was made basic with NaOH, and the gummy product which separated was taken up in Et_2O. This solution was washed with H_2O and after drying over K_2CO_3 an excess of 2 N HCl in *i*-PrOH was added. The solid product (**21**) was removed by filtration and purified by recrystallization from acetone: 1.7 g (34%); mp 205–206 °C. Anal. ($C_{23}H_{37}NO\cdot HCl\cdot 0.25H_2O$) C, H, N.

***cis*-1-(4,4-Diphenylbutyl)-2,6-dimethylpiperidine Monohydrochloride (8). Method E.** Compound 1 (12.0 g) was dissolved in 200 mL of 2 N HCl and warmed on a hot plate for 36 h. The solution was cooled and made strongly basic with NaOH and the viscous product that separated was taken up in Et_2O and dried over K_2CO_3. The addition of 2 N HCl in *i*-PrOH yielded the gummy hydrochloride. The supernatent was decanted and the insoluble salts were recrystallized from absolute EtOH, yielding two fractions. The second crop (6.3 g) was primarily starting material. The first crop (3.8 g; mp 190–202 °C) was purified by three recrystallizations from EtOH to yield pure 1-(4,4-diphenyl-3-butenyl)-2,6-dimethylpiperidine monohydrochloride (**28**): 2.0 g (18%); mp 220–221 °C. Anal. ($C_{23}H_{29}N\cdot HCl$) C, H, N.

Compound **28** (4.7 g) was dissolved in 100 of MeOH, 1 g of palladium on carbon (20%) was added, and the mixture was shaken in an atmosphere of H_2 for 24 h on a low-pressure hydrogenation apparatus. Filtration followed by concentration on a rotary evaporator yielded a gum which was crystallized from *i*-PrOH–Et_2O (1:2) to give **8**: 3.0 g (64%); mp 177–178 °C. Anal. ($C_{23}H_{31}N\cdot HCl$) C, H, N.

***cis*-2,6-Dimethyl-α-phenyl-1-piperidinebutanol Monohydrochloride (16).** A solution of 13.0 g (0.05 mol) of 4-(2,6-dimethyl-1-piperidinyl)-1-phenyl-1-butanone in 80 mL of anhydrous Et_2O was added dropwise to a suspension of 2.1 g (0.05 mol) of lithium aluminum hydride in 25 mL of anhydrous Et_2O. The reaction mixture was stirred at room temperature for 4 h and then cooled and neutralized with aqueous NaOH. The insoluble material was removed by filtration, and the filtrate was diluted to 400 mL by adding Et_2O. A solution of HCl in *i*-PrOH was added and the resulting solid was collected by filtration and recrystallized from *i*-PrOH to yield **16**: 5.9 g (50%); mp 149–150 °C. Anal. ($C_{17}H_{17}NO\cdot HCl$) C, H, N.

Long-Acting Dihydropyridine Calcium Antagonists. 6. Structure–Activity Relationships around 4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[(2-hydroxyethoxy)methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine

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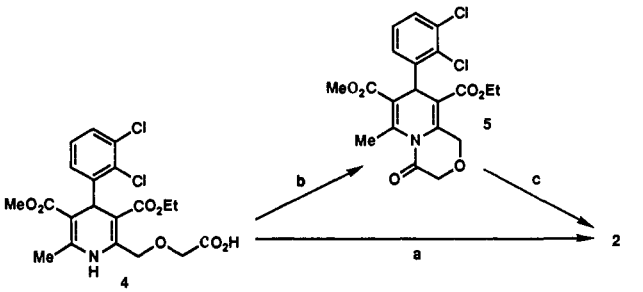
The preparation of 4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-2-[(2-hydroxyethoxy)methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (**2**) is described, and its potent calcium antagonist activity on rat aorta ($IC_{50} = 4 \times 10^{-9}$ M) and marked tissue selectivity in vitro for vascular smooth muscle over cardiac smooth muscle are established. In order to exploit the excellent in vitro profile of compound **2**, a range of analogues were prepared but none were found to have superior calcium antagonist potency and tissue selectivity. Compound **2** has excellent in vivo activity in the anesthetized dog (ED_{50} = 12 μg/kg for reduction of CVR) and a plasma half-life in the conscious dog of 7.2 h. The pharmacokinetic parameters of **2** are compared to those determined for the structurally related compounds amlodipine and felodipine. The plasma clearance for **2** (9.6 mL/min/kg) is similar to that of amlodipine and is consistent with the extended 2-substituent hindering approach to the cytochrome P-450 enzyme responsible for oxidation of the DHP ring to the corresponding pyridine.

We have recently reported[1] the synthesis of a series of novel 1,4-dihydropyridine (DHP) calcium antagonists that 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-substituent in order to improve bioavailability and duration of action over existing agents. From this work we identified amlodipine (**1**), which fulfilled these objectives and which has recently been approved for the treatment of angina and hypertension. We have subsequently reported[2-5] that the presence of a basic center in the substituent on the 2-position of the DHP ring is not an absolute requirement for either calcium antagonist activity or selectivity for vascular over cardiac tissue. For example, DHPs in which the alkoxymethyl group in the 2-position is substituted by heterocycles[2-4] or polar functionality such as ureas or glycinamides[5] are also potent, selective calcium antagonists. Even so, the overall pharmacological and pharmacokinetic profile displayed by amlodipine has so far proved unique when compared to these diverse structural analogues. Thus, we have now replaced the amino function in amlodipine by a hydroxy group **2** since we expected that the similar steric demands and hydrogen-bonding capabilities of these bioisosteres might be reflected in similar biological activities. In addition, we have synthesized a range of analogues related to **2** in an attempt to optimize the calcium antagonist potency and selectivity in this series.

Scheme I[a]



[a] Reagents: (a) BH_3·THF; (b) CDI/4-methylmorpholine/THF; (c) $NaBH_4$/EtOH.

Chemistry

The synthetic routes to the compounds listed in Table I are outlined in Schemes I–III. Direct reduction of the known[3] DHP acid **4** with BH_3·THF gave the alcohol **2** in only 13% yield and an alternative approach, which was higher yielding and more amenable to large-scale synthesis,

(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) Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Gardiner, D. G. *J. Med. Chem.* **1989**, *32*, 562.
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(4) Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1990**, *33*, 1805.
(5) Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1990**, *33*, 585.

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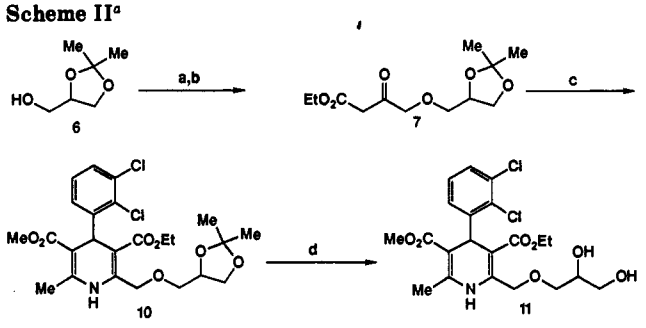
Table I. Data for Compounds Used in the Study[a]

no.	mp, °C	recrystn	formula	yield, %	Ca pIC_{50}[c]	negative inotropy pIC_{25}[c]	selectivity index[d]
2	122–123	Et_2O/hexane	$C_{20}H_{23}Cl_2NO_6$	*e, f*	8.4	7.4	10
3	95–95.5	DIPE[g]	$C_{21}H_{25}Cl_2NO_6$	9	7.5	6.0	30
11	118–121	Et_2O	$C_{21}H_{25}Cl_2NO_7 \cdot 0.5H_2O$	55	7.8	6.9	8
14	110–113	Et_2O/hexane	$C_{21}H_{25}Cl_2NO_6$	41	7.8	7.3	3
15	142–143	DIPE	$C_{22}H_{27}Cl_2NO_6 \cdot 0.5H_2O$	30	8.2	7.2	10
16	88–90	Et_2O/hexane	$C_{25}H_{27}Cl_2NO_7$	17	7.8	6.6	16
17	163–164	Et_2O	$C_{27}H_{30}Cl_2N_2O_6 \cdot 0.5H_2O$	7	7.2	7.5	2
19	135–138	DIPE	$C_{22}H_{27}Cl_2NO_7$	6	7.6	7.0	4
20	foam		$C_{26}H_{30}Cl_2N_4O_6 \cdot H_2O$	21	7.4	7.1	2
21	foam		$C_{26}H_{29}Cl_2N_3O_6S$	27	7.6	7.4	1.6
22	169–180	Et_2O	$C_{25}H_{29}Cl_2N_3O_6$	80	7.4	7.2	1.6
23	149–160	Et_2O	$C_{24}H_{28}Cl_2N_4O_6$	54	7.7	7.2	3
25[h]	110–115	EtOAc	$C_{22}H_{28}Cl_2N_2O_6 \cdot C_4H_4O_4$	34	6.8	6.5	2
26	118–119	MeOH	$C_{21}H_{25}Cl_2NO_5$	83	7.5	6.2	20
amlodipine					8.1	7.2	8
nifedipine					8.4	7.5	8

[a] Compounds 11, 15–17, 19–23, and 25 were obtained and tested as mixtures of diastereoisomers. [b] Negative logarithm of the molar concentration required to block Ca^{2+}-induced contraction of K^+ depolarized rat aorta by 50%; $n = 2$ (±0.3). Nifedipine was used as the standard compound. [c] Negative logarithm of the molar concentration required to depress contraction in the Langendorff-perfused guinea pig heart by 25%; $n = 2$ (±0.3). Nifedipine was used as the standard compound. [d] Selectivity index = Ca pIC_{50}/negative inotropy pIC_{25}. [e] Obtained from acid 4 directly with BH_3·THF in 13% yield. [f] Obtained from acid 4 via amide 5 in 62% yield. [g] DIPE = diisopropyl ether. [h] Characterized as the fumarate salt.

Scheme II[a]



[a] Reagents: (a) NaH/THF; (b) $ClCH_2COCH_2CO_2Et$; (c) methyl 3-aminocrotonate (8)/2,3-dichlorobenzaldehyde (9)/EtOH/heat; (d) $AcOH/H_2O$.

was therefore devised. Reaction of the acid 4 with CDI in the presence of 4-methylmorpholine gave the bicyclic amide 5 via the intermediacy of the corresponding imidazolide; 5 was smoothly reduced with $NaBH_4$ in EtOH to the alcohol 2 in 62% overall yield. The known[6] methyl ether 3 was prepared by the literature route. Hantzsch condensation of the β-keto ester 7 (prepared by the general route described in the literature[1] from ethyl 4-chloroacetoacetate and the alkoxide derived by reacting alcohol 6 with NaH), methyl 3-aminocrotonate (8), and 2,3-dichlorobenzaldehyde (9) afforded the dioxolane 10, which was deprotected with aqueous HOAc to give the diol 11 (Scheme II).

Treatment of 4 with CDI followed by reaction after 30 min of the intermediate imidazolide with Meldrum's acid/pyridine and acid-catalyzed hydrolysis gave a moderate yield (32%) of the ketone 12 after chromatography to remove the unwanted bicyclic amide 5 (Scheme III). Alternatively, 12 could be obtained in 88% yield by $HgSO_4$-catalyzed acid hydrolysis of the known[3] acetylene 13. Reduction of 12 with $NaBH_4$ gave the secondary alcohol 14 while reaction with the appropriate organolithium species afforded the tertiary alcohols 15–17. With use of the Corey ylide,[7] ketone 12 could be transformed smoothly into epoxide 18, which was hydrolyzed by a two-step procedure to the diol 19. Reaction of 18 with the appropriate nucleophilic species afforded compounds 20–23 while heating with $NaN_3/Mg(ClO_4)_2$[8] and reduction[9] of the resulting azide 24 gave the amine 25. Catalytic reduction of the acetylene[3] (13) led to the (propyloxy)methyl derivative 26.

Results and Discussion

In vitro vascular calcium antagonist activity (expressed as a pIC_{50}) was assessed as the concentration of the compound required to inhibit the calcium-induced contraction of potassium-depolarized rat aorta by 50%. Negative inotropy (expressed as a pIC_{25}) was determined in vitro with a Langendorff-perfused guinea pig heart preparation. As we hoped, the alcohol 2 was a potent, selective calcium antagonist with a profile equivalent to that of nifedipine and amlodipine (see Table I). Compound 2 is approximately 10-fold more potent than the methyl ether 3 and the 2-propoxymethyl DHP 26. This difference in activity may be a consequence of the presence of a favorable hydrogen bond between the proton of the hydroxyl group in 2 and a hydrogen-bond acceptor, such as the carbonyl group of an amide, in the vascular DHP receptor; such an interaction is of course not available for 3 and 26. This hypothesis is consistent with the potent calcium antagonist activity reported for the structurally related 1,4-dihydropyridines UK-52,831 (27),[2] UK-56,593 (28),[3] and UK-51,656 (29),[5] since in each case these compounds contain hydrogen atoms capable of interacting in a similar manner with the DHP receptor. Indeed this type of hydrogen-bonding interaction with the DHP receptor may be responsible for the excellent calcium antagonist activity of amlodipine. A recent review by Triggle et al.,[10] in which they propose a similar interaction for a series of 2-[[(2-aminoethyl)-thio]methyl] DHPs, also supports this hypothesis.

Methyl substitution adjacent to the hydroxy function in 2, as in 14 and 15, leads to compounds with similar potency and selectivity. However, none of the analogues

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(7) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867; **1965**, *87*, 1353.
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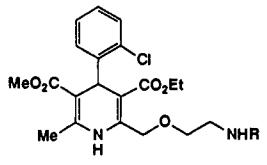
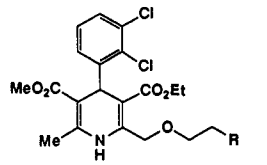
(9) Bayley, H.; Standring, D. N.; Knowles, J. R. *Tetrahedron Lett.* 1978, 3633.
(10) Triggle, D. J.; Langs, D. A.; Janis, R. A. *Med. Res. Rev.* 1989, *9*, 123.



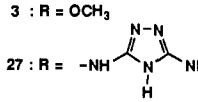
1 : R = H (amlodipine)

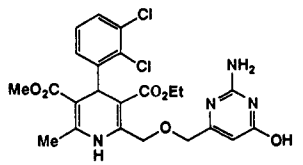
29 : R = CH_2CONH_2 (UK-51,656)



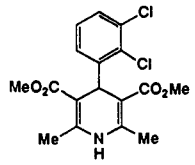
2 : R = OH

3 : R = OCH_3

27 : R =  (UK-52,831)



28 (UK-56,593)



30 (felodipine)

16–25, in which additional functionality has been incorporated into the substituent adjacent to the hydroxy group in 2, have equivalent activity to the parent alcohol (2), and with the exception of 16, they each show poor selectivity for vascular over cardiac tissue. It appears therefore that, for the compounds investigated, compound 2 is the preferred analogue for both calcium antagonist activity and vascular selectivity.

A preliminary in vivo evaluation of the alcohol 2 in instrumented, anesthetized dogs was carried out. The ED_{50} for reduction of coronary vascular resistance (CVR) of 2 was approximately 12 μg/kg, indicating that it is a potent vasodilator with activity comparable to that seen for 27[2] and 28.[3]

In view of the excellent in vivo activity of 2 we investigated its pharmacokinetic profile in dogs. We were pleased to find that the alcohol 2 has a half-life of ca. 7 h, which is a marked improvement over felodipine (30) (see Table II). This improvement in half-life is primarily due to the lower plasma clearance of 2, which is similar to that seen for amlodipine and may be a consequence of the extended 2-substituent hindering binding to the cytochrome P-450 enzyme responsible for oxidation of the DHP system to the corresponding pyridine.[11] The volume of distribution of 2 is similar to that observed for felodipine and is markedly lower than that of amlodipine. Amlodipine has a remarkably large volume of distribution,[12] and a hypothesis to explain this phenomenon has recently been proposed.[13] Thus, it has been suggested from the results of X-ray diffraction studies that the position adopted by amlodipine within biological membrane bilayers favors the existence of a charge–charge interaction between the protonated amino group and a region of negative charge in the phosphate headgroup of the membrane phospholipid. It is proposed[12] that this interaction may account for the large volume of distribution observed for amlodipine in man and animals. The hydroxy group in 2 is not capable of undergoing a charge–charge interaction with the phosphate headgroup in membrane phospholipids, and this may explain the lower volume of distribution of 2 relative to amlodipine.

Table II. Pharmacokinetic Data for Compound 2 in Comparison with Amlodipine[a] and Felodipine[b] in Dogs after Intravenous Administration

compound	plasma clearance, mL min^{-1} kg^{-1}	volume of distribution, L/kg	plasma half-life, h
2	9.6	6.0	7.3
amlodipine	11	25	30
felodipine	39	3.7	1.1

[a] Reference 12. [b] Reference 14.

In conclusion, therefore, we have identified the 2-(2-hydroxyethoxy)methyl DHP 2 as a potent calcium antagonist both in vitro and in vivo in anesthetized dogs with equivalent activity and selectivity to nifedipine and amlodipine. We have also shown that the structure–activity relationship (SAR) of DHPs with substituents in the 2-position bearing hydroxy groups has been optimized in 2. Compound 2 has a half-life of 7.2 h in the dog, and the factors that contribute to this long half-life have been identified and contrasted with the related compounds amlodipine and felodipine.

Experimental Section

Pharmacology. In vitro calcium antagonist activity (pIC_{50}) and negative inotropy (pIC_{25}) were measured as previously described.[1]

In vivo hemodynamic measurements were made in anesthetized beagle dogs as described previously.[1]

Chemistry. All melting points are uncorrected. The structures of all the compounds were determined by ^1H NMR spectroscopy and microanalysis. Microanalytical data was not obtained for intermediate 24. However, its ^1H NMR spectrum was wholly compatible with its proposed structure and TLC data established its purity. ^1H NMR spectra were obtained with a General Electric QE 300 spectrometer using $CDCl_3$ as solvent. The preparation of the acid 4 and the acetylene 13 has been described in a previous publication.[3]

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[(2-hydroxyethoxy)methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (2). Method A: Directly from Acid 4. BH_3·THF (1 M) in THF solution (10 mL, 10 mmol) was added dropwise over 5 min to a stirred, ice-cooled solution of 4 (2.00 g, 4.36 mmol) in THF (20 mL) and the mixture was stirred at room temperature for 24 h and evaporated. The residue was dissolved in Et_2O and the solution was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from Et_2O/hexane to give title compound 2: yield 250 mg (13%); mp 120–122 °C. Anal. ($C_{20}H_{23}Cl_2NO_6$) C, H, N.

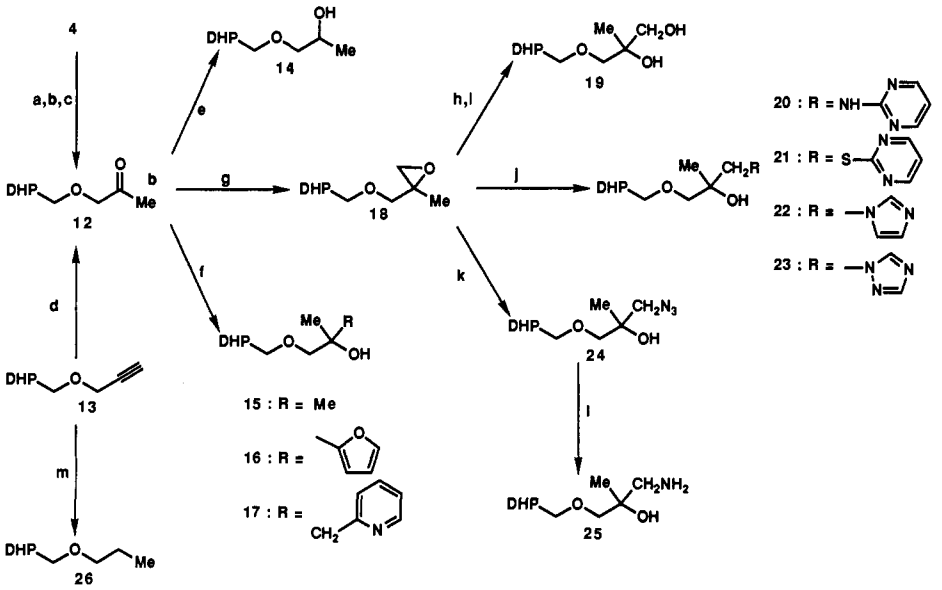
Method B: Via Amide 5. CDI (14.4 g, 89 mmol) was added to a solution of 4 (36.6 g, 80 mmol) and 4-methylmorpholine (14 g, 0.14 mol) in THF (200 mL), and the mixture was stirred at room temperature for 24 h and evaporated. The residue was dissolved in CH_2Cl_2 and the solution was washed with 2 M HCl, water, 5% aqueous $NaHCO_3$ solution, and water, dried over $MgSO_4$, and evaporated. The residue was recrystallized from EtOAc/hexane to give amide 5: yield 29.0 g (82%); mp 173 °C. Anal. ($C_{20}H_{19}Cl_2NO_6$·$0.5H_2O$) C, H, N.

$NaBH_4$ (5.2 g, 0.14 mol) was added portionwise over 15 min to a stirred solution of 5 (29.0 g, 66 mmol) in EtOH, and the mixture was stirred at room temperature for 16 h and evaporated. The residue was dissolved in CH_2Cl_2 and the solution was washed with water, 2 M HCl, and water, dried over Na_2SO_4, and evaporated. The residue was recrystallized from Et_2O to give title compound 4: yield 22.0 g (75%); mp 122–123 °C, whose spectral data was identical with that of the material obtained above.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-2-[(2-methoxyethoxy)methyl]-6-methyl-1,4-dihydropyridine (3). A solution of 9 (3.5 g, 20 mmol), 8 (2.3 g, 20 mmol), and ethyl 4-(2-methoxyethoxy)acetoacetate (4.1 g, 20

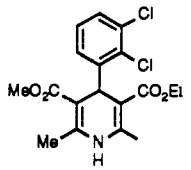
(11) Bocker, R. H.; Guengerich, F. P. *J. Med. Chem.* 1986, *29*, 1596.
(12) Stopher, D. A.; Beresford, A. P.; Macrae, P. V.; Humphrey, M. J. *J. Card. Pharmacol.* 1988, *12* (Suppl. 7), S55.
(13) Mason, R. P.; Campbell, S. F.; Wang, S.; Herbette, L. E. *Mol. Pharmacol.* 1989, *36*, 634.
(14) Humphrey, M. J.; Stopher, D. A. Unpublished results.

Scheme III[a,b]



[a] Reagents: (a) CDI/CH_2Cl_2; (b) 2,2-dimethyl-1,3-dioxolane-4,6-dione/pyridine; (c) $AcOH/H_2O$; (d) $HgSO_4/H_2SO_4$; (e) $NaBH_4/EtOH$; (f) RLi/THF; (g) $Me_3S{=}OI^{-+}$/cetylammonium bromide/$NaOH/H_2O/CCl_3CH_3$; (h) $AcOH/H_2SO_4$; (i) $NaOH/H_2O$; (j) RH/base; (k) $NaN_3/Mg(ClO_4)_2$/dioxane/H_2O; (l) $HS(CH_2)_3SH/Et_3N/MeOH$; (m) 5% Pd on $BaSO_4$/quinoline/MeOH.

[b] DHP =



mmol) in EtOH (30 mL) was heated under reflux for 16 h and evaporated. The residue was chromatographed on silica with toluene as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from DIPE to give title compound **3**: yield 0.86 g (9%); mp 95–95.5 °C (lit.[6] oil). Anal. ($C_{21}H_{25}Cl_2NO_6$) C, H, N.

Ethyl 4-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]acetoacetate (7). A solution of **6** (13.2 g, 0.10 mol) in THF (50 mL) was added dropwise over 30 min to a stirred suspension of NaH (8.0 g, 0.20 mol; 60% dispersion in oil) in THF (150 mL) and the mixture was treated dropwise with a solution of $ClCH_2COCH_2CO_2Et$ (16.5 g, 0.10 mol) in THF (50 mL), stirred at room temperature for 16 h, and evaporated. The residue was treated with 10% aqueous HOAc and extracted into CH_2Cl_2. The CH_2Cl_2 extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica with toluene plus 0–20% EtOAc as eluant. Appropriate fractions were combined and evaporated to give title compound **7**: yield 5.6 g (22%); oil, which was used in the preparation of **10** without further characterization.

Ethyl 4-(2-methoxyethoxy)acetoacetate was prepared in exactly analogous fashion by reaction of a mixture of NaH and 2-methoxyethanol with $ClCH_2COCH_2CO_2Et$ followed by workup as described above, and the crude product was used in the preparation of **3** without further purification or characterization.

4-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]methyl]-2,2-dimethyl-1,3-dioxolane (10). A mixture of **7** (5.6 g, 21.5 mmol), **9** (3.77 g, 21.5 mmol), and **8** (2.48 g, 21.6 mmol) in EtOH (100 mL) was heated under reflux for 16 h and evaporated. The residue was chromatographed on silica with CH_2Cl_2 as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O to give title compound **10**: 0.80 g (7%); mp 135–137 °C. Anal. ($C_{24}H_{29}Cl_2NO_7$) C, H, N.

4-(2,3-Dichlorophenyl)-2-[(2,3-dihydroxypropoxy)methyl]-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (11). A solution of **10** (150 mg, 0.29 mmol) in 60% aqueous HOAc (20 mL) was stirred at room temperature for 72 h and evaporated. The residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ solution, and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica with CH_2Cl_2 as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O to give title compound **11**: yield 76 mg (55%); mp 118–121 °C. Anal. ($C_{21}H_{25}Cl_2NO_7{\cdot}0.5H_2O$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[(2-oxopropoxy)methyl]-1,4-dihydropyridine (12). Method A from Acid 4. CDI (8.00 g, 49.3 mmol) was added portionwise over 30 min to a stirred solution of **4** (20.0 g, 43.6 mmol) in CH_2Cl_2 (400 mL), and the mixture was stirred at room temperature for 2.75 h, treated with a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (6.5 g, 45 mmol) and pyridine (3.6 g, 46 mmol) in CH_2Cl_2 (400 mL), stirred at room temperature for 60 h, washed with ice-cold 4 M HCl and brine, dried over $MgSO_4$, and evaporated. A solution of the residue in water (300 mL) and HOAc (150 mL) was heated under reflux for 5 h and evaporated. The residue was partitioned between Et_2O and 10% aqueous Na_2CO_3 solution and the organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica with CH_2Cl_2 plus 30% hexane as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from EtOH to give title compound **12**: yield 6.5 g (32%); mp 117–119 °C. Anal. ($C_{21}H_{23}Cl_2NO_6$) C, H, N.

Method B from Acetylene 13. A mixture of **13** (1.06 g, 2.37 mmol), $HgSO_4$ (0.1 g), and concentrated H_2SO_4 (0.2 mL) in a mixture of dioxane (20 mL) and water (20 mL) was heated at 60 °C for 2 h, allowed to cool to room temperature, and extracted into Et_2O. The Et_2O extracts were washed with brine, dried over Na_2SO_4, and evaporated to give title compound **12**: yield 0.93 g (88%); mp 119–121 °C, whose spectral data was identical with that of the material obtained above.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[(2-hydroxypropoxy)methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (14). $NaBH_4$ (0.10 g, 2.63 mmol) was added to a solution of **12** (0.46 g, 1.0 mmol) in EtOH and the mixture was stirred at room temperature for 5 h and evaporated. The residue was dissolved in EtOAc and the solution was washed with water, dried over $MgSO_4$, and evaporated. The residue was

crystallized from Et_2O/hexane to give title compound **14**: yield 190 mg (41%); mp 110–113 °C. Anal. ($C_{21}H_{25}Cl_2NO_6$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[(2-hydroxy-2-methylpropoxy)methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (15). MeLi (1.6 M) in Et_2O (1.3 mL, 2.1 mmol) was added dropwise over 5 min to a solution of **14** (0.46 g, 1.0 mmol) in THF (30 mL) at −70 °C, and the mixture was allowed to warm up to room temperature, stirred for 16 h, quenched into saturated aqueous NH_4Cl solution and extracted into EtOAc. The EtOAc extract was washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica with toluene plus 0–50% EtOAc as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from DIPE to give title compound **15**: yield 0.14 g (30%); mp 142–143 °C. Anal. ($C_{22}H_{27}Cl_2NO_6 \cdot 0.5H_2O$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-(2-furyl)-2-hydroxypropoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (16). *n*-BuLi (1.6 M) in hexane (1.4 mL, 2.24 mmol) was added dropwise to an ice-cooled solution of furan (0.10 mL, 1.32 mmol) in THF (20 mL), and the mixture was stirred with ice cooling for 3 h, cooled to −70 °C, treated with a solution of **14** (0.50 g, 1.1 mmol) in THF (20 mL), stirred at −70 °C for 1.5 h, allowed to warm to room temperature, quenched with brine, and extracted into Et_2O. The Et_2O extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on silica with Et_2O plus 30–50% hexane as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O/hexane to give title compound **16**: yield 100 mg (17%); mp 88–90 °C. Anal. ($C_{25}H_{27}Cl_2NO_7$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-hydroxy-2-methyl-3-(2-pyridyl)propoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (17). *n*-BuLi (1.6 M) in hexane (1.35 mL, 2.2 mmol) was added dropwise over 5 min to a stirred solution of 2-methylpyridine (110 μL, 1.1 mmol) in THF (20 mL) and the mixture was stirred at room temperature for 50 min, cooled to −70 °C, treated with a solution of **14** (0.50 g, 1.1 mmol) in THF (20 mL) dropwise over 5 min, stirred at −70 °C for 2 h, allowed to warm up to room temperature, quenched with brine, and extracted into Et_2O. The Et_2O extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from Et_2O to give title compound **17**: yield 40 mg (7%); mp 163–164 °C. Anal. ($C_{27}H_{30}Cl_2N_2O_6 \cdot 0.5H_2O$) C, H, N.

2-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]methyl]-2-methyloxirane (18). A solution of **14** (4.56 g, 10.0 mmol), trimethylsulfoxonium iodide (2.42 g, 11 mmol), and cetyltrimethylammonium bromide (250 mg) in a mixture of CH_3CCl_3 (75 mL) and 5 M aqueous NaOH solution (75 mL) was stirred at 60–65 °C for 100 min and diluted with CH_2Cl_2 and H_2O. The layers were separated, and the aqueous layer was extracted into CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica with toluene plus 0–40% EtOAc as eluant. Appropriate fractions were combined and evaporated, and the residual oil was crystallized from DIPE to give title compound **18**: 2.06 g (44%); mp 107–112 °C. Anal. ($C_{22}H_{25}Cl_2NO_6$) C, H, N.

4-(2,3-Dichlorophenyl)-2-[(2,3-dihydroxy-2-methylpropoxy)methyl]-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (19). A solution of **18** (0.47 g, 1.0 mmol) in AcOH (20 mL) containing concentrated H_2SO_4 (2 drops) was stirred at room temperature for 4.5 h and evaporated. The residue was dissolved in dioxane (10 mL) and the solution was treated with 2.5 M aqueous NaOH solution (10 mL), stirred at room temperature for 18 h, and evaporated. The residue was dissolved in CH_2Cl_2 and the solution was washed with 2 M HCl, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica with CH_2Cl_2 plus 0–1% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from DIPE to give title compound **19**: yield 30 mg (6%); mp 135–138 °C. Anal. ($C_{22}H_{27}Cl_2NO_7$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-hydroxy-2-methyl-3-[(2-pyrimidinyl)amino]propoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (20). NaH (70 mg, 2.3 mmol; 80% dispersion in oil) was added to a solution of 2-aminopyrimidine (0.10 g, 1.05 mmol) in DMF (40 mL) and the mixture was stirred at 45–50 °C for 45 min, treated with **18** (0.47 g, 1.0 mmol), stirred at room temperature for 24 h, and evaporated. The residue was dissolved in EtOAc and the solution was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica with CH_2Cl_2 plus 1–3% MeOH as eluant. Appropriate fractions were combined and evaporated to give title compound **20**: yield 120 mg (21%); foam. Anal. ($C_{26}H_{30}Cl_2N_4O_6 \cdot H_2O$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-hydroxy-2-methyl-3-[(2-pyrimidinyl)thio]propoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (21). A mixture of **18** (0.47 g, 1.0 mmol), pyrimidine-2-thiol (0.12 g, 1.1 mmol), and K_2CO_3 (0.14 g) in EtOH (20 mL) was stirred at room temperature for 18 h and evaporated. The residue was dissolved in EtOAc and the solution was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica with CH_2Cl_2 plus 0–2% MeOH. Appropriate fractions were combined and evaporated to give title compound **21**: yield 160 mg (27%); foam. Anal. ($C_{26}H_{29}Cl_2N_3O_6S$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-hydroxy-3-(1-imidazolyl)-2-methylpropoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (22). NaH (0.18 g, 6 mmol; 80% dispersion in oil) was added to a solution of **18** (0.47 g, 1.0 mmol) and imidazole (0.32 g, 5.0 mmol) in THF (10 mL) and the mixture was stirred at room temperature for 16 h and diluted with EtOAc and water. The layers were separated, and the organic layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica with CH_2Cl_2 plus 0–5% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O to give title compound **22**: 0.43 g (80%); mp 169–180 °C. Anal. ($C_{25}H_{29}Cl_2N_3O_6$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-hydroxy-2-methyl-3-(1-triazolyl)propoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (23). A mixture of **18** (0.80 g, 1.7 mmol), triazole (0.44 g, 6.5 mmol), and NaH (0.24 g, 8 mmol; 80% dispersion in oil) in THF (25 mL) was stirred at room temperature for 43 h and partitioned between EtOAc and H_2O. The layers were separated, and the organic layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica with toluene plus 0–100% EtOAc as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O to give title compound **23**: yield 0.49 g (54%); mp 149–160 °C. Anal. ($C_{24}H_{28}Cl_2N_4O_6$) C, H, N.

2-[(3-Azido-2-hydroxy-2-methylpropoxy)methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (24). A solution of **18** (0.94 g, 2.0 mmol), NaN_3 (0.26 g, 4.0 mmol), and $Mg(ClO_4)_2$ (0.44 g, 2.0 mmol) in a mixture of dioxane (10 mL) and water (10 mL) was stirred at room temperature for 60 h and partitioned between EtOAc and water. The layers were separated, and the organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica with toluene plus 0–20% EtOAc as eluant. Appropriate fractions were combined and evaporated to give title compound **24**: yield 0.90 g (88%); oil; ^1H NMR ($CDCl_3$) δ = 7.67 (1 H, s), 6.96–7.42 (3 H, m), 5.39 (1 H, s), 4.71 (2 H, s), 4.02 (2 H, q, J = 7 Hz), 3.58 (3 H, s), 3.43 (2 H, s), 3.29 (2 H, s), 2.27 (3 H, s), 1.19 (3 H, s), 1.14 (3 H, t, J = 7 Hz).

2-[(3-Amino-2-hydroxy-2-methylpropoxy)methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine Fumarate (25). $HS(CH_2)_3SH$ (1.2 mL, 12 mmol) and Et_3N (1.2 mL, 17 mmol) were added to a solution of **24** (1.54 g, 3.0 mmol) in MeOH (30 mL), and the mixture was stirred at room temperature for 72 h and filtered. The filtrate was evaporated and the residue was partitioned between EtOAc and water. The layers were separated, and the organic layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica with CH_2Cl_2 plus 0–40% MeOH as eluant. Appropriate fractions were combined and evaporated. The residue was dissolved in EtOAc (10 mL) and the solution was treated with a solution of excess fumaric acid in EtOAc and stored at −15 °C for 18 h. The resulting

solid was collected, washed with EtOAc, and dried to give title compound **25**: yield 0.49 g (34%); mp 110-115 °C. Anal. ($C_{22}H_{28}Cl_2N_2O_6 \cdot C_4H_4O_4$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-(propoxymethyl)-1,4-dihydropyridine (26). A solution of **13** (2.0 g, 4.46 mmol) in MeOH (60 mL) containing $Pd/BaSO_4$ catalyst (200 mg) and quinoline (5 drops) was stirred under an atmosphere of hydrogen at room temperature for 1 h, filtered, and evaporated. The residue was chromatographed on silica with CH_2Cl_2 as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from MeOH to give title compound **26**: yield 1.67 g (83%); mp 118-119 °C. Anal. ($C_{21}H_{25}Cl_2NO_5$) C, H, N.

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R and *S* Enantiomers of 11-Hydroxy- and 10,11-Dihydroxy-*N*-allylnoraporphine: Synthesis and Affinity for Dopamine Receptors in Rat Brain Tissue

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The *R*-(−)- and *S*-(+)-enantiomers of 11-hydroxy-*N*-allyl (**4**), and 10,11-dihydroxy-*N*-allyl (**3**) congeners of 11-hydroxy-*N*-*n*-propylnoraporphine (11-OH-NPa, **2**) or *N*-*n*-propylnorapomorphine (NPA, **1**) were synthesized. Binding affinity of these compounds at dopamine (DA) receptor sites was evaluated with a membrane preparation of corpus striatum from rat brain. The *R*/*S* enantiomeric receptor affinity ratio was enhanced by allylic substitution of **3** and **4** and their *R* isomers had high DA receptor affinity similar to that of the *N*-*n*-propyl congeners. These *N*-allylaporphines are proposed as useful precursors to the preparation of their tritiated *N*-*n*-propyl enantiomers.

Introduction

Recently, the *R*-(−)- and *S*-(+)-isomers of certain mono and dihydroxy-*N*-alkylnoraporphines, including 11-hydroxy-*N*-*n*-propylnoraporphine (11-OH-NPa) and *N*-*n*-propylnorapomorphine (NPA), were used to characterize dopamine receptors.[1,2] The monohydroxy aporphines appear to be highly stereoselective D_2-selective agents that can interact at dopaminergic autoreceptor to inhibit tyrosine hydroxylase[3,4] without a direct inhibitory effect on this rate-limiting step in DA synthesis that may occur with catechol aporphines.[5,6] DA autoreceptors have been located on presynaptic dopaminergic neurons possessing a D_2 receptor character with regard to stereospecificity and potency series relationships.[7,8] However, postsynaptic D_2 receptors in the mammalian corpus striatum, and in the anterior pituitary mammotrophs, which regulate the secretion of prolactin, have lower affinity for typical DA agonists than at striatal autoreceptors.[9-11] Accordingly, DA partial agonists with low intrinsic activity can elicit autoreceptor activity selectively.[12-16] Though still unsolved, the mechanism and molecular consequences of activating DA autoreceptors are now receiving intense interest.[17,18] Selective autoreceptor ligands may provide functional modulation of the DA system of the brain without the excessive interference with neuronal activity believed to induce the adverse effects of typical DA antagonists used in the treatment of various neuropsychiatric disorders.[19,20]

It is known that the *R*-(−)-enantiomers of hydroxyaporphines are highly selective agonists at DA receptors, while *S*-(+)-isomers of aporphine analogues, notably NPA and especially its monohydroxy congener 11-OH-NPa, show a moderate affinity for postsynaptic DA receptor sites.[21,22] Behavioral evidence indicates that these *S*-(+)-isomers exert functional antagonism of DA receptor

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