, 123593-90-8; **5p**·2HCl, 123621-19-2; **5q**, 123593-91-9; **5q**·2HCl, 123594-23-0; **5r**, 123593-92-0; **5r**·2HCl, 123594-24-1; **5s**, 123593-93-1; **5s**·2HCl, 123594-25-2; **5t**, 123593-94-2; **5t**·2HCl, 123594-26-3; **5u**, 123593-95-3; **5u**·2HCl, 123594-27-4; **5v**, 123593-96-4; **5v**·2HCl, 123594-28-5; **5w**, 123593-97-5; **5w**·2HCl, 123594-29-6; **5x**, 123593-98-6; **5x**·3HCl, 123594-30-9; **6a**, 110706-35-9; **6a**·2HCl, 123594-31-0; **6b**, 110706-37-1; **6b**·2HCl, 123594-32-1; **7a**, 91-21-4; **7b**, 4965-09-7; **7c**, 25939-81-5; **7d**, 87443-63-8; **7e**, 41565-85-9; **7f**, 29726-60-1; **7g**, 123593-99-7; **7h**, 123594-00-3; **7i**, 123594-01-4; **7j**, 73075-43-1; **7k**, 123594-02-5; **7l**, 33537-99-4; **7m**, 75416-50-1; **7n**, 89315-57-1; **7o**, 75416-53-4; **7p**, 61563-24-4; **7q**, 103030-70-2; **7r**, 76019-13-1; **7s**, 123594-03-6; **7s**·HCl, 123594-05-8; **7t**, 52759-09-8; **7u**, 1745-07-9; **7v**, 88207-92-5; **7x**, 115955-90-3; **8a**, 496-12-8; **8b**, 123594-04-7; **9**, 123594-06-9; **10**, 123594-07-0; **10**·HCl, 123594-33-2; **11**, 123594-08-1; 2-(chloromethyl)-2-imidazoline hydrochloride, 13338-49-3; *N*-acetyl-2,5-dimethoxyphenethylamine, 106274-40-2; 5,8-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 105901-26-6; 3-chlorophthalic anhydride, 117-21-5; 3-chlorophthalimide, 51108-30-6; 5-nitro-1,2,3,4-tetrahydroisoquinoline, 41959-45-9; [^{3}H]yohimbine, 146-48-5; [^{3}H]idazoxan, 79944-58-4; [^{3}H]prazosin, 19216-56-9.

Aporphines as Antagonists of Dopamine D-1 Receptors

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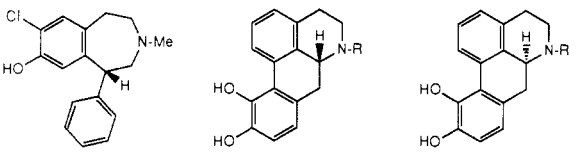
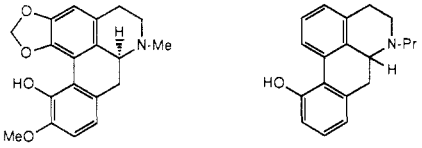
The aporphine alkaloids are a class of compounds known to possess activity at both D-1 and D-2 dopamine receptors. (*R*)-Apomorphine and (*S*)-bulbocapnine are examples of compounds which have agonist and antagonist activity, respectively, at D-1 receptors. A series of optically pure aporphines was synthesized and their activity at D-1 and D-2 dopamine receptors was studied. The (*R*)-aporphines uniformly had greater affinity for both D-1 and D-2 receptors than their *S* antipodes. Dihydroxy compound (*R*)-apomorphine, in accord with previous studies, was found to be a D-1 agonist. Aporphines possessing a single hydroxy group at C-11 are antagonists at the D-1 receptor. The corresponding methoxy compounds are virtually inactive at dopamine receptors. The most potent compounds, (*R*)-11-hydroxyaporphine (*R*-**14**) and (*R*)-10-bromo-11-hydroxyaporphine (*R*-**26**), are more potent than bulbocapnine as D-1 antagonists but are not as selective. A model for binding of aporphines to the D-1 receptor was formulated in which binding interactions between the receptor and the basic nitrogen and the C-11 hydroxy group of the aporphine are required for high-affinity binding to the receptor. The absolute configuration at C-6a determines the orientation of the N-6 lone pair and binding is optimal for the 6a*R* series. The agonist or antagonist activity of an aporphine is determined by the presence or absence, respectively, of a hydroxy group at C-10. A hydrophobic binding site may be present and may account for the high antagonist activity of (*S*)-bulbocapnine.

Studies with dopaminergic agents have led to the identification of two distinct classes of central nervous system (CNS) dopamine receptors, D-1 and D-2. The D-1 receptors are located postsynaptically and are positively linked to adenylate cyclase as its second messenger. In contrast, D-2 receptors are located both pre- and postsynaptically and either are not coupled or are negatively coupled to adenylate cyclase.[1] While much research has concentrated on the function of D-2 receptors in the CNS, until relatively recently, little has been known of the significance of D-1 receptors. The discovery of the D-1 selective antagonist SCH-23390 (**1**) has greatly facilitated research on the function of D-1 receptors in the CNS.[2]

It is now known that functional interaction exists between D-1 and D-2 receptors in the CNS. In dopamine-depleted mice and rats, administration of either a D-1 or a D-2 agonist alone is ineffective in producing stereotypic behavior and increases in locomotor activity. However, when these agents are given in combination, similar increases in these behavioral indices are seen as when (*R*)-apomorphine (**2a**), an agonist at both D-1 and D-2 receptors, is given.[3-5] Similarly, climbing behavior in





normal mice identical with that induced by (*R*)-apomorphine is induced by concomitant administration of a D-1 and a D-2 agonist but not by either treatment alone.[6] Locomotor activity and stereotypy induced by either (*R*)-apomorphine or a selective D-1 or D-2 agonist can be blocked by antagonists selective for either D-1 or D-2 receptors.[7]

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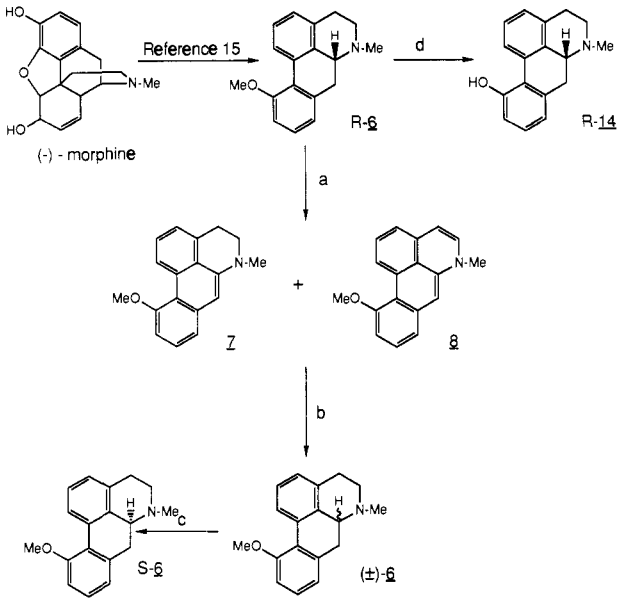
Scheme I[a]

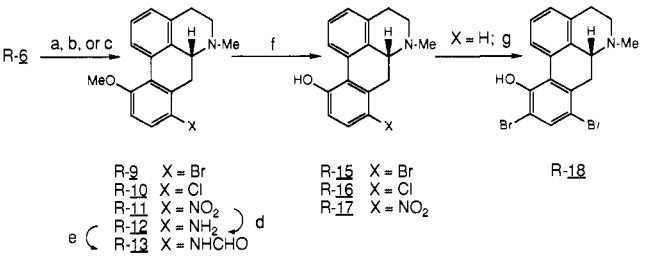


[a] (a) 10% Pd/C, MeCN, Δ; (b) H_2, PtO_2, AcOH; (c) (-)-tartaric acid, recrystallization, NH_4OH; (d) 48% HBr, Δ.

The development of antagonists selective for the D-1 receptor may prove important for the treatment of schizophrenia. While the antipsychotic activity of currently used neuroleptics is well correlated with the affinity of these compounds for the D-2 receptor,[8] studies with 1 indicate that selective antagonists of the D-1 receptor may also possess antipsychotic activity. Compound 1 is active in a number of assays predictive of antipsychotic activity. It is effective in blocking conditioned-avoidance behavior in rats and squirrel monkeys.[9] Compound 1 also blocks apomorphine- and pergolide-induced stereotypy in rats,[7,9] blocks apomorphine-induced climbing in mice,[6] and blocks methamphetamine-induced lethality in grouped mice.[9] Compound 1 is also effective in inducing catalepsy in rats. In addition, a series of antipsychotics has been shown to be effective inhibitors of adenylate cyclase in mice in vivo.[10] The possibility that D-1-selective antagonists may be useful for the treatment of schizophrenia led us to look at a series of aporphines for their ability to block D-1 receptors.

The dopaminergic activity of a number of aporphine alkaloids has been well recognized. (*R*)-apomorphine and both (*R*)- and (*S*)-*n*-propylnorapomorphine (**2b** and **3b**, respectively) are agonists at both D-1 and D-2 receptors.[11a,12] (*S*)-apomorphine (**3a**) has been reported to be an antagonist at both D-1 and D-2 receptors,[11a] while (*S*)-bulbocapnine (**4**) has been reported to be a D-1 receptor antagonist.[13] Recently, (*R*)- and (*S*)-11-hydroxy-*N*-(*n*-propyl)noraporphine (*R*-**5** and *S*-**5**, respectively) have been reported to possess agonist and antagonist activity, respectively, at dopamine receptors.[14]

Scheme II[a]



[a] (a) *N*-bromosuccinimide, CF_3COOH; (b) *N*-chlorosuccinimide, CF_3COOH; (c) $NaNO_3$, CF_3COOH; (d) H_2, Pd/C; (e) $HCOOCOCH_3$; (f) 48% HBr, Δ; (g) NaH, *N*-bromosuccinimide.

We wished to investigate the effect of the nature and position of D-ring substituents of a series of aporphines on their actions at D-1 receptors. The enantiomers of apomorphine[11,12] and 11-hydroxy-*N*-(*n*-propyl)noraporphine[14] differ greatly in their pharmacology. Hence it was necessary to synthesize and test the aporphines in this study in their optically pure forms, allowing additional conclusions to be reached on the effect of absolute configuration on pharmacologic activity.

Chemistry

All of the aporphines in this study were prepared and tested in their optically active forms. The 6a(*R*)-aporphines were prepared from the known (*R*)-(-)-11-methoxyaporphine (*R*-**6**), while (*S*)-(+)-11-methoxyaporphine (*S*-**6**) served as the intermediate for the synthesis of all of the 6a(*S*)-aporphines. *R*-**6** was prepared from (-)-morphine by essentially the method of Ram and Neumeyer[15] (Scheme I). The optical rotation of the hydrochloride salt of *R*-**6** obtained by this route ranged from $[\alpha]_D$ -97.5° to -99.1° (*c* = 1.0, MeOH).

Compound *S*-**6** was prepared from *R*-**6** using a racemization/resolution sequence. Oxidation of *R*-**6** over palladium on carbon in refluxing acetonitrile provided the didehydroaporphine **7** in 74% yield.[12] Upon prolonged heating, varying amounts of tetradehydro product **8** were also formed. Hydrogenation of **7** or mixtures of **7** and **8** over platinum oxide yielded the racemic aporphine **6** in good yield. Resolution of the (-)-tartaric acid salt of racemic **6** by recrystallization from ethanol provided *S*-**6**. The optical rotation of the resulting hydrochloride salt of *S*-**6** was $[\alpha]_D$ +98.6° (*c* = 1.0, MeOH).

The optical purity of this material was assayed by using the HPLC method reported by Ram and Neumeyer.[15] The methyl ether of a sample of *R*-**6** (*R*-**6**·HCl: $[\alpha]_D$ -99.1° (*c* = 1.0, MeOH) was cleaved and the resulting phenol was derivatized using (-)-α-methylbenzyl isocyanate. Analysis of the resulting urethane by reverse-phase HPLC indicated a diastereomer ratio of 1:99, indicating an optical purity of 98% ee. Similar analysis of a sample of *S*-**6** (*S*-**6**·HCl: $[\alpha]_D$ +98.6° (*c* = 1.0, MeOH)) gave a diastereomer ratio of 98.5:1.5, indicating optical purity of 97% ee.

Subsequent transformations were performed with optically active *R*-**6** and *S*-**6** as starting materials.[16] Reaction of *R*-**6** with *N*-bromosuccinimide in trifluoroacetic acid provided *R*-**9** as the sole monobromination product in 75% yield (Scheme II). NMR analysis of the product indicated

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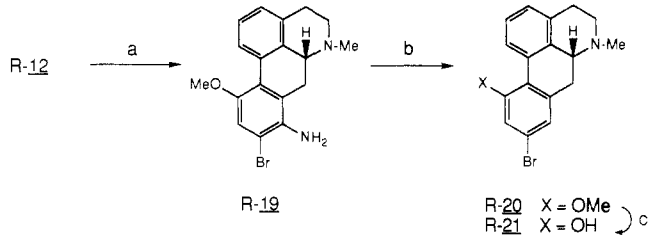
(16) The chemistry discussed below and pictured in the schemes is exemplified for the *R* series only. Analogous chemistry provided the compounds of the *S* series.

Scheme III[a]



[a] (a) *N*-bromosuccinimide, CF_3COOH; (b) (i) $NaNO_2$, 85% H_3PO_4, (ii) H_3PO_2; (c) 48% HBr, Δ.

that the bromine had been incorporated into the D ring and that the remaining two protons in the D ring were ortho to one another (J = 9.9 Hz). Irradiation of the methoxy signal at 3.82 ppm resulted in a large NOE enhancement of the doublet at 6.71 ppm (one of the D-ring protons), indicating that this proton is ortho to the methoxy group. Hence the signal at 6.71 ppm must be due to the proton at C-10 and the bromine must have been incorporated at C-8.[17]

Similarly, R-*6* was found to undergo electrophilic chlorination and nitration upon reaction with *N*-chlorosuccinimide and sodium nitrate, respectively, in trifluoroacetic acid to provide *R*-**10** and *R*-11. In each case, the electrophile was found to be incorporated in good yield and with high regiospecificity at C-8 of the aporphine system. This substitution pattern is the result of attack of the electrophile by the more electron-rich aromatic ring at the position para to the methoxy group. It is notable that none of the 10-substituted product, resulting from attack ortho to the methoxy group, was observed. The 8-aminoaporphine *R*-**12** was obtained by hydrogenation of *R*-11 over palladium on carbon.

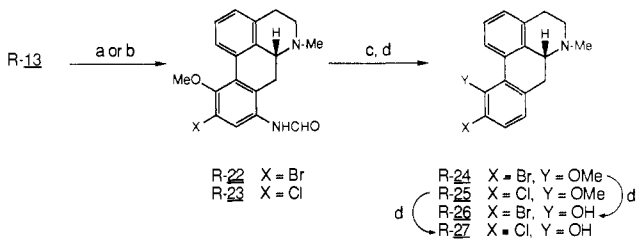
Bromination of the 8-aminoaporphine under the usual conditions provided the C-9 brominated product *R*-**19**. Removal of the amino group by diazotization and reduction with hypophosphorus acid yielded *R*-**20** (Scheme III). The bromine was shown to have been incorporated at C-9 by demonstration of an NOE enhancement of the aromatic proton at 7.10 ppm upon irradiation of the methoxy singlet of *R*-**20**.[17] Apparently, under these bromination conditions, the regiochemistry of electrophilic substitution of the D ring is controlled by the amino group rather than the methoxy group.

It was expected that for the bromination of the nitroanisole *R*-11 the directing effects of the methoxy and nitro substituents would lead to incorporation of the bromine at C-10. In the event, however, bromination under the usual conditions led only to (*R*)-8-nitro-3-bromo-11-methoxyaporphine. Apparently the introduction of the nitro group at C-8 decreases the electrophilic nature of the D ring sufficiently that the bromination occurs in the A ring.

In order to direct bromination into the C-10 position, it was required that the electron-donating properties of the amino group at C-8 be decreased, but not to the extent that the D ring becomes so electron deficient that bromination occurs in the A ring. This was accomplished by formylation of *R*-**12** to give formamide *R*-**13**. Bromination of *R*-**13** with *N*-bromosuccinimide in trifluoroacetic acid gave *R*-**22**

(17) A small NOE enhancement of the most downfield aromatic signal was also observed during irradiation of the methoxy singlet of this compound. Decoupling experiments demonstrated that this signal is from one of the protons on the A ring. Because of the proximity to the methoxy group, this signal must be due to the proton at C-1.

Scheme IV[a]



[a] (a) *N*-bromosuccinimide, CF_3COOH; (b) *N*-chlorosuccinimide, CF_3COOH; (c) (i) 10% HCl, Δ, (ii) $NaNO_2$, H_3PO_4, (iii) H_3PO_2; (d) 48% HBr, Δ.

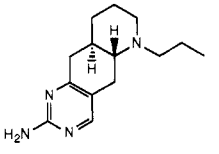
in 44% yield accompanied by the 3,10-dibrominated product in 20% yield. Hydrolysis of the formamide group followed by reductive cleavage of the amino group as before gave *R*-**24** (Scheme IV). Upon irradiation of the methoxy singlet of *R*-**24**, no NOE enhancement of either of the D-ring protons was observed, indicating that the bromine was incorporated at C-10.[17] 10-Chloro compound *R*-**25** was synthesized analogously.

The methyl ethers of these compounds were cleaved with refluxing 48% HBr to provide the corresponding phenols for pharmacologic evaluation. 8,10-Dibromo-11-hydroxyaporphine (*R*-**18**) was prepared by direct bromination of the sodium salt of *R*-14 (formed by treatment with sodium hydride) with *N*-bromosuccinimide.

Pharmacology

The potency and selectivity of the compounds in this investigation were evaluated by their in vitro affinity for the D-1 and D-2 receptors by using ligand displacement assays. The ability of the compounds under study to displace [^{3}H]SCH-23390[18] and [^{3}H]spiperone[19] was used to assess their in vitro affinity for D-1 and D-2 receptors, respectively.

The ability of these compounds to stimulate adenylate cyclase in rat retinal tissue was used as an in vitro functional assay of D-1 agonist activity.[20] (*R*)-Apomorphine served as a positive control for D-1 agonist activity. D-1 antagonist activity was determined in vitro by the ability of a compound to block the adenylate cyclase stimulation caused by 10 μM dopamine in rat retinal tissue. The known D-1 antagonists 1 and (*S*)-bulbocapnine were both effective in inhibiting adenylate cyclase activity under these conditions. The known D-2 agonist quinelorane (**28**)[21] had no effect on either basal or dopamine-stimulated



28

adenylate cyclase activity. Hence, while it has been dem-

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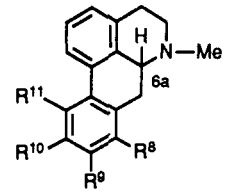
Table I



compound	R^8	R^9	R^{10}	R^{11}	absolute config[a]	in vitro binding (IC_{50}, nM)[b] [H^3]SCH-23390[c]	[H^3]spiperone[d]	adenylate cyclase[e] antagonist activity[f] 0.1 μM	10 μM	agonist activity[g]
(*R*)-apomorphine	H	H	OH	OH	R	432[18]	21 ± 10	–	–	91.5 ± 8.4
(*S*)-apomorphine	H	H	OH	OH	S	3620[h]	680 ± 108	–	42.3 ± 3.9	–
R-**6**	H	H	H	OMe	R	3276 ± 328	2162 ± 314	7.7 ± 6.2	31.7 ± 5.9	–
S-**6**	H	H	H	OMe	S	12100 ± 1196	829 ± 89	0.7 ± 4.6	0.0	–
R-**14**	H	H	H	OH	R	107 ± 11	58 ± 9	31.2 ± 1.7	87.8 ± 1.8	NS[i]
S-**14**	H	H	H	OH	S	5061 ± 515	2242 ± 266	0.8 ± 5.0	38.0 ± 2.4	NS
R-**15**	Br	H	H	OH	R	181 ± 9	449 ± 123	13.1 ± 3.1	83.3 ± 1.5	NS
S-**15**	Br	H	H	OH	S	8611 ± 1345	>10000	11.9 ± 4.9	79.4 ± 2.3	–
R-**16**	Cl	H	H	OH	R	561 ± 27	500 ± 105	12.6 ± 2.2	71.6 ± 2.3	–
R-**17**	NO_2	H	H	OH	R	–	–	7.2 ± 4.2	33.5 ± 3.0	–
R-**18**	Br	H	Br	OH	R	>1000	>1000	8.5 ± 3.8	45.9 ± 0.8	–
R-**21**	H	Br	H	OH	R	818 ± 34	2579 ± 619	5.3 ± 1.8	73.4 ± 3.3	NS
S-**21**	H	Br	H	OH	S	>1000	>1000	16.8 ± 1.8	3.2 ± 5.5	–
R-**26**	H	H	Br	OH	R	171 ± 15	664 ± 111	24.4 ± 2.9	87.8 ± 2.4	NS
S-**26**	H	H	Br	OH	S	3340[h]	2930 ± 342	9.8 ± 2.7	54.2 ± 4.8	–
R-**27**	H	H	Cl	OH	R	637 ± 102	803 ± 119	19.7 ± 3.5	82.0 ± 1.2	–
apocodeine	H	H	OMe	OH	R	13300[h]	2080 ± 247	–	5.7 ± 1.5	NS
bulbocapnine (**4**)					S	739 ± 62	14047 ± 340	24.4 ± 12.3	85.1 ± 5.0	–
SCH-23390 (**1**)						1.3 ± 0.2	>10000	86.0 ± 4.2[j]	89.7 ± 5.6[j]	–
quinelorane (**28**)						>10000	151 ± 23	–	6.8 ± 1.6[k]	NS[k]

[a] Absolute configuration at C-6a. [b] The values and standard errors reported were calculated by nonlinear regression analysis using the ALLFIT computer program of DeLean et al.[23] [c] Binding studies with [^{3}H]SCH-23390 were performed according to the method of W. Billard et al.[18] [d] Binding studies with [^{3}H]spiperone performed according to the method of J. E. Leysen et al.[19] [e] Adenylate cyclase assays were performed according to the method given by Riggs et al.[20] [f] D-1 antagonist activity was determined by performing the adenylate cyclase assay in the presence of 10 μM dopamine. Values in the table are percent inhibition of the 10 μM dopamine control in the presence of 0.1 μM and 10 μM of the test compound. [g] D-1 agonist activity is expressed as percent stimulation of adenylate cyclase over basal levels. The simulation by 10 μM dopamine is defined to be 100%. All compounds were tested for agonist activity at 10 μM except for **28**, which was tested at 100 μM. [h] This value is the average of two determinations. [i] NS = no significant stimulation over basal levels. [j] IC_{50} for SCH-23390 is approximately 0.003 μM. [k] Compound tested at 100 μM.

onstrated in some tissues that D-2 receptors are negatively coupled to adenylate cyclase,[22] D-2 agonists have no effect on adenylate cyclase activity in the rat retina.

Results and Discussion

The results of the pharmacologic testing are found in Table I. Of the compounds tested, only (*R*)-apomorphine possessed D-1 agonist activity. Its enantiomer, (*S*)-apomorphine, was found to have much less affinity for the D-1 receptor and, in accord with previous studies, was found to be a weak D-1 antagonist.[11] (*R*)-11-Hydroxyaporphine (*R*-**14**) possessed greater affinity for the D-1 receptor than (*R*)-apomorphine and, in contrast, is an antagonist at D-1 receptors. In fact, all of the (*R*)-11-monohydroxyaporphines studied were D-1 antagonists. This simple structure determinant for D-1 antagonist activity has not been recognized previously for the aporphines.

Racemic 11-hydroxyaporphine ((±)-**14**) has been previously prepared by Neumeyer and co-workers and was reported to be a dopamine agonist on the basis of the compound's ability to induce contralateral rotation in rats lesioned unilaterally with 6-hydroxydopamine.[24] Turning behavior in the 6-OHDA rat may be induced by either D-1 or D-2 agonists. D-1 antagonists will block rotation induced by a D-1 but not by a D-2 agonist.[25] One possible hypothesis is that 11-hydroxyaporphine induces turning behavior through activation of D-2 receptors which the D-1 antagonist activity of the compound is not able to block. However, results recently obtained at the Lilly Research Laboratories indicate that (*R*)-11-hydroxyaporphine (*R*-**14**) does not possess significant D-2 agonist activity as judged by its inability to decrease serum prolactin levels in the nonreserpinized rat at doses as high as 1.0 mg/kg ip.[26]

The *S* enantiomer of 11-hydroxyaporphine (*S*-**14**) had much decreased affinity for both the D-1 and the D-2 receptor. This correlation was borne out throughout the rest of the series. In each case where both enantiomers of a compound were prepared, the *R* enantiomer had greater affinity in vitro for both the D-1 and the D-2 receptor. In general, the *R*-enantiomer was also the more potent D-1 antagonist, although *R*-**15** and *S*-**15** were equipotent. It is not unexpected that one enantiomer should have higher affinity for the D-1 receptor. It is well-known that the D-1 receptor displays a high degree of stereoselectivity in its interaction with the aminotetralins,[27] benzazepines,[28] and 3-phenylisoquinolines.[29] In

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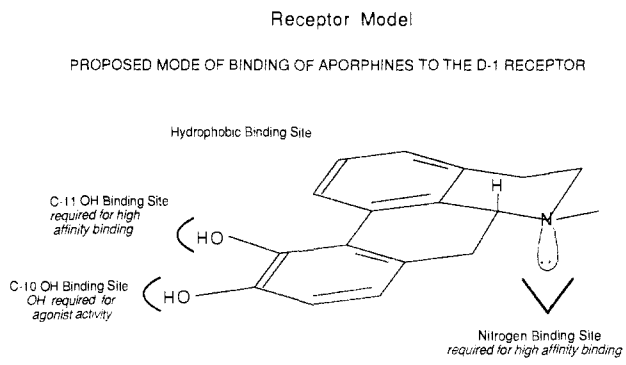

Figure 1.

light of the stereochemical preference displayed throughout this study for the *R* enantiomer, the high affinity and antagonist potency diplayed by (*S*)-bulbocapnine is surprising.

The methoxyaporphines *R*-**6** and *S*-**6** were both found to have greatly decreased affinity for the D-1 receptor relative to their 11-hydroxy counterparts. This would indicate that the C-11 hydroxy group is required for high affinity binding to the D-1 receptor. It is likely that the proton of the C-11 hydroxy group participates in a hydrogen bond with the receptor.

It was found that the D-1 affinity and antagonist potency as well as the D-1/D-2 selectivity could be modulated by the nature and position of substituents on the D ring of the aporphine system. In general, aporphines bearing substituents at C-10 (ortho to the hydroxy group) had higher affinity for the D-1 receptor than those aporphines additionally substituted at the C-8 (para) position. The C-9 (meta) substituted aporphines had the lowest affinity of all. The 8,10-dibromo compound also had greatly decreased activity. In light of the previously discussed agonist activity of the 10,11-dihydroxy compound (*R*)-apomorphine and the antagonist activity of the (*R*)-11-hydroxyaporphine, it is interesting to note that neither the chloro, bromo, nor methoxy substituents at C-10 are capable of mimicking a hydroxy group since all of those derivatives possess D-1 antagonist activity. (*R*)-11-Hydroxy-10-methylaporphine has recently been synthesized by Cannon and co-workers and was reported to be devoid of agonist activity in assays of D-2 dopamine activity.[30] The activity of this compound at D-1 receptors was not studied but the present studies would predict that it would be a D-1 antagonist. The compound in this study which is the most selective for the D-1 receptor is (*R*)-10-bromo-11-hydroxyaporphine (*R*-**26**). While this compound is as potent a D-1 antagonist as (*S*)-bulbocapnine, it is not as selective for the D-1 receptor.

Neumeyer et al. have proposed a model for the binding of aporphines to dopamine receptors.[12] The results of the present study allow the formulation of a receptor model (Figure 1) which confirms many of the features they propose and delineates some additional features of aporphine binding to D-1 receptors. The Neumeyer model postulates the existence of M_1 and M_2, binding sites for the C-11 and C-10 hydroxy groups, respectively; a binding site for the basic nitrogen; and M_3, a binding site for a C-2 hydroxy group, which they postulate causes a decrease in affinity for the receptor. The key features of the model which we propose are outlined in Figure 1 and are discussed in greater detail below.

The data presented here indicate that the interaction of the C-11 hydroxy group of the aporphine with the binding site on the receptor is critical for imparting affinity for the D-1 receptor. All of the (*R*)-11-monohydroxyaporphines investigated in this study possess D-1 antagonist activity as indicated by their affinity for the D-1 receptor and by their ability to inhibit the stimulation of adenylate cyclase induced by dopamine. The methyl ether of the parent compound is much weaker both in affinity and in antagonist activity than the corresponding hydroxy compound. Saari et al. have previously demonstrated that (±)-11-methoxyaporphine ((±)-**6**) was less active than the corresponding hydroxy compound ((±)-**14**) in inducing turning behavior in the 6-hydroxydopamine-lesioned rat.[31] It is likely the formation of a hydrogen bond between the hydroxy group of the ligand and a lone pair on the receptor is required for high affinity binding to the D-1 receptor.

Apparently the C-10 hydroxy group is necessary for receptor activation. Compounds such as apomorphine, which possess hydroxy groups at both C-10 and C-11, are D-1 agonists. The compounds prepared in this study which have only a single hydroxy group at C-11 have affinity for the receptor but no efficacy and hence are antagonists. It is interesting to note that substitution at C-10 with other substituents such as chloro, bromo, and methoxy did not lead to compounds which were able to activate the receptor. Presumably, the hydrogen of the hydroxy group is involved in either an intramolecular or intermolecular hydrogen bonding interaction that leads to the activated state of the receptor. The catechol functionality has been recognized by other groups as being critical in order for D-1 agonist activity to be expressed. It has been previously reported that catechol-substituted aporphine systems such as (*R*)-apomorphine,[13] (*R*)- and (*S*)-*N*-propylnorapomorphine,[12] and (*R*)-2,10,11-trihydroxyaporphine[32] all possess D-1 agonist activity. In the benzazepine system, catecholic systems such as SKF38393 and fenoldopam possess D-1 agonist activity, while the monohydroxybenzazepines SKF83509 and **1** are D-1 antagonists.[33] Catechol substitution on the 3-phenylisoquinoline nucleus also gives rise to D-1 agonists while the monohydroxy compounds are D-1 antagonists.[34]

A third critical feature which was found to influence the affinity of aporphines for the D-1 receptor is the absolute configuration at C-6a. In all cases where both enantiomers of a compound were tested, the *R* enantiomer had greater affinity for the D-1 receptor. With the exception of *R*-**15** and *S*-**15**, which were equipotent, the *R* enantiomer also was more potent as a D-1 antagonist in vitro than the *S* enantiomer. The stereospecificity of the D-1 receptor is well recognized. Presumably the absolute configuration at C-6a determines the orientation of the lone pair on the N-6 nitrogen and in only the *R* antipode is the orientation suitable for binding to the receptor. This finding may seem surprising in light of the previously reported D-1 antagonist activity of (*S*)-apomorphine[11] and (*S*)-bulbocapnine.[13] In

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accord with the other results of this study, however, (S)-apomorphine has a much lower affinity for the D-1 receptor than the R enantiomer. Presumably the inability of (S)-apomorphine to activate the D-1 receptor is due to the inappropriate orientation of the nitrogen lone pair.[35] (R)-Bulbocapnine has not been tested for activity at D-1 dopamine receptors, so it is unknown whether it has higher affinity than its enantiomer. The question of whether the lone pair is oriented axially or equatorially when the aporphine is bound to the D-1 receptor was not addressed in this study.[36]

One feature of the Neumeyer model which is not addressed by the present study is the existance of M_3, a binding site for a 2-hydroxy group.[12] This binding site was postulated to account for the decreased affinity of 2-hydroxy aporphines for dopamine receptors. While it is difficult to imagine how interaction with a binding site would lead to a decrease in affinity, an alternative explanation presents itself. The existence of a hydrophobic binding site on the D-1 receptor has been postulated.[35,37] This binding site has been proposed to interact with the A ring of the aporphines and with the phenyl side chain in the 3-phenylbenzazepines. It may be that the presence of the polar hydroxy group at C-2 decreases the affinity of the phenyl ring for this hydrophobic area of the receptor.[38] The presence of a hydrophobic binding site may also provide an explanation for the relatively high affinity and antagonist potency of (S)-bulbocapnine (4) at the D-1 receptor in spite of the fact that it has the S absolute configuration. The binding energy from interaction with the C-11 hydroxy binding site and the hydrophobic binding site may be sufficiently great that the weaker binding from the basic nitrogen in the S series is overcome. If no other factors are acting, one would expect that (R)-bulbocapnine would be a much more potent D-1 antagonist than (S)-bulbocapnine.

The D-1 antagonist activity and the D-1/D-2 selectivity of this series of aporphines can be modulated by the substituent pattern of the phenolic ring. (R)-11-Hydroxyaporphine was the most potent D-1 antagonist tested. The C-8 and C-10 monosubstituted phenols were roughly equipotent while those phenols bearing additional substitution at C-9 were less potent. The most selective compound for the D-1 receptor, as judged by in vitro ligand binding, was (R)-10-bromo-11-hydroxyaporphine. While some of the more potent compounds prepared in this study had antagonist potency at the D-1 receptor equal to or greater than that of (S)-bulbocapnine, none of these aporphines had selectivity for the D-1 receptor greater than that of (S)-bulbocapnine.

Experimental Section

General Experimental Procedures. All solvents and reagents were used as commercially available except tetrahydrofuran, which was distilled from sodium/benzophenone ketyl prior to use. Moisture and/or air sensitive reactions were run under a positive pressure of nitrogen. Melting points were determined on a Hoover-Thomas Uni-Melt capillary melting point apparatus and are uncorrected. NMR's were recorded on a JEOL FX90Q spectrometer at 90 MHz. Chemical shifts are reported in parts per million downfield (δ) from tetramethylsilane, the internal standard, in the form: chemical shift (multiplicity, coupling constant, number of protons). The NOE studies were performed at 270 mHz with a Bruker WN 270 spectrometer and an ASPECT 3000 computer. All optical rotations were determined at 25 °C on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded with field-desorption (FD) ionization on a Varian MAT 731 mass spectrometer or with electron-impact ionization (EI) on a CEC 21-110 mass spectrometer employing a heated ion source operating at 200 °C. Mass spectral data are reported in the form: m/e of parent ion (relative intensity), m/e of significant fragments (relative intensity). Elemental analyses were performed by the Physical Chemistry Research department of the Lilly Research Laboratories.

6a,7-Dehydro-11-methoxyaporphine (7). To a solution of (R)-(−)-11-methoxyaporphine (R-6,[15] 24.0 g, 90.6 mmol) in acetonitrile (1.2 L) was added 10% palladium on carbon (26.7 g). The mixture was heated to reflux for 4 h under a nitrogen atmosphere. The reaction mixture was filtered hot and the filtrate was concentrated in vacuo to give a green solid (17.6 g, 74%): ^{1}H NMR ($CDCl_3$) δ 3.0 (s, 3 H), 4.0 (s, 3 H), 6.60 (s, 1 H), 6.68–7.5 (m, 6 H), 9.34–9.5 (d, J = 9 Hz, 1 H).

(±)-11-Methoxyaporphine ((±)-6). A solution of dehydroaporphine 7 (17.6 g, 66.9 mmol) in acetic acid (800 mL) was hydrogenated at 50 psi at room temperature for 3 h with platinum oxide (2.0 g) as catalyst. The reaction mixture was filtered and the acetic acid was removed under reduced pressure. The viscous residue was dissolved in dichloromethane and washed with ammonium hydroxide solution. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give a brown oil. Purification by flash chromatography (diethyl ether + trace of NH_4OH) gave an orange, viscous oil (5.7 g, 86%): ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3 H), 2.28–3.42 (m, 7 H), 3.80 (s, 3 H), 6.72–7.25 (m, 6 H), 7.92–8.12 (dd, J = 7.2, 1.8 Hz, 1 H). A small amount of material was converted to the hydrochloride salt. Crystallization (ethanol/diethyl ether) gave a colorless solid. (±)-6·HCl: Mp 253–255 °C dec; MS (EI) m/e 266 (10), 265 (60), 264 (100); $[\alpha]_D$ 0° (c = 1.0, CH_3OH). Anal. ($C_{18}H_{19}NO$·HCl) C, H, N.

(S)-(+)-11-Methoxyaporphine (S-6): Resolution of (±)-6. To a solution of (±)-6 (14.6 g, 55.1 mmol) in boiling ethanol (250 mL) was added (−)-tartaric acid (9.1 g, 60.6 mmol). The solution was allowed to cool to room temperature. The colorless crystals which formed were collected by filtration (10.42 g, mp 135–141 °C). This material was recrystallized five times at which time a constant melting point was achieved [3.16 g; mp 148.5–151 °C; $[\alpha]_D$ +56.3° (c = 1.0, CH_3OH)]. A small portion was converted to the hydrochloride salt. Crystallization (ethanol/diethyl ether) gave a colorless solid. S-6: Mp 245 °C dec. MS (EI) m/e 266 (10), 265 (60), 264 (100); $[\alpha]_D$ +98.6° (c = 1.0 CH_3OH). Anal. ($C_{18}H_{19}NO$·HCl) C, H, N.

(R)-(−)-Hydroxyaporphine Hydrobromide (R-14). A solution of R-(−)-11-methoxyaporphine (R-6)[15] (R-6·HCl: $[\alpha]_D$ −97.5° (c = 1.0, CH_3OH)) (150 mg, 0.5 mmol) in 48% aqueous hydrobromic acid (3 mL) was heated to reflux for 4 h. The suspension was cooled to room temperature and vacuum filtered. The solid was crystallized (methanol/diethyl ether) to give colorless crystals (120 mg, 72%): mp >270 °C dec; MS (EI) m/e 252 (10), 251 (60), 250 (100); $[\alpha]_D$ −65.2° (c = 1.0, CH_3OH). Anal. ($C_{17}H_{17}NO$·HBr) C, H, N.

(S)-(+)-11-Hydroxyaporphine Hydrobromide (S-14). Methyl ether S-6 (260 mg, 0.86 mmol) was converted to phenol S-14 by the procedure described for the synthesis of R-14. Colorless crystals were recovered (170 mg, 59%): mp 273 °C dec; MS (EI) m/e 252 (10), 251 (60), 250 (100). Anal. ($C_{17}H_{17}NO$·HBr) C, H, N.

(R)-8-Bromo-11-methoxyaporphine (R-9). A solution of R-6 (800 mg, 3.02 mmol) in trifluoroacetic acid (20 mL) at 0 °C was treated with N-bromosuccinimide (537 mg, 3.02 mmol). The reaction mixture was allowed to warm gradually to room temperature. After 1 h the reaction mixture was poured over ice; the aqueous solution was made basic with NH_4OH solution and extracted with dichloromethane. The organic extracts were combined, dried (Na_2SO_4), and concentrated in vacuo to give 1.03 g of a light orange glass. Purification by flash chromatography (diethyl ether + trace of NH_4OH) gave a light yellow foam (780 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 2.08–3.40 (m, 5 H), 2.56 (s, 3 H), 3.4–3.72 (m, 2 H), 3.82 (s, 3 H), 6.65–6.76 (d, J = 9.9 Hz, 1 H),

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6.88–7.24 (m, 2 H), 7.28–7.39 (d, J = 9.9 Hz, 1 H), 7.83–8.0 (dd, J = 7.2, 1.8 Hz, 1 H).

(*R*)-8-Bromo-11-hydroxyaporphine Hydrobromide (*R*-15). Methyl ether *R*-9 (780 mg, 2.27 mmol) was converted to phenol *R*-15 by the procedure described for the synthesis of *R*-14. Colorless crystals were recovered (540 mg, 58%): mp >275 °C; MS (FD) m/e 332 (32), 331 (98), 330 (43) 329 (100). mp >275 °C; MS (FD) m/e 332 (32), 331 (98), 330 (43) 329 (100). Anal. ($C_{17}H_{16}NOBr$·HBr) C, H, N.

(*S*)-8-Bromo-11-hydroxyaporphine Hydrobromide (*S*-15). This compound was isolated as a colorless, crystalline solid: mp >275 °C; MS (EI) m/e 331 (52), 330 (100), 329 (55), 328 (91). Anal. ($C_{17}H_{16}NOBr$·HBr) C, H, N.

(*R*)-8-Chloro-11-methoxyaporphine (*R*-10). A solution of *R*-6 (850 mg, 3.20 mmol) in trifluoroacetic acid (20 mL) at 0 °C was treated with *N*-chlorosuccinimide (427 mg, 3.20 mmol). The reaction mixture was allowed to warm gradually to room temperature. After 1 h the reaction mixture was poured over ice; the aqueous solution was made basic with NH_4OH solution and extracted with dichloromethane. The organic extracts were combined, dried (Na_2SO_4), and concentrated in vacuo to give a brown glass. Purification by flash chromatography (diethyl ether + trace of NH_4OH) gave a colorless glass (660 mg, 69%): ^1H NMR ($CDCl_3$) δ 2.08–3.40 (m, 5 H), 2.56 (s, 3 H), 3.50–3.76 (m, 2 H), 3.84 (s, 3 H), 6.72–6.80 (d, J = 7.2 Hz, 1 H), 6.88–7.28 (m, 2 H), 7.12–7.20 (d, J = 7.2 Hz, 1 H), 7.84–8.04 (dd, J = 7.2, 1.8 Hz, 1 H).

(*R*)-8-Chloro-11-hydroxyaporphine Hydrobromide (*R*-16). Methyl ether *R*-10 (660 mg, 2.20 mmol) was converted to phenol *R*-16 by the procedure described for the synthesis of *R*-14. Colorless crystals were recovered (260 mg, 32%): mp >200 °C; MS (EI) m/e 287 (5), 286 (12), 285 (17), 284 (28), 283 (13). Anal. ($C_{17}H_{16}NOCl$·HBr) C, H, N.

(*R*)-8-Nitro-11-methoxyaporphine (*R*-11). To *R*-6 (200 mg, 0.80 mmol) in trifluoroacetic acid (5 mL) at 0 °C was added sodium nitrate (64 mg, 0.80 mmol) and the mixture was allowed to warm gradually to room temperature. After 2 h the reaction mixture was poured over ice; the aqueous solution made basic with NH_4OH solution and extracted with dichloromethane. The organic extracts were combined, dried (Na_2SO_4), and concentrated in vacuo to give a green solid. Purification by flash chromatography (3% methanol in dichloromethane + trace of NH_4OH) gave a light yellow foam (190 mg, 81%): ^1H NMR ($CDCl_3$) δ 2.54 (s, 3 H), 2.20–3.32 (m, 5 H), 3.50–3.84 (m, 2 H), 3.95 (s, 3 H), 6.88–6.96 (d, J = 9 Hz, 1 H), 7.0–7.32 (m, 2 H), 7.84–7.92 (dd, J = 7.2, 1.8 Hz, 1 H), 7.74–8.0 (d, J = 8 Hz, 1 H). A small amount of material was converted to the hydrochloride salt. Crystallization (ethanol/diethyl ether) gave light yellow crystals: mp >210 °C; MS (EI) m/e 311 (18), 310 (92), 309 (100). Anal. ($C_{18}H_{18}N_2O_3$·HCl) C, H, N.

(*R*)-8-Nitro-11-hydroxyaporphine Hydrobromide (*R*-17). Methyl ether *R*-11 (200 mg, 0.64 mmol) was converted to phenol *R*-17 by the procedure described for the synthesis of *R*-14. Pale yellow crystals were recovered (110 mg, 45%): mp >200 °C; MS (EI) m/e 297 (18), 296 (95), 295 (100). Anal. ($C_{17}H_{16}N_2O_3$·HBr) C, H, N.

(*R*)-8-Amino-11-methoxyaporphine (*R*-12). A solution of *R*-12 (4.0 g, 12.9 mmol) in ethanol (75 mL) was hydrogenated at atmospheric pressure at room temperature for 1.5 h with 10% palladium on carbon (0.4 g) as catalyst. The reaction mixture was then filtered and the filtrate was concentrated in vacuo to give the desired product as a colorless solid (3.51 g, 97%): ^1H NMR ($CDCl_3$) δ 2.0–3.90 (m, 9 H), 2.53 (s, 3 H), 3.71 (s, 3 H), 6.52–6.61 (d, J = 8.1 Hz, 1 H), 6.68–6.72 (d, J = 8.1 Hz, 1 H), 6.84–7.24 (m, 2 H), 7.87–8.07 (dd, J = 7.2, 1.8 Hz, 1 H); MS (FD) m/e 282 (3), 281 (23), 280 (100).

(*R*)-8-Amino-9-bromo-11-methoxyaporphine (*R*-19). To a solution of *R*-12 (500 mg, 1.8 mmol) in trifluoroacetic acid (20 mL) was added *N*-bromosuccinimide (318 mg, 1.8 mmol). The reaction mixture was stirred for 8 h at room temperature. The reaction mixture was poured over ice and made basic with a NH_4OH solution. The aqueous mixture was extracted with dichloromethane, and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a brown foam (640 mg). Purification by flash chromatography (3% methanol in dichloromethane + trace of NH_4OH) gave the desired product as a yellow foam (340 mg, 53%): ^1H NMR ($CDCl_3$) δ 1.80–3.32 (m, 9 H), 2.53 (s, 3 H), 3.76 (s, 3 H), 6.84–7.24 (m, 3 H), 7.80–7.98 (dd, J = 8.1, 1.8 Hz, 1 H); MS (EI) m/e 361 (13), 360 (67), 359 (100), 358 (68), 357 (85).

(*R*)-9-Bromo-11-methoxyaporphine (*R*-20). To a solution of *R*-19 (340 mg, 0.95 mmol) in 85% phosphoric acid (15 mL) at 0 °C was added very slowly a solution of sodium nitrite (72 mg, 1.05 mmol) in a minimal volume of water via a syringe beneath the surface of the reaction mixture. The mixture was stirred for 30 min at 0 °C and then added dropwise to 50% hypophosphorous acid (10 mL) at 0 °C. Mild gas evolution was observed. The reaction mixture was stirred at room temperature for 2 h, poured over ice, made basic with NH_4OH solution, and extracted with dichloromethane. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give an orange glass. Purification by flash chromatography (diethyl ether + trace of NH_4OH) gave the desired compound as a colorless solid (210 mg, 64%): ^1H NMR ($CDCl_3$) δ 2.08–3.24 (m, 7 H), 2.48 (s, 3 H), 3.81 (s, 3 H), 6.82–7.00 (m, 4 H), 7.80–7.98 (dd, 7.2, 1.8 Hz, 1 H).

(*R*)-9-Bromo-11-hydroxyaporphine Hydrobromide (*R*-21). Methyl ether *R*-20 (190 mg, 0.55 mmol) was converted to phenol *R*-21 by the procedure described for the synthesis of *R*-14. Colorless crystals were recovered (150 mg, 66%): mp >280 °C; MS (EI) m/e 331 (41), 330 (98), 329 (48), 328 (100). Anal. ($C_{17}H_{16}NOBr$·HBr) C, H, N.

(*S*)-9-Bromo-11-hydroxyaporphine Hydrobromide (*S*-21). This compound was isolated as a colorless, crystalline solid: mp >280 °C. Anal. ($C_{17}H_{16}NOBr$·HBr) C, H, N.

(*R*)-8-Formamido-11-methoxyaporphine (*R*-13). To a solution of *R*-12 (3.5 g, 12.5 mmol) in dry tetrahydrofuran (200 mL) was added formic acetic anhydride (4.0 g, 45 mmol). The solution was stirred for 1 h at room temperature. Volatiles were removed in vacuo, and the remaining light green glass was dissolved in chloroform and then washed with saturated aqueous sodium bicarbonate. The remaining organic phase was dried (Na_2SO_4) and concentrated in vacuo to give a beige foam (3.80 g, 99%): ^1H NMR ($CDCl_3$) δ 2.0–3.28 (m, 7 H), 2.52 (s, 3 H), 3.86 (d, J = 2 Hz, 3 H), 6.75–7.38 (m, 5 H), 7.96 (dd, 7.2, 1.8 Hz, 1 H), 8.18–8.38 (m, 1 H); MS (FD) m/e 310 (3), 309 (15), 308 (60), 307 (4).

(*R*)-8-Formamido-10-bromo-11-methoxyaporphine (*R*-22). To a solution of *R*-13 (600 mg, 1.95 mmol) in trifluoroacetic acid (10 mL) was added *N*-bromosuccinimide (350 mg, 1.95 mmol). The solution was stirred at room temperature for 4 h, poured over ice, made basic with NH_4OH solution, and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give an orange foam. Purification by flash chromatography (tetrahydrofuran + trace of NH_4OH) gave the desired product as an orange glass (330 mg, 44%): MS (FD) m/e 389 (25), 388 (82), 387 (30), 386 (100).

(*R*)-8-Amino-10-bromo-11-methoxyaporphine. A solution of *R*-22 (330 mg, 0.85 mmol) in 10% aqueous HCl (20 mL) was heated to 60 °C for 2 h. The reaction mixture was cooled to room temperature, made basic with NH_4OH solution and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a yellow foam (240 mg, 79%). ^1H NMR ($CDCl_3$) δ 1.72–3.56 (m, 9 H), 2.53 (s, 3 H), 3.48 (s, 3 H), 6.80 (s, 1 H), 6.84–7.24 (m, 2 H), 8.00–8.14 (dd, J = 7.2, 1.8 Hz, 1 H).

(*R*)-10-Bromo-11-methoxyaporphine (*R*-24). To a solution of (*R*)-(−)-8-amino-10-bromo-11-methoxyaporphine (100 mg, 0.28 mmol) in 85% phosphoric acid (5 mL) at 0 °C was added very slowly a solution of sodium nitrite (21 mg, .31 mmol) in a minimal volume of water via a syringe beneath the surface of the reaction mixture. The mixture was stirred for 30 min at 0 °C. The reaction mixture was then added dropwise to 5 mL of 50% hypophosphorous acid at 0 °C. Mild gas evolution was observed. The reaction mixture was stirred at room temperature for 2 h, poured over ice, made basic with NH_4OH solution, and extracted with dichloromethane. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give a yellow glass. Purification by flash chromatography (diethyl ether + trace of NH_4OH) gave the desired compound as a yellow foam (67 mg, 70%): ^1H NMR ($CDCl_3$) δ 2.16–3.40 (m, 7 H), 2.52 (s, 3 H), 3.37 (s, 3 H), 6.71–7.17 (m, 2 H), 7.07–7.15 (d, J = 7.2 Hz, 1 H), 7.27–7.35 (d, J = 7.2 Hz, 1 H), 8.06–8.17 (dd, J = 7.2, 1.8 Hz, 1 H); MS (FD) m/e 346 (20), 345 (98), 344 (23), 343 (100).

(*R*)-10-Bromo-11-hydroxyaporphine Hydrobromide (*R*-26). Methyl ether *R*-24 (89 mg, 0.26 mmol) was converted to phenol *R*-26 by the procedure described for the synthesis of *R*-14. Colorless crystals were recovered (36 mg, 34%): mp >275 °C; MS (EI) *m/e* 331 (50), 330 (100), 329 (57), 328 (95). Anal. ($C_{17}H_{16}NOBr\cdot HBr$) C, H, N.

(*S*)-10-Bromo-11-hydroxyaporphine Hydrochloride (*S*-26). This compound was isolated as a colorless, crystalline solid: mp >200 °C; MS (EI) *m/e* 331 (55), 330 (100), 329 (59), 328 (90). Anal. ($C_{17}C_{16}NOBr\cdot HBr$) C, H, N.

(*R*)-8-Formamido-10-chloro-11-methoxyaporphine (*R*-23). To a solution of *R*-13 (1.00 g, 3.25 mmol) in trifluoroacetic acid (30 mL) was added *N*-chlorosuccinimide (434 mg, 3.25 mmol). The solution was stirred at room temperature for 18 h. The reaction mixture was then poured over ice, made basic with NH_4OH solution, and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a brown foam. Purification by flash chromatography (tetrahydrofuran + trace of NH_4OH) gave the desired product as a pink foam (760 mg, 68%).

(*R*)-8-Amino-10-chloro-11-methoxyaporphine. A solution of *R*-23 (750 mg, 2.15 mmol) in 10% aqueous HCl (20 mL) was heated to 60 °C for 2 h. The reaction mixture was then cooled to room temperature, made basic with NH_4OH solution, and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated in vivo to give a light brown foam (530 mg, 77%). ^1H NMR ($CDCl_3$) δ 1.76–3.67 (m, 9 H), 2.48 (s, 3 H), 3.56 (s, 3 H), 6.64 (s, 1 H), 6.89–7.14 (m, 2 H), 8.00–8.19 (dd, J = 7.2, 1.8 Hz, 1 H).

(*R*)-10-Chloro-11-methoxyaporphine (*R*-25). To a solution of (*R*)-(−)-8-amino-10-chloro-11-methoxyaporphine (530 mg, 1.69 mmol) in 85% phosphoric acid (20 mL) at 0 °C was added very slowly a solution of sodium nitrite (146 mg, 2.11 mmol) in a minimal volume of water via a syringe beneath the surface of the reaction mixture. The mixture is stirred for 30 min at 0 °C. The reaction mixture was then added dropwise to 25 L of 50% hypophosphorous acid at 0 °C. Mild gas evolution was observed. The reaction mixture was stirred at room temperature for 2 h, poured over ice, made basic with NH_4OH solution, and extracted with dichloromethane. The combined extracts were washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and concentrated in vacuo to give an orange glass. Purification by flash chromatography (diethyl ether + trace of NH_4OH) gave the desired compound as a light orange glass (153 mg, 30%): ^1H NMR ($CDCl_3$) δ 2.27–3.44 (m, 7 H), 2.52 (s, 3 H), 3.61 (s, 3 H), 6.71–7.29 (m, 4 H), 8.07–8.20 (dd, J = 7.2, 1.8 Hz, 1 H).

(*R*)-10-Chloro-11-hydroxyaporphine Hydrobromide (*R*-27). Methyl ether *R*-25 (150 mg, 0.50 mmol) was converted to phenol *R*-27 by the procedure described for the synthesis of *R*-14. Colorless crystals were recovered (80 mg, 44%): mp >200 °C. MS (EI) *m/e* 287 (20), 286 (41), 285 (62), 284 (100). Anal. ($C_{17}H_{16}NOCl\cdot HBr$) C, H, N.

(*R*)-8,10-Dibromo-11-hydroxyaporphine Hydrobromide (*R*-18). A 60% suspension of sodium hydride in mineral oil (52 mg, 1.36 mmol) was added to tetrahydrofuran (10 mL) and cooled to 0 °C. To this was added a solution of *R*-(−)-11-hydroxy-6-methylaporphine (*R*-14) (170 mg, 0.68 mmol) in tetrahydrofuran (5 mL) dropwise. The solution was stirred for 30 min at 0 °C. To this homogeneous, purple solution was then added *N*-bromosuccinimide (120 mg, 0.68 mmol) and the solution stirred for 15 min. The reaction mixture was poured into water (50 mL) and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a green foam. Purification by flash chromatography (diethyl ether + trace of NH_4OH) gave a colorless solid (126 mg, 91% dibromo based on NBS): ^1H NMR ($CDCl_3$) δ 2.08–3.24 (m, 5 H), 2.56 (s, 3 H), 3.44–3.53 (d, J = 3.6 Hz, 1 H), 3.60–3.72 (d, J = 3.6 Hz, 1 H), 6.92–7.26 (m, 2 H), 7.17 (s, 1 H), 7.52 (s, 1 H), 7.88–8.04 (dd, J = 7.2, 1.8 Hz, 1 H). The hydromide salt was formed. Crystallization (methanol/diethyl ether) gave colorless crystals: mp >200 °C; MS (EI): 409 (58), 408 (59), 407 (100), 406 (52). Anal. ($C_{17}H_{15}NOBr_2\cdot HBr$) C, H, N.

HPLC Determination of Optical Purity. Samples of *R*-14 and *S*-14 were derivatized with (−)-α-methylbenzyl isocyanate by using the method of Ram and Neumeyer.[15] HPLC analysis of the resulting diastereomers was performed with a 3.9 mm × 15 cm NOVA-PAK C_{18} column (Waters Associates, Inc). The eluent was 50:50, acetonitrile/0.5% aqueous $(NH_4)H_2PO_4$ buffer (pH 2.1) with a flow rate of 1 mL/min. Detection was by UV detector at 214 nm.

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Registry No. (±)-6, 123749-85-9; (±)-6·HCl, 123749-86-0; (*R*)-6, 121617-59-2; (*S*)-6, 123675-04-7; (*S*)-6·HCl, 123675-05-8; 7, 123675-06-9; (*R*)-9, 123675-07-0; (*R*)-10, 123675-08-1; (*R*)-11, 123675-09-2; (*R*)-12, 123675-10-5; (*R*)-13, 123675-11-6; (*R*)-14, 88247-20-5; (*R*)-14·HBr, 83247-89-6; (*S*)-14, 123749-88-2; (*S*)-14·HBr, 123749-87-1; (*R*)-15, 123675-13-8; (*R*)-15·HBr, 123675-12-7; (*S*)-15, 123675-15-0; (*S*)-15·HBr, 123675-14-9; (*R*)-16, 123675-17-2; (*R*)-16·HBr, 123675-16-1; (*R*)-17, 123675-19-4; (*R*)-17·HBr, 123675-18-3; (*R*)-18, 123675-21-8; (*R*)-18·HBr, 123675-20-7; (*R*)-19, 123675-22-9; (*R*)-20, 123675-23-0; (*R*)-21, 123675-25-2; (*R*)-21·HBr, 123675-24-1; (*S*)-21, 123675-27-4; (*S*)-21·HBr, 123675-26-3; (*R*)-22, 123675-28-5; (*R*)-22 deformyl derivative, 123675-29-6; (*R*)-23, 123675-30-9; (*R*)-23 deformyl derivative, 123675-31-0; (*R*)-24, 123675-32-1; (*R*)-25, 123675-33-2; (*R*)-26, 123675-35-4; (*R*)-26·HBr, 123675-34-3; (*S*)-26, 123675-37-6; (*S*)-26·HBr, 123675-36-5; (*R*)-27, 123675-39-8; (*R*)-27·HBr, 123675-38-7.