Absolute Stereochemistry and Dopaminergic Activity of Enantiomers of 2,3,4,5-Tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine

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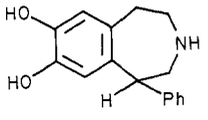
Resolution of the unique dopamine receptor agonist 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (1) was achieved by a stereospecific multistep conversion of the readily separated enantiomers of its O,O,N-trimethylated precursor **2**. The absolute stereochemistry of the antipodes of **2**·MeI was determined by single-crystal X-ray diffractometric analysis, thus permitting assignment of the configuration of stereospecifically related 1, as well as that of the synthetic intermediates. High-performance liquid chromatography of diastereoisomeric derivatives was utilized to determine the enantiomeric excess of the *R* (>97%) and *S* (>89%) isomers of 1. Examination of the isomers in several in vitro and in vivo tests for both central and peripheral dopaminergic activity revealed that activity resided almost exclusively in the *R* isomer. The results suggest that the properly oriented 1-phenyl substituent of 1 is important for dopamine-like activity; it may contribute to receptor binding by interaction with a chirally defined accessory site. Configurational and conformational requirements for receptor binding of 1 are considered in relationship to previously described dopaminergic agents. These studies, in accord with previous suggestions, indicate that (*R*)-1 interacts with dopamine receptors in a conformation in which the catecholic hydroxyls and basic nitrogen are at least nearly maximally separated.

Dopamine (DA) is an important neurotransmitter with receptors in both the central nervous system[1-5] and in certain peripheral tissues.[6-9] Recently, 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (1, SK&F



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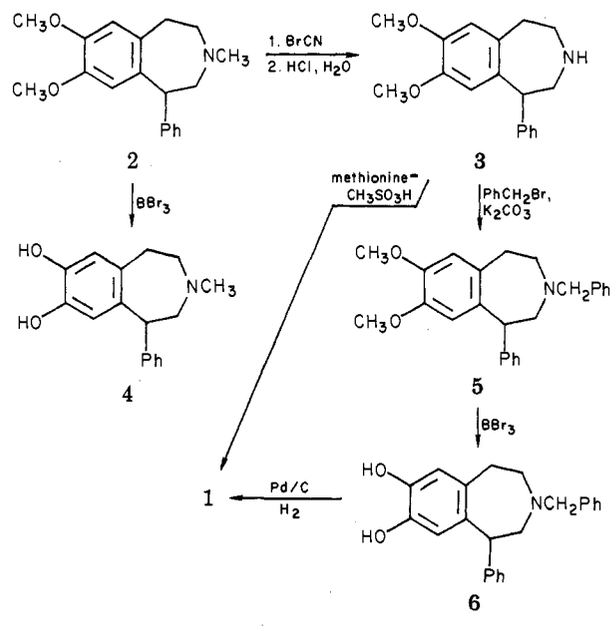
38393) was characterized as a unique agonist of both central[10,11] and peripheral[12-14] DA receptors. This new agent is of particular interest because it is apparently selective for the D-1 subtype[10] in a suggested classification of DA receptors.[4] It displays a binding affinity for [^{3}H]-apomorphine striatal sites that is in the range of that of prototypic DA receptor agonists.[14] The unusual biological profile of 1, coupled with its partial agonism in stimulating striatal adenylate cyclase, prompted the study of a large number of related compounds. Some of these had potent and selective DA receptor agonist[15] and antagonist[16] properties.

Enantiomers of various dopaminergic agents, e.g., apomorphine and a variety of 2-amino-1,2,3-4-tetrahydronaphthalene derivatives,[17] have been utilized to complement structure–activity studies in probing the receptors. Since optical antipodes have identical physical properties, barring differential metabolism it is reasonable to correlate biological differences of isomeric pairs[19-22] with receptor-related events.[23] For example, this feature has been employed for the biological characterization of subpopulations of opioid receptors.[24] In fact, consideration of the enantiomeric selectivity of apomorphine and aminotetralin derivatives in binding to DA receptors has led to a conceptual model that suggests possible binding sites and postulation of a region of steric bulk on the DA receptor surface.[17]

These considerations, combined with the biological uniqueness of 1, suggested examination of the enantiomers of this benzazepine derivative for DA-like activity. It was

Scheme I



anticipated that such studies might advance our understanding of DA receptors[17,25-31] or perhaps the D-1 subtype

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of these sites. In this article are described the separation of the enantiomers of 1, determination of their absolute stereochemistry, and their dopaminergic actions in several test systems. The stereochemistry and conformation of 1 as it relates to previous observations of structural requirements for reaction with DA receptors are considered.

Chemistry. 2,3,4,5-Tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (1)[32,33] was readily obtained as a crystalline base. Although it produced crystalline salts with several optically active acids, namely, (+)-tartaric acid, (+)-10-camphorsulfonic acid, and (−)-menthoxyacetic acid, conditions for separation of the diastereoisomeric salts could not be readily determined. For this reason, resolution of precursors (Scheme I) to 1 was investigated. Recrystallization of the (+)- and (−)-dibenzoyltartaric acid salts of 2 from ethanol effected separation of the enantiomers.[34] The optical isomers of 2 were readily converted, with no apparent racemization, to the corresponding enantiomers of 3 and 4. Resolution of 3 was also achieved via its salt with (+)-10-camphorsulfonic acid; however, yields of the resulting enantiomer (subsequently shown to have the *R* configuration) were poor. In addition, obtention of the second enantiomer requires utilization of less readily available (−)-10-camphorsulfonic acid.

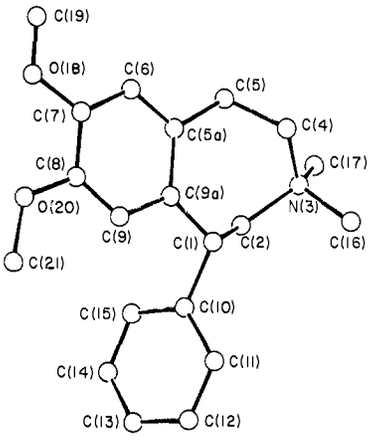

Figure 1. A computer-generated perspective drawing of (+)-2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1-phenyl-1*H*-3-benzazepine (2) methiodide. Hydrogens are omitted for clarity, and the absolute configuration was determined by the use of anomalous scattering from iodide.

Since BBr_3 cleavage of the methoxyl groups of (*R*)- and (*S*)-2 afforded the corresponding isomers of 4 without difficulty, the complex reaction accompanied by apparent partial racemization (not established with certainty) encountered upon attempted similar BBr_3 or HBr methoxyl scission of the enantiomers of 3 to 1 was not anticipated. Although the mechanism of this apparent racemization is not clear, it was determined that overall transformation of the enantiomers of 3 to 1 could be effected by BBr_3 cleavage of the *N*-benzyl enantiomers 5 of 3, followed by catalytic hydrogenolysis of resultant 6. Later, it was found that conversion of the enantiomers of 3 to corresponding (*R*)- and (*S*)-1 could be achieved conveniently by employing the comparatively gentle methionine-methanesulfonic acid procedure[35] for cleavage of the aryl ethers.

High-performance liquid chromatography (HPLC) of diastereoisomeric derivatives[36] was utilized to establish optical purity of the enantiomers of 1. The amide of racemic 1 with α-methoxy-α-trifluoromethylphenylacetic acid[37] afforded two HPLC peaks of equal intensity. Amides of (*R*)- and (*S*)-1 with (−)-α-methoxy-α-trifluoromethylphenylacetic acid under the same conditions gave peaks from which an enantiomeric excess (ee) of about 97% was estimated for the *R* isomer and 89% for the *S* isomer.

The absolute stereochemistry of the enantiomers of 2 was determined by single-crystal X-ray analysis of the methiodide as described under Experimental Section. Since the enantiomers of 1 were stereospecifically synthesized from those of 2, the absolute stereochemistry of 1, as well as that of the intermediate antipodes (Scheme I), may be correlated.

Results and Discussion

Figure 1 is a computer-generated perspective drawing of 2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1-phenyl-

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Table I. Dopaminergic Activity of 1 and Enantiomers

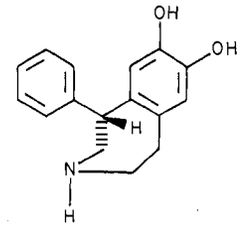
test system[b]	compd[a] (*R,S*)-1	(*R*)-1	(*S*)-1	dopamine
dopamine-sensitive adenylate cyclase stim: EC_{50},[c] M [max response,[d] %, at concn, M]	7.1×10^{-8} ($5.2\text{-}10.6 \times 10^{-8}$) [68, 10^{-5}]	3.2×10^{-8} ($2.0\text{-}5.0 \times 10^{-8}$) [66, 10^{-5}]	[27,[e] 10^{-4}]	3.5×10^{-6} [100, 5×10^{-5}]
inhibn of spiroperidol binding to rat caudate tissue, IC_{50},[c] μM	34.43 (33.42-41.91)	33.86 (28.56-40.14)	197.4 (151.7-257.0)	5.34 (4.18-6.82)
contralateral rotation in lesioned rat: RD_{500},[c] mg/kg, ip	0.7 (0.5-1.0)	0.50 (0.33-0.71)	2.0 = 50 ± 8 rotations[f]	[g]
renal vasodilator act., dogs, ED_{15} ↓ RVR, μg/kg, iv (av max % ↓ RVR, no. of dogs used in test)	31 (19, 3)	25 (18, 1)	550 = 9% ↓ RVR (1)[f]	2.7 (36, 3)

[a] All compounds were tested as their HCl salts. Results are presented in terms of base. [b] Test systems are described and referenced under Experimental Section. [c] 95% confidence limits are indicated in parentheses below values. [d] Percent of cyclic AMP induced by 5×10^{-5} M dopamine. [e] Insufficiently potent for determination of EC_{50}. [f] Not statistically significant. [g] Value for dopamine is not available. Inability of dopamine to enter CNS after peripheral administration requires use of Dopa plus a peripheral decarboxylase inhibitor.[10]

1*H*-3-benzazepine methiodide derived from the enantiomer of **2** having $[\alpha]^{25}_D$ +22.3° (*c* 1, MeOH).[34] Hydrogens are omitted for clarity, and the absolute configuration was predicted using the anomalous scattering contribution from iodine. The configuration at C(1) is *R*. The dimethoxybenzene ring and all attached atoms are planar. The seven-membered ring distorts from planarity in such a fashion as to preserve an approximate twofold axis. Atoms N(3), C(1), C(9a), C(5a), and C(5) are in a plane, and atoms C(2) and C(4) are equally below and above this plane. The torsional angles are as follows: C(5a)–C(9a), 0°; C(5a)–C(5), C(4)–N(3), and C(9a)–C(1), -33°; C(5)–C(4) and C(1)–C(2), +84°; C(4)–N(3) and C(2)–N(3), -45°. All bond distances and angles, which are given in the supplementary material (see paragraph at the end of paper concerning supplementary material), agree well with generally accepted values. These results establish the absolute stereochemistry for antipodes of 1 and other compounds in the stereospecifically related series (Scheme I); however, the compounds in the series need not bear a conformational similarity. Indeed, preliminary single-crystal X-ray diffractometric studies suggest 1·HCl exists with the tetrahydroazepine ring in a chair conformation (J. Clardy, unpublished data).

The *R* and *S* isomers of 1 were examined for their ability to stimulate DA-sensitive adenylate cyclase[10] (D-1 receptor), to displace [^{3}H]spiroperidol binding to rat caudate homogenate (central DA receptors), to induce rotations in rats with unilateral lesions of the left substantia nigra[10] (supersensitive central DA receptors), and in very preliminary experiments to reduce renal vascular resistance in dogs[15] (presumably by a peripheral dopaminergic action). The results of these studies, tabulated in Table I, show that the DA-like activity of 1 residues in the *R* enantiomer. In each of the tests, the *R* antipode was equally or more potent than the racemate, whereas the *S* isomer was devoid of significant activity. These results, coupled with the observation that the 1-dephenyl derivative of 1, i.e., 2,3,4,5-tetrahydro-7,8-dihydroxy-1*H*-3-benzazepine,[38] is nearly two orders of magnitude less potent than (*R*)-1 as a stimulant of DA-sensitive adenylate cyclase ($EC_{50} = 5.2 \times 10^{-6}$ M)[39] and fivefold less effective in inducing contralateral rotations in rats having lesions in the substantia nigra when given directly into the ipsilateral striatum[10] [RD_{500} = 0.9 μg/rat,[40] as compared to an RD_{500} = 0.18 μg/rat, for racemic 1[15]], suggest that the 1-phenyl group of 1 may contribute to receptor binding by interaction with a chirally defined accessory site.

Structure–activity relationship studies of analogues and derivatives of 1 in which the catechol and nitrogen substitutions are modified[41] suggest that these groups may interact with primary DA receptor binding sites. This is consistent with mapping studies of the DA receptor utilizing analogues of the neuroleptic butaclamol,[26] which suggest primary binding functions for the aromatic ring and a nitrogen atom. It may be relevant that in (*R*)-1 (**7**)



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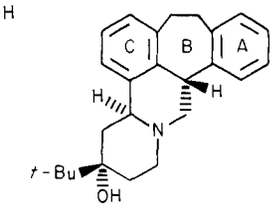

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and in the neuroleptic (13b*S*)-butaclamol (**8**), in which the A ring is considered to simulate the catechol ring of DA (or apomorphine),[26] the absolute stereochemistry at the benzhydrylic position is similar. Also, the 1-phenyl group of **7** and the C ring of **8** are located "to the left of the molecule at the 9 o'clock position", a suggested hydrophobic site on the DA receptor.[30] Clearly, however, the spatial relationship between the aromatic rings and the nitrogen differs in the two molecules.

The flexibility of the DA molecule prohibits definition of its mode of interaction with receptors. It has been suggested that DA may interact with receptors in two conformational extremes, the so-called α and β forms.[42,43] Of particular interest are the 7,8-dihydroxyoctahydro[*f*]-quinoline (**9**),[44] which simulates the α form of DA, and the 8,9-dihydroxy isomer **10**,[45] which simulates the β form. In

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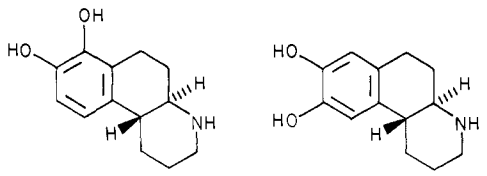

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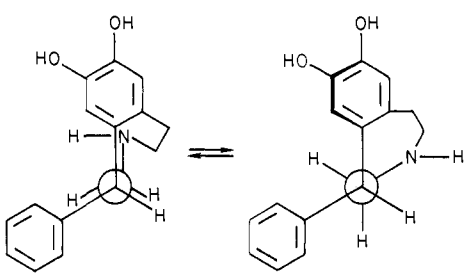
these compounds the trans isomers are highly rigid planar molecules, whereas the cis isomers are capable of flip (trans and gauche) conformations. The trans, but not the cis, isomer **9** produced a high level of central and peripheral DA-like effects.[44] In contrast, the trans isomer **10** exhibited marked peripheral dopaminergic actions but lacked significant central activity.[45] In both series the DA framework is rigidly held in an extended (trans) relationship between the catechol ring and the basic nitrogen. The distance between the "meta" hydroxyl, i.e., the one meta to the ethylamine chain, and the basic nitrogen is 6.4 Å in **9** (as it is in apomorphine), whereas it is about 7.3 Å in **10**. It has been suggested that these differences may account for the differences in reactivity with central vs. peripheral DA receptors.[45]

Conformationally, **1** is unlike most other DA receptor agonists; it is unable to attain an extended (trans) form. The tetrahydroazepine ring of **1**, although imposing some restraints, allows for considerable conformational flexibility. The DA framework in **1** can vary from a nearly folded (fully eclipsed, cis) orientation (**11**) to one in which the catechol ring and basic nitrogen are partially eclipsed (anticlinal) (**12**). Because a rigidly fixed cis orientation



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of the ring and nitrogen of the DA skeleton, as noted in several catecholic tetrahydroisoquinolines, e.g., (−)-1,2-dihydroxyaporphine[46] and (*S*)-salsolinol,[47] apparently prohibits receptor interaction, it seems probable that **1** interacts with the receptor in its most extended partially eclipsed conformation **12**. In this conformation the distance between the nitrogen and either hydroxyl, both of which appear necessary for DA-like activity,[41] is about 7.0 Å. This distance is altered only slightly if the conformation is altered, so that the nitrogen is located about 0.9 Å from the plane of the aromatic ring as it is when the tetrahydroazepine ring is in a chair conformation, a distance found critically important in some DA receptor mapping studies.[26]

In summary, the results of the present study indicate that 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (**1**) interacts with DA receptors in a stereoselective fashion; activity resides almost exclusively in the *R* enantiomer. The 1-phenyl substituent apparently interacts with a chirally defined accessory site on the receptor. Conformational restraints imposed by the tetrahydroazepine ring of **1** prevent attainment of a fully extended relationship between the aromatic ring and the nitrogen atom.[25] It is suggested that in agreement with most suggested DA receptor models,[17,25-31] which require a nearly planar arrangement of the catechol ring and amine moieties in which the nitrogen and phenolic hydroxyl(s) are separated by 7–8 Å,[25] (*R*)-**1** interacts with the receptor in a conformation which permits the hydroxyls and nitrogen to be similarly (i.e., maximally) separated. The hydroxyl binding functional groups on the DA receptor may be complementarily located between the catecholic hydroxyl groups, both of which are required for activity. The conformational and configurational requirements of **1** may account for its selectivity for a subtype (D-1) of DA receptors; however, at present no model seems to adequately rationalize agonist activity of all classes of dopaminergic agents.[48]

Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover Uni-Melt apparatus and were not corrected. Elemental analyses were performed in the Chemical Technologies Department of Smith Kline & French Laboratories. Where analyses are reported by symbols of the elements, results were within ±0.4% of the calculated value. IR spectra were obtained using a Perkin-Elmer 727 IR spectrophotometer. NMR spectra were obtained on a Hitachi Perkin-Elmer R-24 spectrometer (Me_4Si). Although IR and NMR spectral data are reported only where considered significant, the spectra were obtained for all compounds described in this section and were evaluated as consistent with the assigned structures. Mass spectra were obtained using a Hitachi Perkin-Elmer RMV-6E spectrometer. Optical rotations were determined using a Perkin-Elmer 241MC polarimeter. X-ray data and crystallographic calculations were performed as described.[49]

Resolution of 2,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1-phenyl-1*H*-3-benzazepine [(*R*)- and (*S*)-2]. To a solution of 116.0 g (0.39 mol) of 2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1-phenyl-1*H*-3-benzazepine[32] in 1.5 L of EtOH was added a solution of 150.4 g (0.4 mol) of (−)-dibenzoyl-L-tartaric acid monohydrate [from natural tartaric acid, $[\alpha]^{20}_D$ −105° (*c* 1.5, EtOH)] in 1.5 L of EtOH. After standing at 0 °C for 20 h, the colorless crystals were collected and washed with a small volume of cold EtOH and Et_2O: mp 180–181 °C; yield 68.8 g (74%). This **(−)-dibenzoyl-L-tartrate** was recrystallized from MeOH or MeCN without change of melting point: $[\alpha]^{25}_D$ −22.1° (*c* 1, DMF). Anal. $[(C_{19}H_{23}NO_2)_2 \cdot C_{18}H_{14}O_8 \cdot 0.5H_2O]$ C, H, N.

The combined filtrates were set aside. The crystalline salt was suspended in 500 mL of H_2O, excess aqueous NH_3 was added, and the mixture was extracted with EtOAc. After being dried ($MgSO_4$), the extracts were concentrated to give 51.6 g of colorless

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plates of (*S*)-**2** after recrystallization from Et_2O–*n*-C_6H_{14}: mp 103–105 °C; $[\alpha]^{25}_D$ –31.1° (*c* 1, MeOH). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

A **maleate**, prepared in Me_2CO, was recrystallized from MeOH–EtOAc to afford colorless crystals: mp 126–129 °C; $[\alpha]^{25}_D$ –0.6° (*c* 1, MeOH); $[\alpha]^{25}_D$ +12.2° (*c* 1, H_2O); $[\alpha]^{25}_D$ –3.8° (*c* 1, EtOH). Anal. ($C_{23}H_{27}NO_6$) C, H, N.

The ethanolic mother liquors from the preceding preparation of the (–)-dibenzoyl-L-tartrate were concentrated in vacuo. A suspension of the residual solid in H_2O was made alkaline with aqueous NH_3, and the mixture was extracted with EtOAc. Concentration of the extracts gave 73 g of a residual solid. To a solution of this base (73 g, 0.246 mol) in 850 mL of EtOH was added a solution of 94.5 g (0.25 mol) of (+)-dibenzoyl-D-tartaric acid monohydrate [from unnatural tartaric acid, $[\alpha]^{20}_D$ +108° (*c* 5, MeOH)] in 500 mL of EtOH. After the solution was left standing at 0 °C for 20 h, the crystalline product was collected and washed with a small volume of cold EtOH and Et_2O: yield 70.1 g (75.3%); mp 179–180 °C. To a suspension of this salt in 500 mL of H_2O was added excess aqueous NH_3. The mixture was extracted with EtOAc. After being dried ($MgSO_4$), the extracts were concentrated to give 52.1 g of colorless plates of (*R*)-**2** after recrystallization from Et_2O–*n*-C_6H_{14}: mp 105–106 °C; $[\alpha]^{25}_D$ +31.8° (*c* 1, MeOH). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

A **maleate**, prepared in Me_2CO, was recrystallized from Me_2CO–EtOAc to give colorless crystals: mp 127–129 °C; $[\alpha]^{25}_D$ +0.4° (*c* 1, MeOH); $[\alpha]^{25}_D$ –12.3° (*c* 1, H_2O); $[\alpha]^{25}_D$ +3.1° (*c* 1, EtOH). Anal. ($C_{23}H_{27}NO_6$) C, H, N.

A **methiodide**, prepared in EtOH, was recrystallized from MeOH–EtOAc to give colorless crystals: mp 249–251 °C; $[\alpha]^{25}_D$ +22.3° (*c* 1, MeOH). Anal. ($C_{20}H_{26}INO_2$) C, H, N.

Single-Crystal X-ray Analysis of (+)-2,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1-phenyl-1*H*-3-benzazepine [(+)-2·MeI]. The methiodide described in the preceding paragraph was recrystallized from MeOH–diisopropyl ether to give clear, stout acicula. Preliminary X-ray photographs showed orthorhombic symmetry and accurate lattice parameters, determined from a least-squares fit of 13 diffractometer-measured 2θ values, where a = 9.285 (1), b = 11.488 (1), and c = 18.172 (3) Å. Systematic extinctions, the known chirality, and approximate density were uniquely accommodated by space group $P2_12_12_1$ with an asymmetric unit of $C_{20}H_{26}INO_2$ ($\rho \approx 1.50$ g/cc).

All unique diffraction maxima and their Friedel pairs were collected on a computer-controlled diffractometer using a variable speed, 1° ω-scan and graphite monochromated Cu Kα (1.54178 Å) radiation. Of the 3113 reflections examined in this way, 3030 (97%) were considered observed ($|F| \geq 3\,\sigma - F_o$) after correction for Lorenz, polarization, and background effects.

A phasing model was achieved, using a unique set of 1590 reflections, by deconvoluting the Patterson to find the iodine position.[49] After refinement, the iodine phased difference electron-density synthesis revealed all of the nonhydrogen atoms. Full-matrix least-squares refinements with anisotopic heavy atoms, fixed hydrogens, and anomalous scattering for iodine have converged to a standard crystallographic residual of 8.3%. The absolute configuration was checked by carrying out refinement with the larger data set containing Friedel pairs. The enantiomer shown (Figure 1, absolute stereochemistry at C-1 is *R*) was significantly lower; the *R* factor for the other enantiomer was 3.2% higher.[50] Please consult supplementary material paragraph at the end of this article for additional details.

(*S*)-2,3,4,5-Tetrahydro-7,8-dihydroxy-3-methyl-1-phenyl-1*H*-3-benzazepine Hydrobromide [(*S*)-4]. To a stirred solution of 5.94 g (0.02 mol) of (*S*)-**2** in 250 mL of CH_2Cl_2, under N_2, at –70 °C was added dropwise a solution of 15 g (0.06 mol) of BBr_3 in sufficient CH_2Cl_2 to make a total volume of 73 mL. The temperature was allowed to increase. At about –15 °C the temperature began to increase rapidly; this was moderated by external cooling, then the temperature was gradually allowed to come to 25 °C for 1 h, then it was brought to –70 °C, and 100 mL of MeOH was added dropwise. Dry N_2 was rapidly bubbled through the solution (to expel excess HBr) as the temperature again was allowed to rise to 25 °C. The solution was concentrated in vacuo at about 25 °C. The residual liquid was refluxed with 250 mL of MeOH for 15 min, and then the solution was concentrated. This procedure was repeated twice. The residue was dissolved in about 20 mL of MeOH, and EtOAc was added to give 6.42 g (92%) of (*S*)-**4** as colorless crystals: mp 238–239 °C dec; $[\alpha]^{25}_D$ –17.9° (*c* 1, MeOH). Anal. ($C_{17}H_{20}BrNO_2$) C, H, N.

(*R*)-2,3,4,5-Tetrahydro-7,8-dihydroxy-3-methyl-1-phenyl-1*H*-3-benzazepine hydrobromide [(*R*)-4] was prepared in 86% yield by the same procedure utilized for (*S*)-**4**: colorless crystals; mp 239–240 °C; $[\alpha]^{25}_D$ +17.5° (*c* 1, MeOH); $[\alpha]^{25}_D$ –6.2° (*c* 1, H_2O). Anal. ($C_{17}H_{20}BrNO_2$) C, H, N.

(*R*)-2,3,4,5-Tetrahydro-7,8-dimethoxy-1-phenyl-1*H*-3-benzazepine [(*R*)-3]. Method A. To a solution of 14.9 g (0.05 mol) of (*R*)-**2** in 250 mL of benzene was added 6.3 g (0.06 mol) of cyanogen bromide. The resulting mixture was stirred at 50–55 °C for 4 h, cooled at 25 °C, and filtered to remove 2.1 g of a colorless solid. The filtrate was concentrated to leave 13.0 g of (*R*)-3-cyano-2,3,4,5-tetrahydro-7,8-dimethoxy-1-phenyl-1*H*-3-benzazepine as a yellow liquid: IR (Nujol mull) 2225 (CN) cm^{-1}; NMR ($CDCl_3$, Me_4Si) δ 7.27 (s, 5 H, PhH), 6.60 (s, 1 H, 6-H), 6.35 (s, 1 H, 9-H), 4.35 (t, 1 H, PhCH), 3.80 (s, 3 H, CH_3O), 3.61 (s, 3 H, CH_3O), 2.8–3.5 (br m, 6 H, CH_2). A solution of the above cyanamide in 150 mL of HOAc and 120 mL of 3 N HCl was stirred under reflux for 24 h. The residue remaining after concentration of the solution in vacuo was dissolved in H_2O, the solution was made basic with aqueous NH_3, and the resulting mixture was extracted with EtOAc. After being dried ($MgSO_4$, decolorizing C), the extracts were concentrated to leave 9.8 g (69.2%) of a pale yellow liquid: NMR ($CDCl_3$, Me_4Si) δ 7.20 (m, 5 H, PhH), 6.62 (s, 1 H, 6-H), 6.41 (s, 1 H, 9-H), 4.15 (m, 1 H, PhCH), 3.83 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 2.7–3.4 (br m, 6 H, CH_2), 2.0 (s, 1 H, NH, exchanged with D_2O); $[\alpha]^{25}_D$ +17.6° (*c* 1, MeOH). The base was dissolved in Me_2CO, and excess maleic acid was added. After addition of Et_2O, colorless crystals of **(*R*)-3 maleate** were collected: mp 138–141 °C; $[\alpha]^{25}_D$ –2.1° (*c* 1, MeOH). Anal. ($C_{22}H_{25}NO_6 \cdot 0.25H_2O$) C, H, N.

Method B. To a solution of 28.3 g (0.1 mol) of 2,3,4,5-tetrahydro-7,8-dimethoxy-1-phenyl-1*H*-3-benzazepine in 20 mL of EtOH and 50 mL of Et_2O was added a solution of 23.3 g (0.1 mol) of (+)-10-camphorsulfonic acid in 20 mL of EtOH. About 700 mL of Et_2O was added, and the solution was cooled to 0 °C to give 40.3 g of colorless crystals, mp 170–184 °C. After three recrystallizations from a minimum volume of H_2O, 11.2 g (44.2%) of (*R*)-**3** (+)-10-camphorsulfonate, mp 208–210 °C, was obtained. The salt was suspended in water, excess aqueous NH_3 was added, and the mixture was extracted with EtOAc. After being dried ($MgSO_4$), the extracts were concentrated to give 5.9 g (41.7%) of colorless liquid: $[\alpha]^{25}_D$ +17.3° (*c* 1, MeOH).

(*S*)-2,3,4,5-Tetrahydro-7,8-dimethoxy-1-phenyl-1*H*-3-benzazepine [(*S*)-3] maleate was prepared in 78.6% yield as described in method A for (*R*)-**3** maleate: $[\alpha]^{25}_D$ +4.0° (*c* 1, MeOH). Anal. ($C_{22}H_{25}NO_6 \cdot 0.25H_2O$) C, H, N.

(*R*)-3-Benzyl-2,3,4,5-tetrahydro-7,8-dimethoxy-1-phenyl-1*H*-3-benzazepine [(*R*)-5]. A mixture of 14.2 g (0.05 mol) of (*R*)-**3**, 10.9 g (0.063 mol) of benzyl bromide, and 69 g (0.5 mol) of K_2CO_3 in 1 L of Me_2CO was stirred and refluxed for 3 h. After the mixture was filtered, the filtrate was concentrated in vacuo. The residue was dissolved in 2:1 EtOAc–Et_2O. The solution was washed with H_2O, dried ($MgSO_4$, decolorizing C), and concentrated in vacuo to give 17.2 g (92%) of a pale yellow oil: $[\alpha]^{25}_D$ +42.3° (c 1, MeOH); MS, *m/e* 373; NMR ($CDCl_3$, Me_4Si) δ 7.27 (m, 10 H, PhH), 6.65 (s, 1 H, 6-H), 6.32 (s, 1 H, 9-H), 4.22 (m, 1 H, PhCH), 3.84 (s, 3 H, OCH_3), 3.63 (s, 5 H, OCH_3, NCH_2Ph), 2.5–3.2 (br m, 6 H, CH_2); TLC (silica gel, 2:1 *c*-C_6H_{12}–EtOAc) R_f 0.7 (with small spots at R_f 0.75 and 0.8).

(*S*)-3-Benzyl-2,3,4,5-tetrahydro-7,8-dimethoxy-1-phenyl-1*H*-3-benzazepine [(*S*)-5] was prepared (89.5% yield) as described for (*R*)-**5**: $[\alpha]^{25}_D$ –46.8° (*c* 1, MeOH); TLC (silica gel, 2:1 *c*-C_6H_{12}–EtOAc) R_f 0.7 (with trace spots at R_f 0.0, 0.75, and 0.8); MS and NMR were identical with those of (*R*)-**5**.

(*R*)-3-Benzyl-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine [(*R*)-6] was prepared from 17.2 g (0.046 mol) of (*R*)-**5** and 34.6 g (0.138 mol) of BBr_3 in CH_2Cl_2 as described for (*S*)-**3**. Crude HBr salt resulting from this procedure was suspended in H_2O, aqueous NH_3 was added to pH 7–8, and the mixture was extracted with EtOAc. After being washed with H_2O,

(50) W. C. Hamilton, *Acta Crystallogr.*, 18, 502 (1965).

the extracts were dried ($MgSO_4$) and concentrated. The residual red solid was chromatographed on a silica column, eluting with 9:1 benzene/EtOAc. Fractions were monitored by TLC; those with R_f 0.4 (silica gel, 2:1 c-C_6H_{12}– EtOAc) were combined and concentrated to leave 7.7 g (48.7%) of an amorphous solid: $[\alpha]^{25}_D$ +33.4° (c 1, MeOH); MS, m/e 345; NMR ($CDCl_3$, Me_4Si) δ 7.18 (m, 10 H, PhH), 6.51 (s, 1 H, 6-H), 5.99 (s, 1 H, 9-H), 4.9 (m, 2 H, OH), 4.1 (m, 1 H, PhCH), 3.51 (m, 2 H, NCH_2Ph), 2.55–3.05 (br m, 6 H, CH_2).

(*S*)-3-Benzyl-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine [(*S*)-6] was prepared from (*S*)-**5** in 35.5% yield as described for (*R*)-**6**: $[\alpha]^{25}_D$ –33.4° (c 1, MeOH); TLC, NMR, and MS identical with those of (*R*)-**6**.

(*R*)-2,3,4,5-Tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine Hydrochloride [(*R*)-1]. Method A. A solution of (*R*)-**6** (6.9 g, 0.02 mol) in 50 mL of MeOH was made acidic with HCl gas and concentrated at 30 °C in vacuo. The residual HCl salt was dissolved in 90 mL of MeOH, and the solution was added to 1 g of 10% Pd on C suspended in 10 mL of EtOAc. After the mixture was hydrogenated for 2 h on a Parr apparatus at an initial temperature of 25 °C and 60 psi of H_2, it was filtered. The filtrate was concentrated, and the residue was triturated with Me_2CO to give a tan solid. Recrystallization from MeOH–EtOAc gave 4.2 g (72.3%) of light tan crystals: mp 244–246 °C; $[\alpha]^{25}_D$ +15.3° (c 1, MeOH); $[\alpha]^{25}_D$ –10.7° (c 1, H_2O). Anal. ($C_{16}H_{18}ClNO_2$) C, H, N.

Method B. A solution of 3.5 g (12.4 mmol) of (*R*)-**3** in 10 mL of MeOH was acidified with HCl. After the solution was concentrated in vacuo, the residual amorphous solid was dissolved in 150 mL of methanesulfonic acid and 10 mL of H_2O. Methionine (21.0 g, 0.14 mol) was added, and the mixture was heated gently to afford a solution. After being stirred at 25 °C for 4 days, the solution was poured into 200 mL of ice–H_2O and adjusted to pH 8.0 with aqueous NH_3 (until solid no longer was precipitated). The mixture was extracted with EtOAc. After being washed with aqueous $NaHSO_3$ and H_2O, the EtOAc solution was concentrated to give 0.7 g (22.2%) of base as colorless crystals after trituration with Et_2O: mp 167–168 °C; $[\alpha]^{25}_D$ +31.3° (c 1, MeOH). Anal. ($C_{16}H_{17}NO_2 \cdot 0.25H_2O$) C, H, N.

A suspension of the base in 10 mL of MeOH was acidified with HCl, and EtOAc was added to give 0.4 g of colorless, crystalline hydrochloride after washing with Et_2O and drying at 25 °C in vacuo for 2 h: mp 237–238 °C; $[\alpha]^{25}_D$ +15.3° (c 1, MeOH).

(*S*)-2,3,4,5-Tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine Hydrochloride [(*S*)-1]. Method A. (*S*)-**1** was prepared from (*S*)-**6** (71.8% yield) as described for (*R*)-**1**, method A: mp 245–246 °C; $[\alpha]^{25}_D$ –15.0° (c 1, MeOH); $[\alpha]^{25}_D$ +10.2° (c 1, H_2O). Anal. ($C_{16}H_{18}ClNO_2$) C, H, N.

Method B. Cleavage of (*S*)-**3** with excess methionine in methanesulfonic acid as described for the *R* enantiomer (method B) gave 1.3 g (41%) of base, mp 167–168 °C; $[\alpha]^{25}_D$ –31.3° (c 1, MeOH).

Determination of Enantiomeric Purity of (*R*)- and (*S*)-1. Enantiomeric purity of (*R*)- and (*S*)-**1** was carried out by HPLC on diastereoisomeric derivatives[36] with α-methoxy-α-trifluoromethylphenylacetic acid.[37] Derivatization of racemic **1** was performed as follows. To a solution of 0.1 g (0.343 mmol) of **1** in a solution of 0.075 g (1.87 mmol) of NaOH and a trace of ascorbic acid in 10 mL of H_2O, through which argon was bubbled, was added at 0 °C a solution of 0.095 g (0.377 mmol) of racemic α-methoxy-α-trifluoromethylphenylacetyl chloride[37] in 10 mL of THF. The mixture was stirred at 25 °C for 5 min, then it was acidified with 2.5 N HCl, and 20 mL of H_2O was added. The mixture was extracted with EtOAc. After the extracts were washed with H_2O, they were dried and concentrated to give 0.16 g of a viscous liquid. TLC (silica gel, 20% MeOH–80% $CHCl_3$) failed to separate the diastereomers, R_f 0.9.

The same procedure was applied to 0.01 g (0.0392 mmol) of (*R*)- and (*S*)-**1** using (–)-α-methoxy-α-trifluoromethylphenylacetyl chloride to provide the corresponding enantiomeric (–)-α-methoxy-α-trifluoromethylphenylacetamide derivatives.

Analytical HPLC separations were performed on 4 mm × 30 cm μ-Bondapak C_{18} prepacked columns (Waters Associates) operated at 45 °C. Elution was carried out using 55% 0.6 M $NaClO_4$ adjusted to pH 2.5 with $HClO_4$ in acetonitrile at a rate of 0.5 mL/min. Ultraviolet detection at 250 nm was employed. The diastereoisomeric mixture of the racemic α-methoxy-α-trifluoromethylphenylacetamide derivative of **1** gave a base-line separation of 38 min for the *R* diastereomer and 41 min for the corresponding *S* diastereomer. When peak heights were used to estimate optical purity, the *S* isomer showed an enantiomeric excess (ee) of at least 89%. The *R* isomer showed an ee of at least 97%.

2,3,4,5-Tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (1) base was prepared from 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine hydrobromide[32] or the corresponding hydrochloride (prepared by refluxing the HBr salt with a large excess of concentrated hydrochloric acid). A concentrated aqueous solution of the salt containing a trace of ascorbic acid was adjusted to pH 8 by addition of concentrated aqueous NH_3 under N_2. The precipitated solid was filtered, and washed twice with equal volumes of H_2O, a small volume of acetonitrile, and Et_2O. The crystals, mp 136–140 °C, were triturated with Et_2O and then dried at 100 °C at 0.1 torr for 24 h. Anal. ($C_{16}H_{17}NO_2 \cdot 0.5H_2O$) C, H, N.

Attempted Resolution of 2,3,4,5-Tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (1) by Recrystallization of Salts with Optically Active Acids. Crystalline salts with several optically active acids were obtained, but solvent conditions for separation of the resulting diastereomers were not determined.

2,3,4,5-Tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (1) L-Tartrate. To a solution of 2.55 g (10.0 mmol) of **1** and 1.50 g (1.0 mmol) of L-tartaric acid (natural) in 10 mL of EtOH was added Et_2O until cloudiness was observed. The lightly stoppered solution was allowed to stand at 25 °C until crystals were observed (about 1 h), and then it was held at 0 °C for 2 days. The crystalline product, 3.3 g (81%), mp 255–258 °C dec, was collected. Further recrystallization from EtOH–Et_2O, as well as various other solvent systems, failed to elevate the melting point, and a base liberated from the salt showed no significant optical rotation. Elemental analysis was suggestive of a mixed tartrate and hydrogen tartrate. Anal. Calcd for $C_{16}H_{17}NO_2 \cdot C_4H_6O_6$: C, 59.25; H, 5.72; N, 3.46. Anal. Calcd for $(C_{16}H_{17}NO_2)_2 \cdot C_4H_6O_6$: C, 65.90; H, 6.06; N, 4.24. Found: C, 61.95; H, 6.30; N, 3.72.

2,3,4,5-Tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (1) (+)-10-Camphorsulfonate. A solution of 2.55 g (1.0 mmol) of **1** and (+)-10-camphorsulfonic acid monohydrate (2.50 g, 1.0 mmol) in 10 mL of EtOH was adjusted to the cloud point by addition of Et_2O. After standing at 25 °C for 3 days, the solution formed crystals. The mixture was held at 0 °C for 2 days, and then 3.5 g (72%) of colorless crystals, mp 244–246 °C dec, were collected. Two recrystallizations from EtOH–Et_2O failed to change the melting point, and a base liberated from the salt had no significant optical rotation. Anal. ($C_{26}H_{33}NO_6S$) C, H, N.

2,3,4,5-Tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (1) (–)-Menthoxyacetate. A solution of 2.55 g (1.0 mmol) of **1** and 2.14 g (1.0 mmol) of (–)-menthoxyacetic in 10 mL of EtOH was diluted with Et_2O until cloudiness was noted. The loosely stoppered flask was allowed to stand at 25 °C until crystals appeared (about 2 weeks). The crystals, 2.4 g (52%), melted at 203–204.5 °C. The melting point was unchanged upon further recrystallization from EtOH–Et_2O. Base liberated in the usual manner failed to give significant optical rotation. Anal. ($C_{28}H_{39}NO_5$) C, H, N.

Methoxy Cleavage of (*R*)-2,3,4,5-Tetrahydro-7,8-dimethoxy-1-phenyl-1*H*-3-benzazepine [(*R*)-3] with BBr_3 was performed using 1.7 g (6 mmol) of (*R*)-**3** and 4.5 g (18 mmol) of BBr_3 in CH_2Cl_2 as described for conversion of (*S*)-**2** to (*S*)-**4**. The gray crystalline HBr salt (1.58 g, 78.2%) melted at about 210–212 °C with softening, starting at 192 °C: $[\alpha]^{25}_D$ +9.7° (c 1, MeOH); $[\alpha]^{25}_D$ –6.8° (c 1, H_2O).

Refluxing (*R*)-**3** with excess concentrated hydrobromic acid for 2 h resulted in a similar, apparently partially racemized, product.

Biological Testing. Stimulation of dopamine-sensitive adenylate cyclase was measured using rat striatal homogenates employing a modification of the procedures of Kebabian et al.[51] and Carenzi et al.[52] as described previously.[10] The EC_{50} is defined

(51) J. W. Kebabian, G. L. Petzold, and P. Greengard, *Proc. Natl. Acad. Sci. U.S.A.*, **69**, 2145 (1972).

as the molar concentration of compound that gives half maximal stimulation of cyclic AMP production over the concentration range tested.

Spiroperidol binding was determined by a modification of the method of Fujita and Saito.[53] Male Charles River rats are decapitated. Caudates are dissected at 0 °C, frozen on dry ice, and stored at −80 °C. Frozen homogenates are homogenized in 50 volumes of 50 mM Tris-HCl buffer, pH 7.4, at 25 °C with a Polytron homogenizer (setting number 7 for 15 s) and centrifuged at 50000*g* for 15 min. The pellet is rehomogenized in 50 volumes of fresh buffer and again centrifuged. The resulting pellet is homogenized to 100 volumes of pH 7.4 Tris-HCl buffer containing 0.1% ascorbic acid, 5 mM ethylenediaminetetraacetic acid, and 10 μM pargyline. After being incubated at 37 °C for 15 min, the homogenate is cooled to 0 °C. To assay incubation vessels (in triplicate) there is added 0.2 mL of [^{3}H]spiroperidol (final concentration is about 0.2 nM) and 0.8 mL of buffer (control) or buffer with test compound (samples), or buffer with 1 μM (+)-butaclamol (nonspecific), or buffer, compound, and 1 μM (+)-butaclamol (compound specific). The homogenate (1 mL) is added to the assay vessels and the mixture is incubated at 37 °C for 30 min. After being held at 0 °C for 15–30 min, 4.5 mL of cold Tris-HCl buffer is added to the samples, the mixture is filtered through a Whatman GF/B filter, and the filter cake is washed with cold Tris-HCl buffer (3 × 4.5 mL). The filters and retained material are transferred to scintillation vials, 10 mL of Aquasol 2 is added, the mixture is shaken vigorously for 30 min, and the radioactivity is counted. The IC_{50} is the concentration of compound that produces 50% inhibition of specific spiroperidol binding.

Rotation in rats with lesions in the substantia nigra was determined as previously described.[10] The RD_{500} is defined as the dose calculated to produce 500 bodily rotations during a 2-h test period.

Renal vasodilator activity[15] was measured in anesthetized dogs surgically prepared for electromagnetic measurement of renal blood flow. Blood pressure was measured from the carotid artery. Drugs were infused into a antecubital vein. Renal vascular resistance (RVR) was calculated as the ratio of mean arterial blood pressure to mean blood flow. Cumulative dose–response data were obtained by infusing the compound at progressively increasing (generally threefold) concentrations. The ED_{15} ↓ RVR is the average maximum cumulative dose that decreases RVR by 15%.

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Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, bond angles, and observed and calculated structure factors (11 pages). Ordering information is given on any current masthead page.

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Synthesis of 2-(Alkylamino)-5,6- and -6,7-dihydroxy-3,4-dihydroquinazolines and Evaluation as Potential Dopamine Agonists[1]

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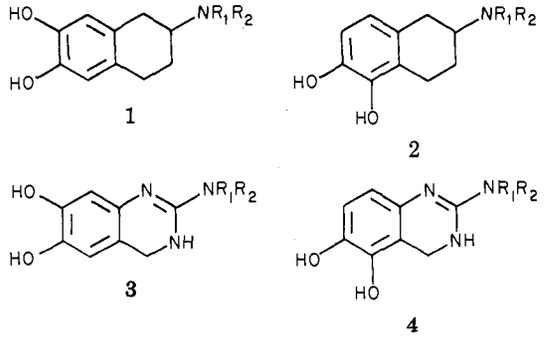
Based upon the known dopaminergic properties of 2-aminodihydroxy-1,2,3,4-tetrahydronaphthalenes (ADTN's), heterocyclic congeners were prepared. Several 2-(alkylamino)-5,6- and -6,7-dihydroxy-3,4-dihydroquinazolines were synthesized and tested for a dopamine-like vasodilatory action in the canine renal artery. The 6,7-disubstituted series had a weak antagonist effect against dopamine. Neither 5,6- nor 6,7-dihydroxy substitution gave dopamine agonists. Measured pK_a values confirmed the expectation that the dihydroquinazolines were more basic than dopamine, one possible reason for the lack of dopamine-like action.

The interesting pharmacological profile of the 2-(alkylamino)-6,7- and -5,6-dihydroxy-1,2,3,4-tetrahydronaphthlenes (ADTN's; 1 and 2), particularly as dopaminergic agents, has led us to prepare heterocyclic congeners of these compounds. Encouraged by the biological activity of the previously reported 2-(alkylamino)-3,4-dihydroquinazolines,[3] as well as by the action of 2-[(3,4-dihydroxyphenyl)amino]imidazoline (DPI) as an α-adrenergic and dopamine agonist at selected sites,[4] it seemed worthwhile to employ the dihydroquinazoline ring system as the parent nucleus for this study. Since the activity of the tetrahydronaphthalenes varies with both the N-substitution[5] as well as the location of the hydroxy groups,[6] it was concluded that the target compounds should be representative of these structural modifications, with the



	R_1	R_2
a	H	H
b	H	CH_3
c	CH_3	CH_3
d	*n*-C_3H_7	*n*-C_3H_7

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(1) Taken, in part from the Ph.D. Thesis of John A. Grosso, Purdue University, 1980.
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