Rat Tail-Flick Procedure.[9] Male albino rats (100–120 g) were used for this study. Two control reaction times were determined 30 min apart and prior to intraperitoneal injection of test drug. An ED_{80} dose of morphine was administered 10 min later subcutaneously, and reaction times were then determined 20 min later. The narcotic antagonist activity was determined from the difference between the groups and control groups which received morphine alone. For agonist activity, the drug was administered subcutaneously, the ED_{80} of morphine was eliminated, and the animals were retested 20 min postdrug.

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Aporphines. 36.[1] Dopamine Receptor Interactions of Trihydroxyaporphines. Synthesis, Radioreceptor Binding, and Striatal Adenylate Cyclase Stimulation of 2,10,11-Trihydroxyaporphines in Comparison with Other Hydroxylated Aporphines[2]

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The presence of the A ring of aporphines and the addition of substituents to it and to other portions of the aporphine ring systems can extend explorations of the dimensions and other characteristics of the dopamine receptor. Accordingly, the synthesis and some physical and pharmacological properties of a series of (−)-2,10,11-trihydroxyaporphines (**3a–g**) are described. Structure–activity relationships among mono-, di-, and trihydroxyaporphines were evaluated against the high-affinity (nanomolar) binding of [^{3}H]apomorphine (APO) and [^{3}H]spiroperidol (SPR) with a subcellular fraction (P_4) of caudate nucleus from bovine brain. In addition, DA-sensitive adenylate cyclase activity was evaluated in homogenates of rat brain striatal tissue. The rank order of displacement of [^{3}H]APO by potent aporphines ($IC_{50} \leq 30$ nM) correlated approximately with their ability to stimulate cyclic AMP synthesis. Potency orders against the two ligands were dissimilar; for example, increasing the size of N^6-alkyl substituents *increased* potency vs. [^{3}H]SPR but not vs. [^{3}H]APO binding. Moreover, [^{3}H]SPR binding correlated poorly with cyclase activity or [^{3}H]APO binding, suggesting a closer relationship of [^{3}H]APO binding to dopamine-sensitive adenylate cyclase activity.

The existence of receptor surfaces has been offered as an explanation for structure–activity relationships of various classes of drugs and their relative agonist or antagonist properties and toxicity. Rigid analogues have been prepared in attempts to constrain receptor-active molecules in an hypothesized receptor-preferred conformation, for example, by the addition of an extra ring system or the introduction of a triple bond to limit carbon-chain flexibility. We have applied such a rigid-analogue approach to the evaluation of the receptor-site-preferred conformation of dopamine (DA) by securing the catechol and the amino groups of DA in a rigid conformation in apomorphine (APO) and related aporphines, which have served as useful models for studying the characteristics of DA receptors.[3,4] While it is generally accepted that the catechol moiety is required to produce optimum interactions with the DA receptor,[5-9] the presence of a catechol group is not sufficient to confer agonist activity on aporphines or phenethylamines.[5] Thus, for example, (±)-isoapomorphine (9,10-dihydroxyaporphine) and (−)-1,2-dihydroxyaporphine were inactive in behavioral or biochemical tests designed to reflect DA-agonist activity.[7,8,10,11] In previous studies we evaluated 8-, 10-, or 11-hydroxylated aporphines and found that (±)-11-hydroxy-*N*-*n*-propylnoraporphine (**2b**) yields apparent DA-receptor agonist activity when administered to rats in vivo.[12,13] Our earlier studies using behavioral and striatal cyclase activities as indexes of DA-receptor agonist activity of monohydroxyaporphines, such as 8-, 10-, or 11-hydroxy-*N*-propylnoraporphines, suggested that a hydroxyl function at the 11 position of the aporphine ring may contribute more to receptor binding[5] and in vivo biological activity than at the 10 position.[8,12-16] The 8-hydroxy-substituted apor-

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(2) Presented in part at the Second Chemical Congress of the North American Continent, Las Vegas, NV, Aug, 1980 (see "Abstracts of Papers", American Chemical Society, Washington, DC, Abstr MEDI 16), and at the Symposium on Clinical Pharmacology of Apormorphine and Other Dopaminomimetics, Villasimus (Cagliari), Italy, Sept 1980.
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Table I. *N*-Alkylnormorphothebaines Prepared by Alkylation of Normorphothebaine with Alkyl Halides (RX)

no.	RX	R_f[a]	mp,[b] °C dec	% yield[c]	eluting solvents[d]	$[\alpha]_{546}$,[a] deg	formula	anal.[e]
5b	C_2H_5I	0.19	209–211	65	A		$C_{19}H_{21}NO_3 \cdot HCl \cdot 0.5H_2O$	C, H, N
5c	n-C_3H_7I	0.24	214–216	51	A	−60 (25)	$C_{20}H_{23}NO_3 \cdot HCl \cdot 1.5H_2O$	C, H, N
5d	$CH_2{=}CHCH_2Br$	0.30	204–206	54	B	−97.7 (23)	$C_{20}H_{21}NO_3 \cdot HCl$	C, H, N
5e	$CH{\equiv}CCH_2Br$	0.34	175–176	75	C	−143 (21)	$C_{20}H_{19}NO_3$	C, H, N

[a] Solvent system: 5% (vols) methanol in chloroform. [b] 5b–d were determined as hydrochloride salts and 5e was determined as the free base. [c] After column chromatographic purification. [d] Solvent systems for column chromatography: A = 5% CH_3OH in $CHCl_3$; B = 3% CH_3OH in $CHCl_3$; C = CH_3OH–Et_2O–$CHCl_3$ (3:32:65). [e] All values are ± 0.4% of theory.

Table II. Physical Properties of *N*-Alkyl-2,10,11-trihydroxynoraporphines

no.	R	mp, °C dec[a]	% yield	$[\alpha]_{546}$, deg	formula	anal.[e]
3b	C_2H_5	238–241	85	−80.0 (25)	$C_{18}H_{10}NO_3 \cdot HBr \cdot H_2O$	C, H, N
3c	n-C_3H_7	203–206	70	−62.5 (25)	$C_{19}H_{21}NO_3 \cdot HBr \cdot 2H_2O$	C, H, N
3d	$CH_2CH{=}CH_2$	208–210	89	−63.5 (21)	$C_{19}H_{19}NO_3 \cdot HBr \cdot 0.5H_2O$	C, H, N
3e	$CH_2CBr{=}CH_2$	180–184	38[b]	−30.5 (25)	$C_{19}H_{18}BrNO_3 \cdot HCl \cdot 0.5H_2O$	C, H, N
3g	$CH_2C{\equiv}CH$	178–181	17[c]	*d*	$C_{19}H_{17}NO_3 \cdot HCl \cdot H_2O$	C, H, N

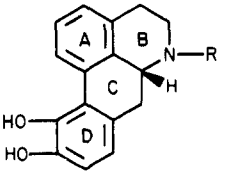
[a] 3b–d were determined as hydrobromide salts; 3e and 3g were determined as hydrochloride salts. [b] After further purification through acetoxy derivation and acid hydrolysis. [c] Overall yield from normorphothebaine (5) and after further purification through acetoxy derivation and acid hydrolysis. [d] At the concentration of 9.8 mg/10 mL of EtOH, polarimeter readings taken at 5-min intervals after the solution was prepared showed: −0.052, −0.046, −0.038, −0.027, and −0.001. [e] All values are ± 0.4% of theoretical predictions.

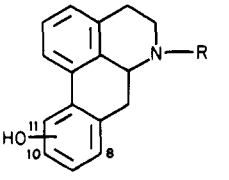
phines[16] lacked dopaminergic activity and demonstrated weak interactions in displacing [^{3}H]APO from calf caudate tissue binding sites.[5]

Considerable attention has been given to the α- and β-rotameric forms of the extended or trans-anti DA conformation, represented by two of the most active DA agonists, apomorphine and the aminotetralin 2-amino-6,7-dihydroxytetrahydronaphthalene (A-6,7-DTN). Apomorphine and the aminotetralin A-5,6-DTN are considered to exist in the trans-α-rotameric form, whereas A-6,7-DTN and isoapomorphine are held in the trans-β-rotameric form.[17-20] In aminotetralins, the trans-β-rotameric form of DA incorporated in A-6,7-DTN is more active than the A-5,6-DTN both centrally[21] and at the peripheral vascular DA receptor.[22] McDermed et al.[23] have determined the absolute configuration of the enantiomers of A-6,7-DTN, which corresponds to an absolute configuration *opposite* to that of the more active (−) enantiomer of APO.

These and other observations led to an hypothesis relating the mode of binding of such agonists to DA receptors.[3] Factors which appear to exert important influences on binding include the following: (A) the appropriate configuration at the chiral center, (B) the location of the hydroxyl groups (particularly the hydroxyl group meta to the aminoethyl fragment), and (C) the interaction of the nitrogen atom to a putative nucleophilic center on the receptor.

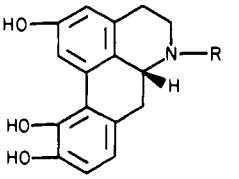
The present studies were designed to examine further the structure–activity relationships among DA, dihydroxyaporphines (**1a–c**), monohydroxyaporphines (**2b**, **7a,b** and **8**), and several novel trihydroxyaporphines (**1d** and **3a–f**). Aporphines allow the incorporation of additional functional groups, which can interact with other possible sites and may influence receptor affinities or pharmacological activity. This article presents the synthesis and characterization of the novel 2,10,11-trihydroxynoraporphines (**3a–f**) having the 6a(*R*) configuration. The activity of mono-, di- and trihydroxylated





1a, R = CH_3 [(−)APO]
b, R = n-C_3H_7 [(−)NPA]
c, R = n-C_3H_7 [(±)NPA]
d, R = CH_2CH_2OH
e, R = CH_2CH_2Cl

2a, R = CH_3; 11-OH
b, R = n-C_3H_7; 11-OH
7a, R = CH_3; 10-OH
b, R = n-C_3H_7; 10-OH
8, R = n-C_3H_7; 8-OH



3a, R = H
b, R = CH_3 (2-OH-APO)
c, R = C_2H_5
d, R = n-C_3H_7 (TNPA)
e, R = $CH_2CH{=}CH_2$
f, R = $CH_2CBr{=}CH_2$
g, R = $CH_2C{\equiv}CH$

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aporphines against the high-affinity (nanomolar) binding of [^{3}H]apomorphine (APO) and [^{3}H]spiroperidol (SPR) was evaluated with a subcellular fraction (P_4) of bovine brain tissue, and DA-sensitive adenylate cyclase activity was evaluated in homogenates of corpus striatum tissue from rat brain.

Chemistry. The syntheses of the N-substituted 2,10,11-trihydroxynoraporphines (**3a–g**) are outlined in Scheme I. Thebaine (**4**) was either directly subjected to acid rearrangement[24] to give one of the precursors, morphothebaine (**5a**), or N-demethylated to give the intermediate northebaine according to the procedure of Pohland and Sullivan.[25] Acid-catalyzed rearrangement of northebaine yielded normorphothebaine (**6**) as described by Granchelli et al.[24] Alkylation of **6** (Scheme I) with alkyl halides was carried out in acetonitrile with or without the presence of potassium iodide to yield the N-substituted normorphothebaines (**5a–e**; Table I). Treatment of **5a–d** with 48% (w/v) HBr at elevated temperature gave the desired products (**3b–g**, Table II). With *N*-propargylnormorphothebaine (**5g**), however, under similar conditions, 1 mol of HBr was found to add across the side-chain triple bond, in addition to the desired O-demethylation, yielding the *N*-(2′-bromoallyl) derivative (**3f**). *N*-Propargyl-2,10,11-trihydroxynoraporphine (**3g**) was obtained by directly alkylating the noraporphine **3a** with propargyl bromide. The N-substituted 2,10,11-trihydroxynoraporphines thus obtained were optically active (Table II). During determination of optical activity, the *N*-propargyl derivative (**3g**) displayed levorotation initially but racemized and lost optical activity during 30 min in alcoholic solution at 25 °C.

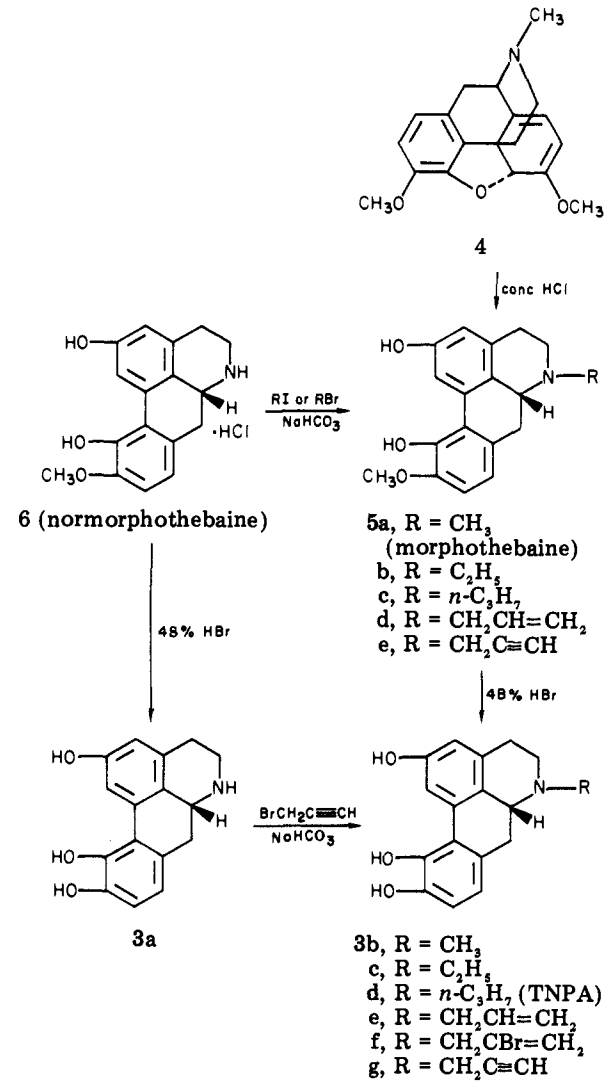
Pharmacology. The ability of aporphines (50 μM) to stimulate DA-sensitive adenylate cyclase was evaluated with homogenates of rat corpus striatum in the presence of excess ATP and a potent inhibitor of phosphodiesterase (IBMX); cyclic AMP (cAMP) was then assayed by a protein-binding method.[5] Typical basal activity (without DA agonist present) was 1.2 ± 0.1 pmol of cAMP formed per 2.5 min of assay (±SEM).

Binding assays were carried out with a membrane fraction recovered from osmotically shocked and Polytron-disrupted membranes prepared from rapidly frozen protease-free calf caudate nuclei.[5,9] Ligands included (−)-[8,9-^{3}H]apomorphine hydrochloride (APO; New England Nuclear; 40 Ci/mmol) and 1-phenyl[4-^{3}H]spiroperidol (SPR; New England Nuclear; 30 Ci/mmol). Blanks were defined by adding 10 μM excess unlabeled (±)-A-6,7-DTN (obtained from Burroughs Wellcome Laboratories) in the [^{3}H]APO assay or 1 μM (+)-butaclamol (donated by Ayerst Laboratories) in the [^{3}H]SPR assay. Details concerning the binding assay methods are provided in the legend to Table III and elsewhere.[5,9,27]

Results and Discussion

Effects of Aporphines on Binding of [^{3}H]Apomorphine (APO) and [^{3}H]Spiroperidol (SPR) to Calf Caudate Membranes. The present results extend our observations indicating the importance of a catechol moiety for competition with the binding of [^{3}H]APO to the calf caudate membrane preparation (P_4) studied.[5] Thus, the

Scheme I. Synthesis of (−)-2,10,11-Trihydroxyaporphines



nine most potent aporphines evaluated had such a catechol moiety with OH groups at positions 10 and 11 (Table III; **1a–d** and **3a–e**) and yielded IC_{50} values ≤30 nM. Hence, location of hydroxyl groups in the 10 and 11 positions of the aporphine (analogous to the trans-α-rotamer of DA) appeared to be required for high-affinity binding. Such conformational requirements have also been reported previously for stimulation of DA-sensitive adenylate cyclase in striatal homogenates.[8,17]

Comparison of (±)-11-hydroxy-*N*-*n*-propylnoraporphine (**2a**) with (±)-10-hydroxy-*N*-*n*-propylnoraporphine (**7b**) in the [^{3}H]APO binding assay (IC_{50} = 36 vs. 700 nM, respectively; Table III) suggests that an hydroxyl at the 11 position of the aporphine ring may contribute more to [^{3}H]APO binding than at the 10 position. Because the 11 position in the aporphine ring corresponds to the meta position on catecholamine molecules, this finding is consistent with adrenergic cardiovascular responses, in which phenethylamines with single hydroxyl groups are reportedly more potent as agonists than para-hydroxylated monophenolic compounds,[28,29] and with additional comparisons of monophenolic phenethylamines against binding

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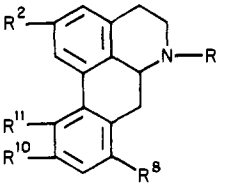
Table III. Inhibition of Binding of [^{3}H]Apomorphine (APO) and [^{3}H]Spiroperidol (SPR) and Striatal Cyclase Stimulation by Aporphines



no.	compd	R(N)	R^{10}	R^{11}	R^2	R^8	IC_{50},[a] nM [^{3}H]APO	IC_{50},[a] nM [^{3}H]SPR	cyclase act. (stimulation)[b]
1a	(−)-apomorphine	CH_3	OH	OH	H	H	1.0	860	+++
1b	(−)-10,11-dihydroxy-*N*-*n*-propylnoraporphine	$CH_2CH_2CH_3$	OH	OH	H	H	2.5	280	+++
1c	(±)-10,11-dihydroxy-*N*-*n*-propylnoraporphine	$CH_2CH_2CH_3$	OH	OH	H	H	5.0	670	++
3b	(−)-2,10,11-trihydroxyaporphine	CH_3	OH	OH	OH	H	10	4 400	++
3e	(−)-2,10,11-trihydroxy-*N*-allylnoraporphine	$CH_2CH{=}CH_2$	OH	OH	OH	H	24	725	+
1d	(−)-10,11-dihydroxy-*N*-(hydroxyethyl)noraporphine	CH_2CH_2OH	OH	OH	H	H	25	⩾5 000	+
3c	(−)-2,10,11-trihydroxy-*N*-ethylnoraporphine	CH_2CH_3	OH	OH	OH	H	25	900	+
3d	(−)-2,10,11-trihydroxy-*N*-*n*-propylnoraporphine	$CH_2CH_2CH_3$	OH	OH	OH	H	25	600	+
3a	(−)-2,10,11-trihydroxynoraporphine	H	OH	OH	OH	H	30	9 200	+
2b	(±)-11-hydroxy-*N*-*n*-propylnoraporphine	$CH_2CH_2CH_3$	H	OH	H	H	36	700	+
7a	(±)-10-hydroxyaporphine	CH_3	OH	H	H	H	112	⩾5 000	+
3g	(−)-2,10,11-trihydroxy-*N*-propynylnoraporphine	$CH_2C{\equiv}CH$	OH	OH	OH	H	143	>10 000	+
5a	(−)-morphothebaine	CH_3	OCH_3	OH	OH	H	204	>10 000	NT[c]
1e	(−)-*N*-(chloroethyl)norapomorphine	CH_2CH_2Cl	OH	OH	H	H	394	>10 000[d]	*e*
7b	(±)-10-hydroxy-*N*-*n*-propylnoraporphine	$CH_2CH_2CH_3$	OH	H	H	H	700	⩾5 000	NT
9	(−)-apocodeine	CH_3	OCH_3	OH	H	H	2400	>10 000	NT
10	(±)-*N*-*n*-propylnorapocodeine	$CH_2CH_2CH_3$	OCH_3	OH	H	H	⩾5 000	4 700	NT
8	(±)-8-hydroxy-*N*-*n*-propylnoraporphine	$CH_2CH_2CH_3$	H	H	H	OH	>10 000	⩾5 000	NT

[a] Competition by aporphines for the binding of ^{3}H-labeled apomorphine (0.5 nM) or spiroperidol (9.4 nM) was evaluated with the P_4 fraction of calf caudate homogenates as described in Pharmacology Section. Specific binding of each ligand was defined by use of (±)-ADTN (10 μM) as displacers of [^{3}H]APO or [^{3}H]SPR, respectively. Values for IC_{50} were calculated using log probit analysis of data from at least three separate determinations with at least four concentrations of each compound. SD was less than ±5% of each mean value. [b] Cyclase activity was assessed at 50 μM of each test substance as (+) < 40%, (++) 41–60%, or (+++) 61–80% increase of cAMP above basal activity. [c] NT = not tested. [d] Datum provided by Dr. Bruce Cohen, Mailman Research Center, whose cooperation is gratefully acknowledged. [e] NCA (1e), under some conditions, actually *inhibits* the cyclase activity.[32]

of [^{3}H]APO.[5] These findings are supported by McDermed et al.[23] with (−)-2-amino-5-hydroxy-1,2,3,4-tetrahydronaphthalene, which binds to DA receptors such that the orientation required of the amino group is controlled primarily by the location of the hydroxyl group in the meta position. The 5-hydroxyl group in this aminotetralin presumably binds to the same site as in the 11-hydroxyaporphines.[3]

The aporphines differ from the aminotetralins principally by the incorporation of an additional aromatic ring. The presence of this extra benzene ring (ring A) allows for the addition of other functional groups as with the 2-hydroxyaporphines described here. The present results indicate that 2-OH substitution of APO or NPA *decreased* affinity for [^{3}H]APO and [^{3}H]SPR by 10-fold and 2- to 5-fold, respectively (Table III, **1a** vs. **3b**; **1b** vs. **3d**). These results suggest that important interactions occur between the 2-OH of the A ring and a region of the DA receptor. The additional aromatic ring may interact with specific portions of the receptor and give further indications of the dimensions and other characteristics of the DA receptor.

The 10,11 positioning of the catechol, by itself, is evidently not adequate to compete for the binding of [^{3}H]-APO, since several 10,11-dihydroxyaporphine derivatives displaced [^{3}H]APO at relatively high IC_{50} values (see Table III).[5] These weakly bound catechol compounds indicate the importance of N-substitution in modifying interactions with the binding sites involved.[5] For example, compound **1d** in Table III has a 10,11-dihydroxy moiety but also contains an hydroxyethyl group at the N^6 position. This compound was 25 times less potent than APO against binding of [^{3}H]APO (IC_{50} = 25 vs. 1 nM), possibly indicating interference with crucial binding sites by the hydroxyethyl group. This effect may be attributable either to increased hydrophilic characteristics or altered charge interactions at putative binding sites. Similarly, *N*-(chloroethyl)norapomorphine (**1e**; NCA), which has long-acting DA antagonistic properties in vivo[30,31] and blocks

DA-sensitive adenylate cyclase in vitro,[31,32] had an IC_{50} of 394 nM against binding of [^{3}H]APO. While this relatively low binding value indicates only moderate potency of interaction with APO binding sites, it may suffice to permit subsequent irreversible and possibly covalent interaction similar to that of phenoxybenzamine (another chloroethyl-substituted agent) with adrenergic receptors.[9,32]

Thus, it seems that in addition to the presence and conformational requirements of the catechol moiety, the substituent on the N^6 position in the aporphine ring also plays an important part in the presumed DA–receptor interactions, as defined in the present [^{3}H]APO binding assay.[5] Several other comparisons of IC_{50} values from Table III provide further support of this point: (–)-APO (**1a**; IC_{50} = 1.0 nM) vs. (–)-NPA (**1b**; 2.5 nM), 2-hydroxyapomorphine (**3b**; 10 nM) vs. (–)-2-hydroxy-*N*-ethylnorapomorphine (**3c**; 25 nM) or (–)-2-OH-NPA (**3d**; 25 nM), as well as the monophenolic compound (±)-10-hydroxyaporphine (**7a**; 112 nM) vs. (±)-10-hydroxy-*N*-propylnoraporphine (**7b**; 700 nM).

These and other similar comparisons[5] indicate that the compounds with an *N*-*n*-propyl or *N*-ethyl group consistently yield somewhat lower binding affinities than their *N*-methyl congeners. This result, in the case of APO (**1a**) vs. NPA (**1b**) (which exhibited a 2.5:1 difference in potency of binding vs. [^{3}H]APO: 1.0 vs. 2.5 nM; Table III), was unexpected in view of the reportedly greater in vivo potency of NPA in several behavioral or neuroendocrine indexes of presumed DA-receptor stimulation.[13,33] On the other hand, the in vitro potency of APO and NPA in stimulating DA-sensitive adenylate cyclase has also been reported to be nearly identical.[8] This difference in rank potency of APO vs. NPA in the radioreceptor assays and the stimulation of adenylate cyclase, as compared with the in vivo behavioral data, may reflect poorly understood pharmacokinetic factors, such as membrane permeability and enzyme degradation, which would be more evident in an in vivo paradigm.

In contrast to the potency order of *N*-propyl analogues of APO against the binding of [^{3}H]APO, both (–)-NPA (**1b**) and (–)-2,10,11-trihydroxy-*N*-*n*-propylnoraporphine (**3d**) were 3- to 7-fold *more* potent than the corresponding *N*-methyl compounds (**1a** and **3b**) against the binding of [^{3}H]spiroperidol (SPR) (Table III). Moreover, the potency of 2,10,11-trihydroxyaporphines against binding of [^{3}H]-SPR *increased* with increasing size of the *N*-alkyl substituent (propyl > ethyl > methyl > H; **3a–d**, Table III). These trends may reflect increased lipophilicity of the aporphines with a larger *N*-alkyl substituent or dissimilar receptor characteristics or binding sites defined by labeled DA antagonists and agonists.

The rank potency of [^{3}H]APO displacement by many of the compounds of Table III correlated approximately with their ability to stimulate cAMP synthesis by tissue containing DA-sensitive adenylate cyclase. Thus, (–)-APO and (–)-NPA, with IC_{50}'s against [^{3}H]APO binding of 1.0 and 2.5 nM, respectively, potently stimulated cAMP formation, while the (±)-NPA (**1c**) and (–)-2-OH-APO (**3b**) (IC_{50} = 5 and 10 nM, respectively) moderately stimulated cyclase activity. Other compounds (**3e–g**) with IC_{50}'s ranging from 24 to 143 nM weakly stimulated adenylate cyclase. Conversely, [^{3}H]SPR binding correlated poorly with cyclase activity or with [^{3}H]APO binding, suggesting a closer link between [^{3}H]APO binding and DA-stimulated cyclase activity. While most 10,11-hydroxylated aporphines were generally more potent against the binding of [^{3}H]APO than [^{3}H]SPR, the highest potency against the binding of [^{3}H]SPR was found with (–)-NPA (IC_{50} = 280 nM; Table III).

Finally, it should be noted that O-methylation considerably reduced the potency of aporphines against [^{3}H]APO binding or DA-cyclase stimulated production of cAMP. Thus, morphothebaine (**5a**; IC_{50} = 204 nM), apocodeine (**9**; 2400 nM), and (±)-*N*-*n*-propylnorapocodeine (**10**; ≥5000 nM) (Table III) all contain methyl ether moieties in the 10 position. This reduction in potency may be brought about by the bulk of the additional methyl group, which may interfere with ligand–receptor interactions at one of the putative binding sites. These findings are consistent with previous in vivo observations[11–16] of DA agonist inactivitiy of such O-methylated aporphines as apocodeine (**9**) and *N*-*n*-propylnorapocodeine (**10**).

Conclusions

The present results support the hypothesis that novel 2,10,11-trihydroxyaporphines displace [^{3}H]APO from calf caudate membrane fractions and stimulate adenylate cyclase production of cAMP by rat striatal tissue in potencies indicative of DA-agonist interactions. This class of compounds may be useful to elucidate dopaminergic mechanisms in both in vitro paradigms such as receptor binding and enzyme stimulation assays, as well as in vivo systems such as stereotyped behaviors in rodents.

Experimental Section

General Methods. All melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN. Thin-layer chromatography (TLC) used precoated silica gel 13179, polyethylene terphthalate sheets (Eastman Kodak, Rochester, NY). Column chromatography was on silica gel (Baker, 5-3405, 50–200 mesh). IR spectra were obtained with a Perkin-Elmer Model 700 or Beckman IR-10 spectrophotometer. The NMR spectra were measured in $CDCl_3$ or CD_3OD on a Varian T-60 spectrometer, and chemical shifts are reported in parts per million (δ) downfield from $(CH_3)_4Si$ as internal standard. Mass spectra were determined on a 12-90-G Nuclide mass spectrometer. Optical rotations were obtained on a Perkin-Elmer polarimeter (Model 141).

***N*-Alkylnormorphothebaine (5).** A mixture of normorphothebaine hydrochloride[24] (5.10 g, 0.016 mol), $NaHCO_3$ (5.0 g, 0.06 mol), alkyl iodide (0.02 mol), and potassium iodide (0.014 mol, added only when alkyl bromide was used) in 130 mL of acetonitrile was heated at 100 °C under N_2 for 16 h. The reaction mixture was cooled and filtered, and the filtrate was evaporated. The residue was treated with 100 mL of $CHCl_3$ and filtered, and the filtrate was concentrated to approximately 5 mL, which was then chromatographed on silica gel (1:30) packed and eluted with a mixed solvent system to give the desired compounds in yields ranging from 51 to 75%, with melting points given in Table I. The IR, NMR and mass spectra were consistent with the assigned structures in all cases. UV (EtOH) spectral data were as follows: for **5c**, λ_{max} 268 nm (log ϵ 4.14), 278 (4.14), 305 (3.89); for **5d**, λ_{max} 270 nm (log ϵ 4.07), 279 (4.09), 303 (3.81); for **5e**, λ_{max} 270 nm (log ϵ 4.16), 276 (4.19), 303 (3.92).

***N*-Alkyl-2,10,11-trihydroxynoraporphine Hydrobromides (3c–e).** A mixture of *N*-alkylnormorphothebaime (1.8 mol) in 18 mL of 48% (w/v) HBr was heated at 130–135 °C under nitrogen for 3–4 h. The reaction mixture was cooled and evaporated in vacuo. The residue was recrystallized from a methanol–ethyl ether mixture to give an off-white solid, with yields and melting points given in Table II. The IR, NMR, and mass spectra were consistent with the assigned structures in all cases. UV (EtOH) spectral

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data were as follows: for **3c**, λ_{max} 271 nm (log ϵ 4.15), 279 (4.16), 303 (3.90); for **3d**, λ_{max} 270 nm (log ϵ 4.13), 280 (4.15), 303 (3.86); for **3e**, λ_{max} 270 nm (log ϵ, 4.14), 279 (4.15), 301 (3.90).

***N*-(2-Bromoallyl)-2,10,11-trihydroxynoraporphine Hydrochloride (3f).** A mixture of *N*-propargylnormorphothebaine (5e; 0.30 g, 0.93 mol) in 10 mL of 48% (w/v) HBr was heated and evaporated in the same manner as described for the preparation of **3c-e**, to give a dry solid (0.35 g). Further purification of the product was carried out through the preparation of its triacetoxy derivative, followed by subsequent hydrolysis as follows: the residue was diluted with 10 mL of CF_3CO_2H, and 4.0 mL of acetyl bromide was added dropwise. After the initial exothermic reaction subsided, the reaction mixture was heated at 90 °C under nitrogen for 2 h and evaporated. The residue was taken up with 50 mL of $CHCl_3$, washed with 30 mL of 3% (w/v) $NaHCO_3$ in brine, dried, and concentrated to approximately 2 mL of a solution, which was then chromatographed on silica gel packed and eluted with $CHCl_3/Et_2O$ (1:1) to give a pure product with an R_f of 0.32 (in $CHCl_3$) on TLC. The triacetoxy derivative underwent alcoholysis after being treated with a mixture of 25 mL of absolute methanol and 12.5 mL of ethereal HCl for 16 h. The reaction mixture was evaporated to a residue, which was recrystallized from a methanol and ethyl ether mixture to give an off-white solid: yield 120 mg (38%); mp 180-184 °C; TLC R_f 0.40 ($CH_3OH/CHCl_3$, 1:6); NMR (CD_3OD) δ 2.77-4.40 (broad signals, H at C-4, C-5, C-6a, C-7, NCH_2), 6.43-7.10 (m, 5, H at C-3, C-8, C-9, C=CH_2), 7.9-8.0 (d, 1, H at C-1); UV (EtOH) λ_{max} 271 nm (log ϵ 4.11), 279 (4.12), 303 (3.86); MS, *m/e* 388 (M^+). Anal. ($C_{19}H_{18}NO_3Br \cdot HCl \cdot 0.5H_2O$) C, H, N.

***N*-Propargyl-2,10,11-trihydroxynoraporphine (3g).** A mixture of normorphothebaine hydrochloride (6; 1.5 g, 4.7 mol) in 48% (w/v) HBr was heated at 130 °C under nitrogen for 3 h and evaporated in vacuo. The residue was taken up with a minimal amount of absolute methanol, and the solution was added dropwise to 200 mL of ethyl ether to give a precipitate. Filtration of the mixture yielded the intermediate 2,10,11-trihydroxynoraporphine (**3a**; 1.55 g). A mixture of **3a**, propargyl bromide (0.54 g, 4.5 mol), $NaHCO_3$ (0.92 g, 11 mol), and 0.3 g of potassium iodide in 75 mL of acetonitrile was heated at reflux under nitrogen for 18 h, cooled, and filtered. The filtrate was evaporated to a residue, which was taken up with 5 mL of a chloroform and methanol mixture (1:1), and the solution was added dropwise to 100 mL of ethyl ether to result in precipitation. The supernatant was decanted and evaporated to give the crude desired product (0.45 g, 32%). Further purification of the product was carried out through the preparation of its triacetoxy derivative, followed by column chromatography and acid hydrolysis in the same manner as the preparation of **3f** to give pure **3g** as hydrochloride salt: yield 275 mg (17%); mp 178-181 °C; NMR ($CDCl_3/CD_3OD$) δ 2.8-4.4 (broad signals, H at C-4, C-5, C-6a, C-7, NCH_2, C≡CH), 6.4-6.7 (m, 3 H at C-3, C-8, C-9), 7.8 (d, 1, H at C-1); UV (EtOH) λ_{max} 238 nm (log ϵ 4.40), 259 (4.40), 280 (4.14), 306 (4.03), 358 (3.62), 376 (3.61); MS, *m/e* 307 (M^+). Anal. ($C_{19}H_{17}NO_3 \cdot HCl \cdot H_2O$) C, H, N.

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Analgesic Narcotic Antagonists. 8.[1] 7α-Alkyl-4,5α-epoxymorphinan-6-ones

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The preparation of a series of 7α-alkylated dihydrocodeinones is described. *N*-(Cyclopropylmethyl) (P series) or *N*-(cyclobutylmethyl) (B series) 7α-methyl (a series) or 7α,8β-dimethyl (b series) substituted dihydronorcodeinones (**7**) were prepared from the appropriately substituted *N*-(cycloalkylmethyl)-4-hydroxymorphinan-6-ones (**5**) by dibromination, 4,5-epoxy ring closure, and catalytic debromination. Treatment of **7** with BBr_3 gave low yields of the corresponding 3-phenols **8**. Alternatively, reaction of dihydrocodeinone (**10**) with dimethylformamide dimethyl acetal gave the 7-[(dimethylamino)methylene] adduct **11**, which was hydrogenated to 7α-methyl- (**12**) or 7α-(hydroxymethyl)dihydrocodeinone (**13**). Treatment of **11** with lithium reagents, followed by hydrogenation, gave a mixture of 7α-alkyl (**15c-f**) compounds and the corresponding 4,5-epoxy-cleaved products **16**. Reaction of **11** with α-ethoxyvinyllithium gave intermediate **17**, which on hydrolysis and hydrogenation yielded the 6,7-furyl (**18**) or pyrroyl (**19**) derivative. *N*-(Cycloalkylmethyl)-14-hydroxydihydronorcodeinones **23P,B** reacted with dimethylformamide dimethyl acetal to give **25P,B**, which were hydrogenated to the 7α-methyl compounds **26P,B** and O-demethylated to give **27P,B**. The 7α-methyl-*N*-methyl compounds were about equipotent with dihydrocodeinone. Derivatives with larger alkyl groups were less potent. Corresponding *N*-(cycloalkylmethyl) compounds did not show strong mixed agonist-narcotic antagonist activity.

We recently reported[2] that reaction of thebaine with lithium dimethylcuprate yields 7β-methyldihydrothebaine-φ (**1**). The facile preparation of this 4,5α-epoxy-cleaved 7-alkylated product allowed entry into a series of 7-methyl-8-alkylmorphinan-6-ones and -isomorphinan-6-ones with potent analgesic activity.[3] These compounds were converted to their corresponding *N*-(cycloalkylmethyl) derivatives, several of which had interesting mixed agonist-narcotic antagonist properties. In view of the modification in the pharmacological profile of opiate derivatives by the incorporation of alkyl groups in the C ring,[3,4] we have now extended our work to the preparation of the 4,5α-epoxy counterparts of these previously reported

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