$MgSO_4$, and concentrated in vacuo. The oily residue was chromatographed on silica gel using CH_2Cl_2 as eluent to give **10** (13.6 g, 95%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.27 (m, 6 H), 1.4–1.9 (m, 8 H), 3.3–3.9 (m, 13 H), 4.45 (s, 2 H), 4.55 (br s, 1 H), 7.28 (m, 5 H). Anal. ($C_{21}H_{35}O_7P$) C, H.

(*S*)-Diethyl [[3-[(Methylsulfonyl)oxy]-1-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]propoxy]methyl]phosphonate (12). A mixture of **10** (11.3 g, 26.3 mmol) and 10% palladium on activated carbon (5.6 g) in EtOH (200 mL) was hydrogenated in a Parr hydrogenator at 50 psi for 16 h. The catalyst was filtered through Celite and washed with MeOH, and the combined solvents were evaporated to give **11** (8.4 g, 93%) as a colorless oil. This material was used for the next step without purification. Thus, a solution of **11** (3.8 g, 11.2 mmol) and methanesulfonyl chloride (1.6 g, 13.6 mmol) in CH_2Cl_2 (60 mL) was added at 0 °C to a solution of triethylamine (2.35 g, 23 mmol) in CH_2Cl_2 (5 mL). After stirring at 0 °C for 2 h, the CH_2Cl_2 was washed with 30% H_3PO_4 and brine, dried over $MgSO_4$, and evaporated in vacuo. The crude oil was chromatographed on silica gel using CH_2Cl_2 as eluent to give **12** (4.0 g, 85%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.25 (m, 6 H), 1.4–2.0 (m, 8 H), 2.95 (s, 3 H), 3.40 (m, 2 H), 3.6–4.4 (m, 11 H), 4.55 (br s, 1 H).

(*S*)-2-Amino-6-chloro-9-[3-[(diethylphosphono)methoxy]-4-(tetrahydro-2*H*-pyran-2-yloxy)butyl]purine (13). To a suspension of 57% sodium hydride in mineral oil (200 mg, 14.6 mmol) in dry DMF (30 mL) was added 2-amino-6-chloropurine (1.35 g, 8 mmol) under nitrogen. After stirring at 25 °C for 45 min, the mixture was heated at 55 °C for 2 h. To this solution was added at 25 °C a solution of **12** (3.28 g, 8 mmol) in DMF (8 mL) and the mixture was heated at 65 °C for 5 h. The solution was then concentrated in vacuo, taken up in CH_2Cl_2, washed with water, 30% H_3PO_4, aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2–5% MeOH as eluent to give **13** (2.1 g, 52%) as a slightly yellow, hard oil: ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 6 H), 1.3–2.1 (m, 8 H), 3.40 (m, 2 H), 3.6–4.4 (m, 13 H), 4.65 (br s, 1 H), 5.51 (s, 2 H), 7.86 (s, 1 H). Anal. ($C_{19}H_{31}N_5O_6PCl$) C, H, N.

(*S*)-9-[4-Hydroxy-3-(phosphonomethoxy)butyl]guanine Disodium Salt (3). To a solution of **13** (2.5 g, 5.1 mmol) in CH_3CN (40 mL) was added at 0 °C bromotrimethylsilane (3 mL) under nitrogen. After stirring at 0 °C for 3 h, the volatiles were removed in vacuo, the residual oil was dissolved in 2 N HCl (10 mL), and the solution was heated at 110 °C. Water was then evaporated in vacuo and the residue was adjusted to pH 8 with aqueous $NaHCO_3$. Evaporation of water gave an amorphous solid which was purified by C-18 reverse phase column under 8 psi of pressure using water as eluent to give **3** (800 mg, 47%) as a white solid: ^1H NMR (D_2O) δ 1.95 (m, 2 H), 3.36 (m, 1 H), 3.435 (dd, J = 3.8, 12.3 Hz, 1 H), 3.54 (d, J = 9.4 Hz, 2 H), 3.7 (dd, J = 3.8, 12.3 Hz, 1 H), 4.12 (t, J = 7.2 Hz, 2 H), 7.88 (s, 1 H); ^{13}C NMR (D_2O) δ 32.570, 42.340, 64.005, 67.833, 69.854, 80.793, 80.947, 117.816, 142.079, 153.300, 155.502, 160.889; UV max (H_2O) 252 nm (ϵ 12159), 274 nm (ϵ 8882). Anal. Calcd for $C_{10}H_{14}N_5O_6PNa_2 \cdot 2.5H_2O$: C, 28.42; H, 4.55; N, 16.65. Found: C, 28.36; H, 5.14; N, 16.15.

In a manner similar to that described for the synthesis of **3**, compounds **14** and **15** were prepared by coupling of **12** and adenine and cytosine. The spectroscopic data are as follows.

(*S*)-9-[4-Hydroxy-3-(phosphonomethoxy)butyl]adenine disodium salt (14): ^1H NMR (D_2O) δ 1.98 (m, 2 H), 3.30 (m, 1 H), 3.43 (dd, J = 3.6, 12.3 Hz, 1 H), 3.48 (d, J = 10.0 Hz, 2 H), 3.67 (dd, J = 3.6, 12.3 Hz, 1 H), 4.2 (t, J = 7.2 Hz, 2 H), 7.92 (s, 1 H), 8.03 (s, 1 H); UV max (H_2O) 262 nm (ϵ 12642). Anal. Calcd for $C_{10}H_{14}N_5O_6PNa_2 \cdot 3.5H_2O$: C, 28.12; H, 3.91; N, 16.05. Found: C, 28.30; H, 4.45; N, 16.55.

(*S*)-1-[4-Hydroxy-3-(phosphonomethoxy)butyl]cytosine (15): ^1H NMR (D_2O) δ 1.91 (m, 2 H), 3.45 (m, 1 H), 3.53 (d, J = 9.6 Hz, 2 H), 3.6–3.9 (m, 4 H), 6.03 (d, J = 7.2 Hz, 1 H), 6.72 (d, J = 7.2 Hz, 1 H); UV max (H_2O) 282 nm (ϵ 9486). Anal. Calcd for $C_{19}H_{16}N_3O_6P$: C, 34.74; H, 5.14; N, 13.50. Found: C, 34.64; H, 5.35; N, 13.02.

Synthesis and Dopamine Receptor Affinities of Enantiomers of 2-Substituted Apomorphines and Their *N*-*n*-Propyl Analogues

Yigong Gao,† Ross J. Baldessarini,‡ Nora S. Kula,‡ and John L. Neumeyer*,†

Section of Medicinal Chemistry, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115, and Departments of Psychiatry and Neuroscience Program, Harvard Medical School and Mailman Research Center, McLean Division of Massachusetts General Hospital, Belmont, Massachusetts 02178.
Received November 30, 1989

Syntheses of (*R*)-(−)-2-methoxyapomorphine (*R*-**8**), its antipode *S*-**8**, and its (*R*)-(−)-*N*-*n*-propyl *R*-**9** derivative are described. The dopaminergic receptor affinities of these compounds and their 2-unsubstituted counterparts (*R*)-(−)-apomorphine (*R*(−)-APO, *R*-**1**), (*S*)-(+)-apomorphine (*S*(+)-APO, *S*-**1**), and (*R*)-(−)-*N*-*n*-propylnorapomorphine (*R*(−)-NPA, *R*-**2**), as well as those of (*R*)-(−)-2-chloroapomorphine (*R*(−)-2-Cl-APO, *R*-**6**), (*R*)-(−)-2-bromoapomorphine (*R*(−)-2-Br-APO, *R*-**6**), were determined with tissue membrane preparations of corpus striatum from rat brain. Contribution of both an *N*-*n*-propyl and a 2-hydroxy in (*R*)-(−)-2-hydroxy-*N*-*n*-propylnorapomorphine (*R*(−)-2-OH-NPA, *R*-**7**) or a methoxy group in (*R*)-(−)-2-methoxy-*N*-*n*-propylnorapomorphine (*R*(−)-2-OCH_3-NPA, *R*-**9**) produced the highest D_2 affinity (0.053 and 0.17 nM) and D_2 over D_1 selectivity (17300 and 10500 times) of the compounds evaluated. The structure–affinity relationships of these 2-substituted aporphines suggest that secondary binding sites of D_2 receptors interact with 2-substituents on the A ring of aporphines through H-bonding.

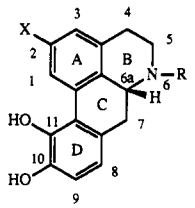
The rigid structure of aporphine alkaloids can be related to several conformations of the neurotransmitter dopamine (DA) (cis,trans-α-rotamer and trans-β-rotamer).[1,2] This unique character of aporphine derivatives has stimulated extensive study of the structure–activity relationship (SAR) of a large number of such compounds.[3] This work supports the conclusion that the α-rotamer is the biologically relevant conformation in aporphines to provide high affinity and dopaminergic activity, such as the prototype DA agonists (*R*)-(−)-apomorphine (**1**, *R*(−)-APO) and (*R*)-(−)-*N*-*n*-propylnorapomorphine (**2**, *R*(−)-NPA).

Novel 2-substituted (*R*)-(−)-apomorphines have been prepared in our laboratories.[4] These compounds, with

† Northeastern University.
‡ Harvard Medical School.

(1) Horn, A. S.; Rodgers, J. R. *J. Pharm. Pharmcol.* **1980**, *32*, 521–524.
(2) Kaiser, C.; Jain, T. *Med. Res. Q.* **1985**, *5*, 145–229.
(3) Neumeyer, J. L. *Synthesis and structure–activity relationships of aporphines as dopamine receptor agonists and antagonists.* Philipson, J. D., Roberts, M. F., Zenk, M. H., Eds.; Chemistry and Biology of Isoquinoline Alkaloids; Springer-Verlag: Berlin, 1985; pp 146–169.

0022-2623/90/1833-1800$02.50/0

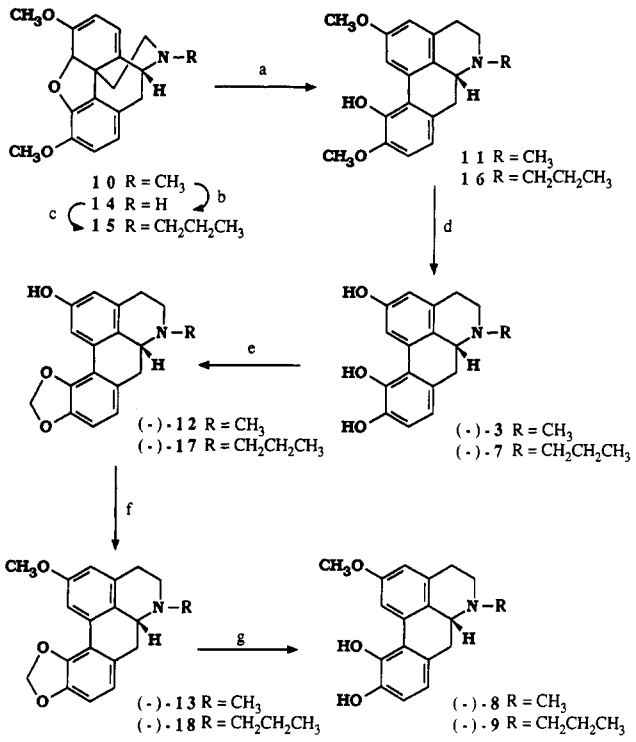


	Compound	X	R
1	(R)-APO	H	CH_3
2	(R)-NPA	H	$CH_2CH_2CH_3$
3	(R)-2-OH-APO	OH	CH_3
4	(R)-2-F-APO	F	CH_3
5	(R)-2-Br-APO	Br	CH_3
6	(R)-2-Cl-APO	Cl	CH_3
7	(R)-2-OH-NPA	OH	$CH_2CH_2CH_3$
8	(R)-2-OCH_3-APO	OCH_3	CH_3
9	(R)-2-OCH_3-NPA	OCH_3	$CH_2CH_2CH_3$

halo or amino groups at the 2-position, provided additional insights regarding interactions between aporphines and DA receptors. (*R*)-(−)-2-Fluoroapomorphine (*R*(−)-2-F-APO) was found to be a very potent and highly selective agonist for the D_2 receptor subtype.[4] In contrast, (*R*)-(−)-2-aminoapomorphine (*R*(−)-2-NH_2-APO) showed lower DA receptor affinity than APO.[4] To account for these findings, we proposed that there might be a lipophilic cleft on the putative D_2 receptor that may interact with 2-substituents on the A ring of aporphines. This lipophilic cleft would repel relatively hydrophilic groups, such as amino, so as to disrupt binding at other functional sites involved in ligand–DA receptor interaction.[4] It was proposed further that a steric factor also is involved in the hydrophobic interaction between the 2-substituent and the putative lipophilic cavity. This hypothesis was put forward to explain the somewhat lower affinity of (*R*)-(−)-2-bromoapomorphine (*R*(−)-2-Br-APO) as compared to its 2-fluoro congener, in which the halogen is much smaller in size. Whether these assumptions apply independently to functional groups on the A ring or to the effects of these groups on the A ring through electronic or resonance effects is not clear. Additional modification at the 2-position of aporphines should provide further information. Since a methoxy group is a more lipophilic group than an amino or a hydroxy group, and less bulky than a bromo group, the synthesis and pharmacologic assessment of 2-methoxyaporphines were undertaken.

The enantiomers of various aporphines have been utilized to complement SAR studies of DA receptors.[5-8] The *R*-(−) enantiomers of APO, NPA, and 11-hydroxy-*N*-*n*-propylnoraporphine (11-OH-NPa) have shown predicted potent activity as DA agonists. Their corresponding antipodal *S*-(+) enantiomers, which exhibit identical physical properties, exert DA antagonistic activity in rodent behavioral paradigrams and this effect of *S*(+)-NPA may be selective for *limbic* DA systems.[7,8] This enantiomeric difference has been considered recently in proposing a model of the DA receptor surface.[6] Examination of how 2-substituents relate to enantiomeric activity also may advance knowledge of DA receptors, perhaps specifically the D_2 subtype. In this report we present the synthesis

Scheme I[a]



[a] Reagents: (a) CH_3SO_3H; (b) ethyl azodicarboxylate; NH_2NH_2; (c) nPrI, K_2CO_3; (d) HBr; (e) CH_2Br_2, NaOH, DMSO; (f) CH_2N_2, ether; (g) BCl_3, CH_2Cl_2.

and preliminary pharmacological characterization of (*R*)-(−)- and (*S*)-(+)-2-methoxyapomorphine [*R*(−)-2-OCH_3-APO (*R*-8) and *S*(+)-2-OCH_3-APO (*S*-8)]. Additionally, since an optimal size of the *N*-alkyl substituent on the aporphine skeleton appears to be of significant value as a steric or lipophilic pharmacophore responsible for high affinity, selectivity, and dopaminergic activity,[9] results with the relevant (*R*)-(−)-*N*-*n*-propyl analogue (*R*-9) also are reported for comparison with *R*(−)-2-OCH_3-APO (*R*-8).

Chemistry

Our synthetic route is based on the use of (*R*)-(−)- and (*S*)-(+)-2,10,11-trihydroxyaporphine (*R*-3 and *S*-3) and (*R*)-(−)-2,10,11-trihydroxy-*N*-*n*-propylnoraporphine (7) which were previously synthesized from the alkaloids thebaine or bulbocapnine and characterized in one of our laboratories.[10,11] Selective protection of the catechol function (10,11-dihydroxy moiety) in trihydroxyaporphines, as described previously in the synthesis of (*R*)-(−)-2-fluoroapomorphine,[4] followed by O-methylation of the free 2-hydroxy group with diazomethane yielded 2-methoxy-10,11-(methylenedioxy)aporphines. Several reported methods[12,13] of O-demethylenation failed to demethylenate without affecting the 2-methoxy group. However, a more facile cleavage of the aromatic methylenedioxy group, using boron trichloride as the demethylenating agent, was attempted.[13,14] This reaction was

(4) Ramsby, S.; Neumeyer, J. L.; Grigoriadis, D.; Seeman, P. *J. Med. Chem.* **1989**, *32*, 1198–1201.
(5) Neumeyer, J. L.; Reischig, D.; Arana, G. W.; Campbell, A.; Baldessarini, R. J.; Kula, N. S.; Watling, K. J. *J. Med. Chem.* **1983**, *26*, 516–521.
(6) Neumeyer, J. L.; Froimowitz, M.; Baldessarini, R. J.; Campbell, A.; Gao, Y. *J. Receptor Res.* **1988**, *8*, 83–96.
(7) Froimowitz, M.; Neumeyer, J. L.; Baldessarini, R. J. *J. Med. Chem.* **1986**, *29*, 1570–1573.
(8) Gao, Y.; Zong, R.; Campbell, A.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **1988**, *31*, 1392–1396.
(9) Gao, Y.; Ram, V. J.; Campbell, A.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **1990**, *33*, 99–44.
(10) Neumeyer, J. L.; Arana, G. W.; Ram, V. J.; Kula, N. S.; Baldessarini, R. J. *J. Med. Chem.* **1982**, *25*, 990–992.
(11) Neumeyer, J. L.; Law, S.-J.; Meldrum, B.; Anlezark, G.; Watling, K. J. *J. Med. Chem.* **1981**, *24*, 898–899.
(12) Trammell, G. L. *Tetrahedron Lett.* **1978**, *18*, 1525–1528.
(13) Teitel, S.; O'Brien, J.; Brossi, A. *J. Org. Chem.* **1972**, *37*, 3368–3369.

Table I. Affinity of 2-Substituted Aporphines at Striatal Dopamine Receptors[a]

no.	compd	K_i, nM agonist	K_i, nM D_1	K_i, nM D_2	D_2/D_1 potency ratio
R-1	*R*(−)-APO	3.70	236	11.1	21.2
R-3	*R*(−)-2-OH-APO	2.18	800	0.38	2,100
R-8	*R*(−)-2-OCH_3-APO	16.4	<10,000	1.12	>9,000
R-6	*R*(−)-2-Cl-APO		74.5	22.3	3.30
R-5	*R*(−)-2-Br-APO		106	17.7	6.00
S-1	*S*(+)-APO	47.4	2,980	58.3	51.1
S-3	*S*(+)-2-OH-APO	511	851	100	8.50
S-8	*S*(+)-2-OCH_3-APO	162	<10,000	34.7	>300
R-2	*R*(−)-NPA	1.50	340	0.80	425
R-7	*R*(−)-2-OH-NPA	1.15	915	0.053	17,300
R-9	*R*(−)-2-OCH_3-NPA	3.84	1,780	0.17	10,500

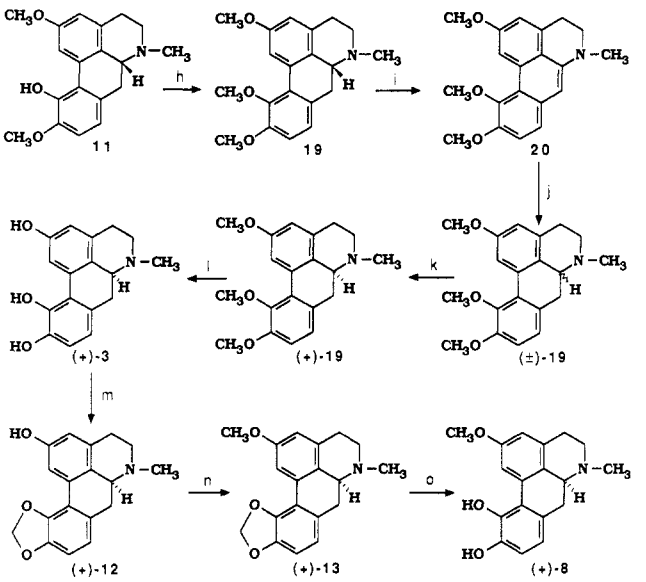
[a] Radioreceptor assays were carried out with the following tritiated ligands: DA agonist ([±]-[^{3}H]ADTN, 0.5 nM), D_1 antagonist ([^{3}H]-SCH-23390, 0.3 nM), and D_2 antagonist ([^{3}H]spiperone, 0.15 nM), using rat striatal tissue for the D_1 and D_2 assays and calf striatal tissue for the agonist assay. Values of experimentally determined IC50 (SEM of which average ≤±10% of the mean) were converted to K_i values, using the following experimentally determined values of K_d: 1.5 nM ([^{3}H]ADTN), 0.34 nM ([^{3}H]SCH-23390), and 0.03 nM ([^{3}H]spiperone).

influenced by several factors, including the molar ratio of substrate and reagent, reaction temperature, and time. The weaker nucleophilic character of the chloride ion compared to bromide may discriminate between the monomethoxy and the methylenedioxy functions and so afford proper control of reaction conditions.[13] Synthesis of (*R*)-(−)-2-methoxyapomorphine (*R*-**8**) from thebaine is outlined in Scheme I. Thus, rearrangement of thebaine (**10**) was carried out as previously described[15] to give compound (*R*)-(−)-**11**, which was converted to (*R*)-(−)-2,10,11-trihydroxyaporphine (*R*-**3**)[10] with 48% HBr. The catechol group on the aporphine D ring was protected by conversion to a 10,11-methylenedioxy group by methylenation of *R*-**3**, with dibromomethane and NaOH in DMSO[4] to obtain *R*-**12**. The 2-hydroxy group of *R*-**12** then was 2-O-methylated with diazomethane to afford *R*-**13**. Selective cleavage of the 10,11-methylenedioxy group of *R*-**13** was accomplished with boron trichloride to afford *R*-**8**. (*R*)-(−)-2-Methoxy-*N*-*n*-propylnoraporphine (*R*-**9**) also was prepared by this procedure as described in Scheme I. Thebaine (**10**) was N-demethylated to give northebaine (**14**),[16] which was alkylated with propyl iodide and K_2CO_3 in EtOH to afford **15**. The free base of **15** was converted to compound *R*-**9** following the same procedure for conversion of compound **10** to compound *R*-**8**.

An alternative route, not involving the aporphine alkaloid (*S*)-(+)-bulbocapnine as a starting material as reported previously,[10] was used to obtain (*S*)-(+)-2,10,11-trihydroxyapomorphine (*S*-**3**). Thus, compound **11** was methylated with diazomethane to provide (*R*)-(−)-2,10,11-trimethoxyapomorphine (*R*-**19**), which was racemized by dehydrogenation with 10% palladium on carbon in acetonitrile to give **20**, followed by reduction with sodium cyanoborohydride to afford racemic **19** (Scheme II). Resolution of (±)-**19** was accomplished by fractional recrystallization of the diastereomeric dibenzoyltartrate, a procedure that has been applied successfully to resolving similar racemic aporphine compounds.[5,8] The 2,10,11-trihydroxy intermediate *S*-**3** was obtained by O-demethylation of *S*-**19** with 48% HBr and then carried through the synthesis previously described for its antipode *R*-**3** to give compound (*S*)-(+)-2-methoxyapomorphine (*S*-**8**) as the expected product.

(*R*)-(−)-2-Chloroapomorphine (**6**) and (*R*)-(−)-2-bromoapomorphine (**5**) also were synthesized in several steps from (*R*)-(−)-thebaine by published procedures.[17]

Scheme II[a]



[a] Reagents: (h) CH_2N_2, ether; (i) 10% Pd/C, CH_3CN, Δ; (j) $NaCNBH_3$, pH = 3; (k) L(−)-dibenzoyltartaric acid; K_2CO_3; (l) 48% HBr; (m) CH_2Br_2, NaOH, DMSO; (n) CH_2N_2, ether; (o) BCl_3, CH_2Cl_2.

Results and Discussion

The DA-receptor affinities of (*R*)-(−)- and (*S*-(+)-2-substituted aporphine derivatives (**3**, **5**–**9**) and their 2-unsubstituted counterparts [*R*(−)- and *S*(+)-APO and *R*(−)-NPA] were determined with tissue membrane preparations of corpus striatum from rat brain. These results are summarized in Table I with affinities expressed as the inhibition constant K_i. The (*R*)-2-substituted aporphine derivatives evaluated showed lower affinity at D_1 receptor sites labeled with [^{3}H]SCH-23390 than at D_2 sites labeled with [^{3}H]spiperone, and correspondingly greater D_2:D_1 selectivity. With the (*R*)-(−)-2-hydroxy- or 2-methoxy-substituted analogues of *R*(−)-APO, 2-substitution led to a 2100-fold and >9000-fold D_2 over D_1 selectivity, respectively (Table I), but this pattern was not found with (*S*)-(+)-2-substituted analogues of APO or with 2-halogenated (Cl, Br) analogues of *R*(−)-APO. (*R*)-(−)-2-Methoxyapomorphine exhibited a 9.9-fold higher affinity at DA agonist sites labeled with [^{3}H]ADTN and a 31-fold higher affinity at D_2 sites than its *S*-(+) enantiomer. This

(14) McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289–2292.
(15) Granchelli, F. E.; Filer, C. N.; Soloway, A. H.; Neumeyer, J. L. *J. Org. Chem.* **1980**, *45*, 2275–2278.
(16) British Patent 1 124 441 (to Eli Lilly and Co.) (Aug 21, 1968).
(17) Berenyi, S.; Markleit, S.; Rantal, F. *Acta Chim. Hung.* **1985**, *120*, 201–205.

observation is consistent with the 5.3-fold greater D_2 affinity of $R(-)$- than $S(+)$-APO (Table I) as well as with previous reports that the R configuration of aporphine derivatives such as NPA and 11-hydroxy-*N*-*n*-propylnoraporphine (11-OH-NPa) is more favorable for high affinity at DA receptors, especially of the D_2 type.[5,7,8] Surprisingly, the enantiomeric pair of 2-OH-APO, derived as intermediates in the present synthetic methods, showed a 263-fold enantioselectivity at D_2 sites, compared to a 5.3-fold selectivity with R over S isomer of APO and 31-fold selectivity for R over S isomer of 2-OCH_3-APO.

Introduction of the 2-methoxy substituent into $R(-)$-APO resulted not only in the unexpected 10-fold gain of D_2 affinity compared to APO but also a virtual loss of D_1 affinity as well as a 4-fold lower affinity at agonist sites (Table I). This pattern also was observed with the *N*-*n*-propyl analogue $R(-)$-2-OCH_3-NPA (**9**), which had a 5-fold increase of affinity at D_2 sites, a 5-fold decrease of affinity at D_1 sites, and a 2-fold decrease of affinity at agonist sites compared to $R(-)$-NPA. The reason for this reversal in D_2 vs ADTN affinity is not clear. A possible explanation is that the D_2 receptor site could require more lipophilic groups on the A ring of aporphine than the high-affinity agonist sites (which may represent D_1 as well as D_2 receptors) labeled with the relatively hydrophilic ligand ADTN.[18,19]

Recent studies confirmed the importance of the *N*-alkyl side chain of aporphines and found that substituents with a three-carbon unit resulted in a higher affinity and selectivity for D_2 receptor sites.[9] These results are substantiated by the present study. Without a 2-methoxy substituent, introduction of a *n*-propyl group in place of a methyl group increased affinity by 14-fold at D_2 receptors [$R(-)$-NPA vs $R(-)$-APO], and when these congeners contained a 2-methoxy or 2-hydroxy group, the *N*-propyl analogues $R(-)$-2-OCH_3-NPA and $R(-)$-2-OH-NPA bound with higher affinity to D_2 sites (both by about 7-fold) than the corresponding *N*-methylaporphines. Due to the contribution of both a *N*-propyl and a 2-hydroxy (or methoxy) function in $R(-)$-2-OH-NPA (**7**) and $R(-)$-2-OCH_3-NPA (**9**), these compounds showed the highest D_2 affinity (0.053 and 0.17 nM) and D_2 over D_1 selectivity (17 300 and 10 500 times), respectively, for the compounds evaluated in this series (Table I).

Electron-donating groups, such as hydroxy or methoxy, even though they are much less lipophilic than the fluoro group, evidently are more likely to interact with binding sites on the D_2 receptor as shown by the gain of affinity for $R(-)$-2-OH-APO and $R(-)$-2-OH-NPA by factors of 30 and 15, respectively. An improvement of affinity was also obtained with 2-methoxy-substituted analogues. By contrast, only a hydroxy group, but not a methoxy group, is capable of donating a hydrogen atom in a hydrogen bond. Furthermore, a 2-fluoro substituent not only induces an opposite inductive effect on the electronic structural characteristics of the benzo-A-ring to that of 2-hydroxy or methoxy functions but also lacks a hydrogen atom for a hydrogen bond. The 2-hydroxy, 2-methoxy, or 2-fluoro substituent effect on the D_2 receptor with their lipophilicity and inductive effect as well as H-bond by donating the hydrogen atom seems to be paradoxical. An alternate hypothesis for the effects of 2-substituents may relate to their ability to accept a hydrogen bond that is donated from the receptor. On that basis, the 2-unsubstituted, 2-chloro, and 2-bromo compounds cannot participate in such hydrogen-bonding interactions and hence have lower affinity for the D_2 receptor. Our results cannot rule out the possibility of size restriction of a hypothetical hydrophobic cavity on the D_2 receptor as an explanation for the decrease in affinity of a large 2-bromo group.

The present experiments indicate that 2-substitution on the A ring of apomorphine greatly affects ability to compete with DA receptor–radioligands, especially at D_2 sites. These leads should encourage further efforts to develop potent D_2 dopaminergic aporphines and to enlarge the range of SAR of this versatile class of rigid DA analogues.

Experimental Section

All chemicals were used as received from the manufacturer. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were obtained with a Varian T-60 or XL-300 spectrometer using TMS as the internal reference. Mass spectra of novel compounds were determined with a high-resolution Finnigan 4021 mass spectrometer. Optical rotations were obtained with a Perkin-Elmer Model 241 polarimeter. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA; analyses are reported by symbols of the elements within ±0.4% of calculated values.

(*R*)-(−)-2-Methoxy-10,11-(methylenedioxy)aporphine Hydrochloride (*R*-13·HCl). Compound (−)-12·HCl (3.7 g, 11.2 mmol), prepared as previously described,[4] was dissolved in 10 mL of MeOH and allowed to react with an excess of CH_2N_2 in ether (prepared from 34 g of Diazald) overnight. The solvents were evaporated and crude products were purified by flash chromatography. The resulting oil was dissolved in the ether (400 mL) and then precipitated by the addition of HCl/ether solution. Solid was collected by filtration to give 3.4 g of *R*-13·HCl. Yield: 88.2%; mp 237–238 °C. Mass spectrum: m/z 309 (M^+). ^1H NMR ($CDCl_3$, TMS) δ 7.56 (d, J = 2 Hz, 1 H, 1-H), 6.72 (m, 2 H, 8,9-H), 6.65 (d, J = 2 Hz, 1 H, 3-H), 6.05 (s, 1 H, OCHO), 5.98 (s, 1 H, OCHO), 3.82 (s, 3 H, OCH_3), 3.58–3.71 (m, 4 H), 3.32–3.43 (m, 3 H), 3.15 (s, 3 H, NCH_3). Anal. ($C_{19}H_{19}NO_3$·HCl·0.75H_2O) C, H, N.

(*R*)-(−)-2-Methoxyapomorphine Hydrochloride (*R*-8·HCl). Compound *R*-13·HCl (190 mg, 0.55 mmol) was dissolved in 5 mL of CH_2Cl_2 under a N_2 atmosphere. Solution of 1 M BCl_3 (1 mL, 1 mmol) in hexane was added at 0 °C. The flask was closed with a Teflon seal, and the reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with MeOH and evaporated to dryness. The residue was dissolved in MeOH, refluxed for 15 min, and evaporated again; this procedure was repeated twice. The product was recrystallized from ether/MeOH to give 160 mg of *R*-8·HCl (87%). Mp: 248–250 °C dec. Mass spectrum: m/z 297 (M^+). ^1H NMR (CD_3OD, TMS): δ 8.0 (d, J = 2 Hz, 1 H, 1-H), 6.59–6.69 (m, 3 H, ArH), 4.20 (m, 1 H), 3.74 (s, 3 H, OCH_3), 3.25–3.65 (m, 4 H), 3.09 (s, 3 H, NCH_3), 2.7–3.0 (m, 2 H). $[\alpha]^{25}_D$: −115.4 (c 0.2, MeOH). Anal. ($C_{18}H_{19}NO_3$·HCl·0.5H_2O) C, H, N.

***N*-*n*-Propylnorthebaine (15).** Compound 14·HCl (20.8 g, 62.3 mmol) was prepared as described previously,[16] and K_2CO_3 (19.4 g, 140.4 mmol) was suspended in absolute EtOH (150 mL). Propyl iodide (12 g, 70.6 mmol) in 50 mL of absolute EtOH was added to the reaction mixture and refluxed overnight. The solvent was evaporated to dryness and remaining residue extracted with ether, washed with water, dried over anhydrous $MgSO_4$, concentrated to a smaller volume, and left standing over several hours. Crystals of the product were collected by filtration to afford 15 g of 15 (71%). Mp: 135–136 °C. Mass spectrum: m/z 339 (M^+). ^1H NMR ($CDCl_3$, TMS): δ 6.59 (m, 2 H, ArH), 5.50 (d, 1 H, —CH=), 5.23 (s, 1 H, OCH), 5.0 (d, 1 H, —CH=), 3.72 (s, 3 H, OCH_3), 3.58 (s, 3 H, OCH_3), 2.4–3.2 (m, 9 H), 1.4–1.8 (m, 2 H), 1.0 (t, 3 H, CH_3). Anal. ($C_{21}H_{25}NO_3$) C, H.

(*R*-(−)-2,10-Dimethoxy-11-hydroxy-*N*-*n*-propylnoraporphine Hydrochloride (*R*-16·HCl). Compound 15 (10 g, 29.5 mmol) was dissolved in 40 mL of methanesulfonic acid. The mixture was heated to 90–95 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with 150 mL of water and adjusted to pH 8 with concentrated aqueous ammonia. The mixture was extracted with chloroform, and combined extracts were washed with water and dried over anhydrous $MgSO_4$, filtered, and then evaporated to dryness. The product was con-

(18) Arana, G. W.; Baldessarini, R. J.; Lamont, J. S.; Amlicke, D.; Neumeyer, J. L. *Biochem. Pharmacol.* **1983**, *32*, 2873–2880.
(19) Seeman, P. *Pharmcol. Rev.* **1981**, *32*, 229–287.

verted to the HCl salt with HCl/ether to yield 10.6 g (96%) of 16·HCl, which was directly used in next step without further purification.

(*R*)-(−)-2,10,11-Trihydroxy-*N*-*n*-propylnoraporphine Hydrobromide (7·HBr). Compound 16·HCl (10.6 g, 28.2 mmol), 48% HBr (100 mL), and glacial acetic acid (100 mL) were combined and heated at 130 °C with stirring for 4 h. The resulting dark reddish solution was evaporated to dryness by vacuum. The residue was dissolved in small amount of MeOH and then dropped with stirring into ether. The off-white solid was filtered to give 11 g of 7 as the HBr salt (99%). Mp: 203–206 °C. $[\alpha]^{25}_{546}$: −62.0 (*c* 0.2, MeOH). [Lit.[11] Mp: 203–206 °C. $[\alpha]^{25}_{548}$: −62°.]

(*R*)-(−)-2-Hydroxy-10,11-(methylenedioxy)-*N*-*n*-propylnoraporphine Hydrochloride (17·HCl). Finely ground NaOH (2.75 g, 68.8 mmol) was added to a solution of 7·HBr (9 g, 22.9 mmol) in 200 mL of dry DMSO at ambient temperature under N_2 and stirred for 1 h. CH_2Br_2 (5.18 g, 29.8 mmol) was added and the mixture was heated at 80 °C for 4 h. After cooling, the solution was poured into ice–water and extracted with AcOEt. Drying (over $MgSO_4$) and evaporation of the organic solvent under reduced pressure gave an oil. The product (compound 17) was isolated by flash chromatography (5% MeOH in CH_2Cl_2 as eluent) and converted to the HCl salt by HCl/ether to give (4.04 g (49%) of 17·HCl. Mp: 225–226 °C. Mass spectrum: *m/z* 323 (M^+). ^{1}H NMR (CD_3OD, TMS): δ 7.6 (d, *J* = 2 Hz, 1 H, 1-H), 6.9 (d, *J* = 8 Hz, 1 H, 8- or 9-H), 6.8 (d, *J* = 8 Hz, 1 H, 8- or 9-H), 6.68 (d, *J* = 2 Hz, 1 H, 3-H), 6.19 (s, 1 H, OCHO), 6.04 (s, 1 H, OCHO), 4.4 (m, 1 H), 3.9 (m, 1 H), 3.2–3.68 (m, 5 H), 3.1 (dd, 1 H), 2.92 (m, 1 H), 1.8–2.0 (m, 2 H), 1.15 (t, 3 H, CH_3). Anal. ($C_{20}H_{21}NO_3$·HCl·$2H_2O$) C, H, N.

(*R*)-(−)-2-Methoxy-10,11-(methylenedioxy)-*N*-*n*-propylnoraporphine Hydrochloride (18·HCl). Compound 17·HCl (1.1 g, 3.06 mmol) was dissolved in 5 mL of MeOH and allowed to react with an excess of CH_2N_2 in ether (prepared from 24 g of Diazald) overnight. The solvents were evaporated, and crude products were purified by flash chromatography. The resulting oil was converted to the HCl salt to give 0.67 g of 18·HCl. Yield: 59%. Mp: 250–251 °C. $[\alpha]^{25}_D$: −73.1° (*c* 0.08, MeOH). Mass spectrum: *m/z* 337 (M^+). ^{1}H NMR ($CDCl_3$, TMS): δ 7.6 (d, *J* = 2 Hz, 1 H, 1-H), 6.78 (d, 1 H, *J* = 8 Hz, 8- or 9-H), 6.75 (d, *J* = 2 Hz, 1 H, 3-H), 6.7 (d, 1 H, *J* = 8 Hz, 8- or 9-H), 6.10 (s, 1 H, OCHO), 5.94 (s, 1 H, OCHO), 4.38 (m, 1 H), 3.85 (m, 1 H), 3.75 (s, 3 H, OCH_3), 3.0–3.6 (m, 6 H), 2.79 (t, 1 H), 1.7–1.95 (m, 2 H), 1.05 (t, 3 H, CH_3). Anal. ($C_{21}H_{23}NO_3$·HCl) C, H, N.

(*R*)-(−)-2-Methoxy-*N*-*n*-propylnorapomorphine Hydrochloride (9·HCl). The title compound 9·HCl was synthesized from the methylenedioxy derivatives 18 (200 mg, 0.535 mmol) as described for compound 8 above. After recrystallization from MeOH/ether, the 163 mg (83%) of 9·HCl as crystals was collected by filtration. Mp: 225–227 °C. Mass spectrum: *m/z* 325 (M^+). ^{1}H NMR ($CDCl_3$, TMS): δ 8.0 (d, *J* = 2 Hz, 1 H, 1-H), 6.67 (m, 3 H, ArH), 4.2 (m, 1 H), 3.82 (m, 1 H), 3.77 (s, 3 H, OCH_3), 3.52 (m, 1 H), 3.15–3.27 (m, 4 H), 3.05 (m, 1 H), 2.68 (t, 1 H), 1.7–1.9 (m, 2 H), 1.05 (t, 3 H, CH_3). Anal. ($C_{20}H_{23}NO_3$·HCl·$0.75H_2O$) C, H, N.

(*R*)-(−)-2,10,11-Trimethoxyaporphine (*R*-19). Compound 11 (14.3 g, 45.9 mmol) as free base was prepared from thebaine (10) as previously described[4] and then treated as described for (−)-13 to give 14.5 g of *R*-19 as the free base (97%). As described for *R*-13·HCl, a small amount of compound 19 was converted to the HCl salt for characterization: Mp: 254–255 °C. $[\alpha]^{25}_D$: −152.2° (*c* 0.22, MeOH). Mass spectrum: *m/z* 325 (M^+). ^{1}H NMR (CD_3OD, TMS): δ 7.93 (d, *J* = 2 Hz, 1 H, 1-H), 7.10 (d, *J* = 8 Hz, 1 H, 8- or 9-H), 6.95 (d, *J* = 8 Hz, 1 H, 8- or 9-H), 6.75 (d, *J* = 2 Hz, 1 H, 3-H), 4.23 (dd, 1 H), 3.90 (s, 3 H, OCH_3), 3.86 (d, 1 H), 3.82 (s, 3 H, OCH_3), 3.76 (dd, 1 H), 3.70 (s, 3 H, OCH_3), 3.50 (d, 1 H), 3.35 (m, 1 H), 3.2 (s, 3 H, NCH_3), 3.1 (t, 1 H), 2.89 (m, 1 H). Anal. ($C_{20}H_{23}NO_3$·HCl) C, H, N.

2,10,11-Trimethoxy-6a,7-didehydroaporphine (20). Compound *R*-19 (14 g, 43 mmol) in 60 mL of CH_3CN was refluxed with 14.5 g of 10% palladium on charcoal under an N_2 atmosphere for 6 h, when TLC indicated complete conversion to 20. The catalyst was removed by filtration, and the filtrate was evaporated to afford 10 g of 20 as a yellow-greenish oil with only a major single spot on TLC (in $CHCl_3$/MeOH, 9:1, vol). The oily product was used for further reaction without additional purification.

(*RS*)-(±)-2,10,11-Trimethoxyaporphine ((±)-19). Compound 20 (10 g, 30 mmol), which was obtained from the last step, was dissolved in 100 mL of absolute EtOH, and 14 g (0.22 mol) $NaCNBH_3$ was added; EtOH/HCl was added to bring the pH to 3.0, which was maintained over 4 h by several additions of HCl/EtOH. After evaporation of the reaction mixture, the pH was adjusted to 8 with saturated aqueous K_2CO_3 solution, and the free base of (±)-19 was extracted from $CHCl_3$ as 10 g of an oil. $[\alpha]^{25}_D$: 0° (*c* 0.2, MeOH).

(*S*)-(+)-2,10,11-Trimethoxyaporphine Hydrochloride (*S*-19·HCl). Racemic (±)-19 (10 g, 31 mmol) and (−)-dibenzoyl-L-tartaric acid (8.2 g, 21.8 mmol) were dissolved under reflux in EtOAc (50 mL) for 30 min. After the mixture was allowed to cool to room temperature, the white solid obtained was collected by filtration and washed with EtOAc. The colorless diastereomeric salt was recrystallized with EtOH and its specific rotation determined; this process was repeated three times until a constant rotation of $[\alpha]^{25}_D$ −16.43° (*c* 0.56, MeOH) was obtained. The resulting 3.9 g of product was then converted to the HCl salt, which afforded 1.8 g of *S*-19·HCl. Mp: 253–254 °C. $[\alpha]^{25}_D$: +151.5°. Mass spectrum: *m/z* 325 (M^+). The ^{1}H NMR spectrum was identical with that of *R*-19·HCl. Anal. ($C_{20}H_{23}NO_3$·HCl) C, H.

(*S*)-(+)-2,10,11-Trihydroxyaporphine Hydrobromide (*S*-3·HBr). Compound *S*-19·HCl (0.5 g, 1.38 mmol), 48% HBr (15 mL), and glacial AcOH (10 mL) were stirred at 130 °C for 4 h. The resulting dark reddish solution was evaporated to dryness by vacuum. The residue was crystallized from EtOH and filtered to give 0.37 g of *S*-3 as the HBr salt (73.5%). Mp: 267–268 °C. $[\alpha]^{20}_{546}$: +100.5° (*c* 0.2, MeOH). [Lit.[10] Mp: 229–131 °C. $[\alpha]^{20.5}_{546}$: +100.36°.] Mass spectrum: *m/z* 283 (M^+). ^{1}H NMR (CD_3OD, TMS): δ 8.05 (d, *J* = 2 Hz, 1 H, 1-H), 6.8 (d, *J* = 8 Hz, 1 H, 8- or 9-H), 6.72 (d, *J* = 8 Hz, 1 H, 8- or 9-H), 6.62 (d, *J* = 2 Hz, 1 H, 3-H), 4.15 (dd, 1 H), 3.8 (m, 1 H), 3.33–3.5 (m, 2 H), 3.2 (s, 3 H, NCH_3), 2.92–3.12 (m, 2 H), 2.83 (t, 1 H). Anal. ($C_{17}H_{17}NO_3$·HBr) C, H.

(*S*)-(+)-2-Hydroxy-10,11-(methylenedioxy)aporphine Hydrochloride (*S*-12·HCl). Compound *S*-3·HBr (380 mg, 1.04 mmol) was methylenated with CH_2Br_2 (236 mg, 1.36 mmol) and NaOH (125 mg, 3.1 mmol) as previously described for *R*-17 to give 200 mg (58% yield) of *S*-12·HCl. TLC showed the identical spot as compound *R*-12·HCl.

(*S*)-(+)-2-Methoxy-10,11-(methylenedioxy)aporphine Hydrochloride (*S*-13·HCl). Compound *S*-12·HCl (200 mg, 0.6 mmol) was O-methylated with excess of CH_2N_2 as previously described for *R*-13 to give 160 mg (77%) of white solids as the HCl salt: mp 236–238 °C. Mass spectrum: *m/z* 309 (M^+). The ^{1}H NMR spectrum was identical with that of *R*-13. Anal. ($C_{19}H_{19}NO_3$·HCl·$0.25H_2O$) C, H, N.

(*S*)-(+)-2-Methoxyapomorphine Hydrochloride (*S*-8·HCl). Compound *S*-13·HCl (110 mg, 0.32 mmol) was demethylenated with BCl_3 (1 M in 1 mL of hexane) as previously described for *R*-8 to give 35 mg (33%) of white crystals: mp 247–248 °C; $[\alpha]^{25}_D$ +112.6° (*c* 0.18, MeOH). Mass spectrum: *m/z* 297 (M^+). The ^{1}H NMR spectrum was identical with that of *R*-8. Anal. ($C_{18}H_{19}NO_3$·HCl·$0.25H_2O$) C, H, N.

Pharmacology. The affinity of 2-substituted apomorphine derivatives at cerebral DA receptor sites was evaluated with a cell membrane preparation of corpus striatum from rat brain (D_1 and D_2) or calf brain (agonist assay) and three representative tritium-radiolabeled ligands (Table I). These included a dopaminergic agonist [^{3}H]ADTN [(±)-6,7-dihydroxy-2-aminotetralin],[18] D_1 antagonist [^{3}H]SCH-23390[20] (both obtained from Du Pont–New England Nuclear Corp., Boston, MA) and D_2 antagonist [^{3}H]-spiperone[21,22] (obtained from Amersham Searle Inc., North Chicago, IL). The dopaminergic agonist ligand was incubated at 0.5 nM (60 min at 25 °C), D_1 antagonist at 0.3 nM (30 min at 30 °C), and D_2 antagonist at 0.15 nM (15 min at 37 °C). Specific binding was determined, with the following quenching agents: (*R*)-(−)-apomorphine (from Research Biochemicals Inc. (RBI),

(20) Faedda, G.; Kula, N. S.; Baldessarini, R. J. *Biochem. Pharmacol.* **1989**, *38*, 473–480.
(21) Cohen, B. M.; Herschel, M.; Miller, E.; Mayberg, H.; Baldessarini, R. J. *Neuropharmacology* **1980**, *19*, 663–668.
(22) Kula, N. S.; Baldessarini, R. J.; Bromley, S.; Neumeyer, J. L. *Life Sci.* **1985**, *37*, 1051–1057.

Natick, MA), 10 μM (vs [^{3}H]ADTN); *cis*-(*Z*)-flupenthixol (a gift of Dr. John Hyttel of Lundbeck Labs., Copenhagen, Denmark), 300 nM (vs [^{3}H]SCH-23390), and (+)-butaclamol (from RBI, Natick, MA), 1 μM (vs [^{3}H]spiperone) for the agonist, D_1, and D_2 assays, respectively. Half-maximal inhibitory concentrations (IC50 ± SEM) of each test agent were determined by using nonlinear least squares[23-25] analysis and converted to K_i according to Cheng and Prusoff.[26] All results were repeated at least twice, and the repeated values are means.

Acknowledgment. This work was supported by USPHS Grants NS-15439 (J.L.N.) and MH-47370 and MH-34006 (R.J.B.) and an award from the Bruce J. Anderson Foundation (R.J.B.) and a grant in aid from Research Biochemicals Inc. (Y.G.). We also thank Mallinckrodt Inc. for the generous gift of thebaine and Research Biochemicals Inc. for gifts of (*R*)-(−)-apomorphine hydrochloride, (*S*)-(+)-apomorphine hydrochloride, and (*R*)-(−)-*N*-*n*-propylnorapomorphine hydrochloride. We also thank Dr. John Hyttel of Lundbeck Laboratories for the generous gift of *cis*-(*Z*)-flupenthixol.

(23) Svendsen, C. N.; Froimowitz, M.; Hrbek, C.; Campbell, A.; Kula, N.; Baldessarini, R. J.; Cohen, B. M.; Babb, S.; Teicher, M. H.; Bird, E. D. *Neuropharmacology* **1988**, *27*, 1117–1124.
(24) Teicher, M. H. ALLFIT (APPLESOFT), 1983, Biomedical Computing Technology Information Center, Vanderbilt University, Nashville, TN.
(25) DeLean, A.; Munson, P. Z.; Rodbard, D. *Am. J. Physiol.* **1978**, *253*, 97–102.
(26) Cheng, Y-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.

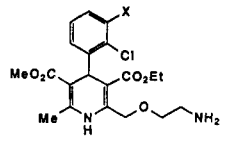
Long-Acting Dihydropyridine Calcium Antagonists. 5. Synthesis and Structure–Activity Relationships for a Series of 2-[[(*N*-Substituted-heterocyclyl)ethoxy]methyl]-1,4-dihydropyridine Calcium Antagonists

David Alker,*[†] Simon F. Campbell,[†] Peter E. Cross,[†] Roger A. Burges,[‡] Anthony J. Carter,[‡] and Donald G. Gardiner[‡]

Pfizer Central Research, Sandwich, Kent CT13 9NJ, United Kingdom. *Received September 27, 1989*

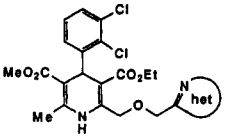
The synthesis of a series of 1,4-dihydropyridines which have N-linked heterocycles at the terminus of an ethoxymethyl chain at the 2-position is described. The calcium antagonist activity on rat aorta of this class of DHPs is compared with their negative inotropic activity as determined by using a Langendorff-perfused guinea pig heart model. The compounds examined show a wide range of selectivity for vascular over cardiac tissue, with those analogues which possess an amide group at the terminus of the 2-substituent proving the most selective. From the in vitro data obtained for a series of 1,2,3-triazoles, it is possible to conclude that the SARs for binding to the calcium channels in vascular and cardiac tissue are different. One of the compounds, 2-amino-1-[2-[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-4(3*H*)-imidazolone (**20b**, UK-55,444), was identified as a potent ($IC_{50} = 8 \times 10^{-9}$ M) calcium antagonist which is 40-fold selective for vascular over cardiac tissue and which has a significantly longer duration of action (>3 h) than nifedipine in the anesthetized dog on intravenous administration.

We have recently reported[1] the synthesis and structure–activity relationships (SARs) of a series of novel 1,4-dihydropyridine (DHP) calcium antagonists which contain a basic side chain on the 2-position of the DHP ring. The aim of this program was to modify the physicochemical properties of the DHP 2-substituents in order to improve bioavailability and duration of action over existing agents. From this work we identified amlodipine (**1a**), which fulfilled our objectives, and this compound is



1a : X = H (amlodipine)
1b : X = Cl

currently in late-stage clinical development for the treatment of angina[2,3] and hypertension.[4,5] We subsequently reported that the presence of a basic center on the substituent on the 2-position of the DHP ring was not an absolute requirement for either calcium-antagonist activity or selectivity for vascular tissue over the heart. For example, DHPs of general structure I in which the alkoxyalkyl group in the 2-position is substituted at its terminus



I: N het = substituted five- or six-membered ring heterocycle

by heterocycles are also potent, selective calcium antagonists.[6,7] Morever, in the previous paper in this series[8] we demonstrated that the primary amino group in **1a** could be replaced by polar functionality such as ureas and glycinamides. From this work we identified UK-51,656 (**2**) as having equivalent in vitro activity to nifedipine but with markedly longer duration of action in anesthetized dogs (of the order of 5 h). In order to extend the SARs in this

[†] Department of Chemistry.
[‡] Department of Biology.

(1) Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Stubbs, J. K.; Burges, R. A.; Gardiner, D. G.; Blackburn, K. J. *J. Med. Chem.* **1986**, *29*, 1696.
(2) Glasser, S. P.; West, T. W. *Am. J. Cardiol.* **1988**, *62*, 518.
(3) Kinnard, D. R.; Harris, M.; Hossack, K. F. *J. Am. Coll. Cardiol.* **1988**, *12*, 791.
(4) Webster, J.; Robb, O. J.; Jeffers, T. A.; Scott, A. K.; Petrie, J. C.; Towler, H. M. *Br. J. Clin. Pharmacol.* **1987**, *24*, 713.
(5) Julius, S. *J. Cardiovasc. Pharmacol.* **1988**, *12*, Suppl. 7, S27.
(6) Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Gardiner, D. G. *J. Med. Chem.* **1989**, *32*, 562.
(7) Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1989**, *32*, 2381.
(8) Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1990**, *33*, 585.

0022-2623/90/1833-1805$02.50/0