Synthesis, Conformation, and Dopaminergic Activity of 5,6-Ethano-Bridged Derivatives of Selective Dopaminergic 3-Benzazepines

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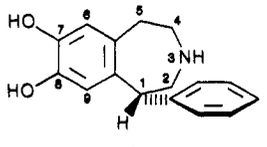
To probe the suggestion that D-1 (DA_1) dopamine receptors might possess an accessory π-binding site in a location complementary to a suitably oriented aromatic ring (i.e., in an axial orientation approximately orthogonal to the catechol nucleus) in agonists such as 2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine-7,8-diol (**1**) and 3′,4′-dihydroxynomifensine (**2**) that are selective for this subtype, *cis*- and *trans*-2,3,4,8,9,9a-hexahydro-4-phenyl-1*H*-indeno[1,7-*cd*]azepine-6,7-diol were prepared. These compounds are 5,6-ethano-bridged derivatives of the D-1 selective dopamine receptor agonist **1**. Introduction of the bridge reduces the conformational mobility of the parent molecule. Comprehensive conformational analyses by molecular mechanical methods indicated that both the cis and trans isomers could attain a conformation that places the phenyl substituent in an axial orientation. X-ray analysis of the trans isomer showed an axial disposition of the phenyl ring; however, NMR studies suggest that this conformation is fixed in the trans isomer, but not in the cis. The dopamine receptor binding affinity and intrinsic activity of the cis isomer were considerably greater than those of its trans counterpart; the cis isomer also demonstrated a high degree of selectivity for the D-1 subtypes. One possible explanation of these results, suggested by the molecular modeling studies, is that both the axial orientation of the phenyl postulated to be required for binding to the receptor and a putatively requisite location of the nitrogen in approximately the plane of the catechol ring can be attained only by the cis isomer in which the tetrahydroazepine ring is in a twist conformation. Conversely, these results might simply suggest a preference of the D-1 receptors for benzazepine agonists having the phenyl group in an equatorial orientation. Still another possibility is that the D-1 receptor binding site is in a sterically hindered area accessible only to compounds that are relatively planar. However, it requires an axial 1-phenylbenzazepine for strong binding. Thus, a conformationally flexible cis isomer could more readily achieve the different conformations required to both gain access to and bind with the D-1 site.

Enantiomeric pairs serve as particularly valuable probes of receptors because they have identical physical properties, and thus, unless they undergo differential metabolism, pharmacological differences[1-4] may fairly certainly be associated with receptor-related events.[5] On the basis of study of the dopamine receptor activating properties of enantiomers of two classes of compounds, namely 1-phenyltetrahydro-3-benzazepine derivatives[6,7] and 3′,4′-dihydroxynomifensine,[8] selective for the D-1[9] (DA_1)[10] receptors, a new location for an accessory binding site, perhaps unique for this subpopulation of dopamine receptors, has been postulated.[8]



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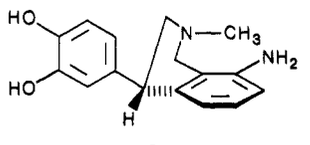

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The dopaminomimetic (*R*)-benzazepine **1** and (*S*)-3′,4′-dihydroxynomifensine (**2**) are both accomodated by the hypothetical model of the dopamine receptor suggested by McDermed et al.[11-13] In addition, when fitted into the model the 1-phenyl substituent of **1** and the benzo-fused ring of the tetrahydroisoquinoline **2** can reside in almost identical locations, approximately parallel to, and planar with, a suggested proteinaceous site of steric occlusion on the hypothetical dopamine receptor surface. It was this observation that led to the suggestion of a secondary binding site located in the proteinaceous D-1, DA_1 receptors in a position complementary to the properly oriented aromatic ring of the subtype selection agonists. The possibility that the increased D-1, DA_1 receptor selectivity and activating potency[6] of **1** and **2** might be the consequence of, e.g., π–π nonbonded interactions between the aromatic ring of the agonist and the complementary residues of Phe, Tyr, or Trp in the receptor surface was thus advanced.[8] To further probe the validity of this concept, a study of compounds that more rigidly hold the aromatic moiety of selective dopamine receptor agonists in an optimum position for interaction with the proposed accessory binding site in the D-1, DA_1 receptor subtype was undertaken. Examination of Dreiding models indicated that through a remote steric effect both the cis (4*R*,9a*S*) and trans (4*R*,9a*R*) isomers of the 5,6-ethano-bridged derivatives of **1** i.e., *trans*- and *cis*-2,3,4,8,9,9a-hexahydro-4-phenyl-1*H*-indeno[1,7-*cd*]azepine-6,7-diols (**3** and **4**, respectively) would semirigidly orient the phenyl group in

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0022-2623/87/1830-1303$01.50/0

Scheme I

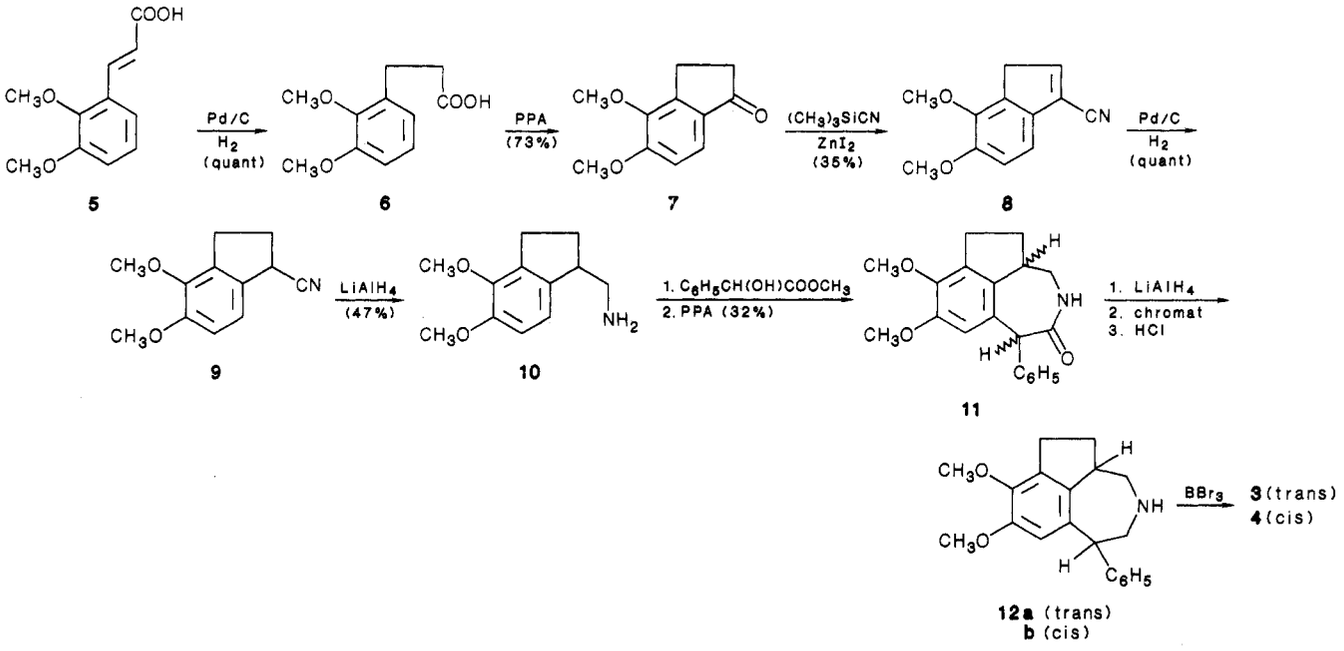
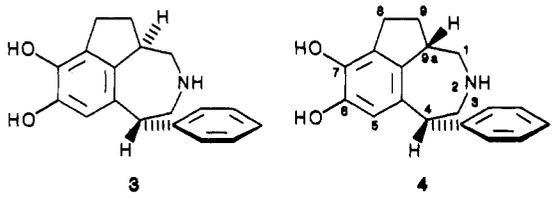


Table I. Pharmacological Properties of a Benzazepine (1) and Two 5,6-Ethano-Bridged Derivatives [(±)-3, (±)-4] at Dopamine Receptors

compd	[^{3}H]fenoldopam binding, rat striatum: K_{Bind} ± SE,[a] μM	dopamine-sensitive adenylate cyclase stimulation[a]		[^{3}H]spiroperidol binding, bovine pituitary: K_{Bind}, μM or [% inhibn (μM)[a]]
		ED_{50}, μM or [% above control (μM)]	% DA stim (μM)	
(±)-4(cis)	0.024 ± 0.005	0.43	62 (10)	[14% (10)]
(±)-3(trans)	1.22[b]	[20% (10)]	15 (10)	[0% (10)]
1[c]	0.0051 ± 0.0009	0.063	66 (10)	33.9[d]
DA[e]	0.15 ± 0.024	3.5	100 (50)	2.35

[a] Test procedures for determinations of K_{Bind} and ED_{50} values are described in the Experimental Section. [b] $N = 1$. [c] *R* enantiomer.[18] [d] IC_{50} for displacement of [^{3}H]spiroperidol binding from rat caudate homogenate. In this test system dopamine has an $IC_{50} = 5.34$ μM.[7] [e] Dopamine.[18]

a location suitable for interaction with the postulated secondary binding site on the D-1, DA_1 subpopulation of dopamine receptors. Thus, although on the basis of extensive structure–activity relationship studies[14-16] the resulting substitution at position 5 and 6 of the parent 1 would be anticipated to be relatively unfavorable for receptor interaction, the synthesis and examination of dopaminergic activity and selectivity of racemic **3** and **4** were undertaken.



Chemistry. The racemates of the target compounds **3** and **4** were obtained as outlined in Scheme I. Accordingly, 2,3-dimethoxycinnamic acid (**5**)[17] was hydrogenated to the propionic acid **6**, which was cyclized to the indanone **7** with PPA. Treatment of **7** with trimethylsilyl cyanide in the presence of ZnI_2 afforded the cyanoindene **8**, which was sequentially reduced (Pd/C, H_2; $LiAlH_4$) to give the cyanoindan **9** followed by the (aminomethyl)indan **10**. Condensation of **10** with methyl mandelate followed by PPA cyclization produced a mixture of *cis*- and *trans*-**11**, which was reduced ($LiAlH_4$) to give a mixture of trans and cis isomers **12a** and **12b**, respectively. The mixture was separated by chromatography. Stereochemical assignments of **12a** and **12b** were made on the basis of detailed ^{1}H NMR analysis involving two-dimensional COSY spectra, NOE measurements and observation of certain long-range couplings as described below. Confirmation of the trans stereochemistry of **12a** was obtained by single-crystal X-ray diffractometric analysis of the hydrochloride as described in the Experimental Section and in the supplementary material. An ORTEP diagram of the structure thus determined is presented in Figure 1. Methoxyl scission of **12a** and **12b** afforded **3** and **4**, respectively.

Results. Biology. The affinities of **1** and its semirigid congeners **3** and **4** for D-1 dopamine receptor binding sites were evaluated in a test involving displacement of [^{3}H]-fenoldopam from homogenized rat striatum.[18] Affinity for D-2 receptors was estimated from the ability of the

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Table II. Simplex Energy Values (kcal/mol) for 5,6-Ethano-Bridged Benzazepines[a]

compd	ring conf	phenyl orient	stretch	bend	tors	van der Waals	total
3a(trans)	chair	ax	0.33	5.03	6.45	−8.78	3.03
	twist	eq	0.19	6.27	5.16	−7.59	4.05
4a(cis)	chair	eq	0.29	4.77	6.35	−7.77	3.64
	twist	ax	0.20	6.46	5.52	−8.73	3.45
4(desphenyl)	chair		0.22	4.63	5.86	−5.98	4.73
	twist		0.14	6.14	4.98	−5.49	5.78

[a] Determined as described in the text.

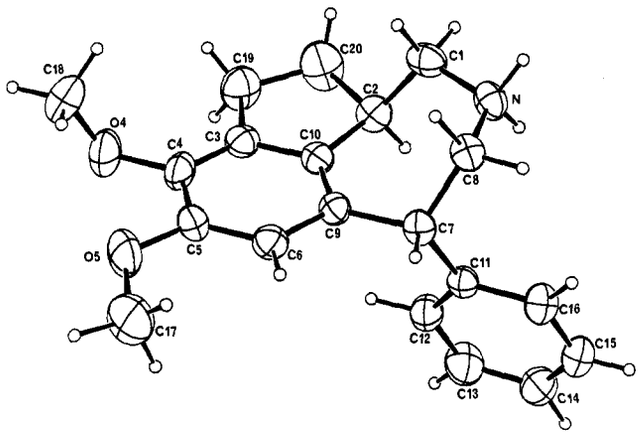

Figure 1. An ORTEP diagram of *trans*-6,7-dimethoxy-2,3,4,8,9,9a-hexahydro-4-phenyl-1*H*-indeno[1,7-*cd*]azepine hydrochloride (**12a**) determined by single-crystal X-ray analysis.

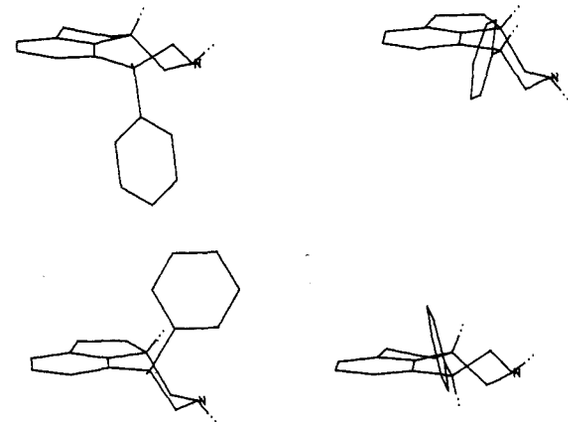

Figure 2. SIMPLEX minimum-energy structures of *cis*- and *trans*-hexahydro-4-phenyl-1*H*-indeno[1,7-*cd*]azepines: (a) upper left, cis, twist-axial, (b) upper right, cis, chair-equatorial, (c) lower left, trans, chair-axial, (d) lower right, trans, twist-equatorial.

compounds to displace [^{3}H]spiroperidol from homogenized bovine pituitary.[18] As a measure of efficacy at the D-1 receptors, a test that measures the ability of the compounds to stimulate dopamine-sensitive adenylate cyclase was employed.[18] The results of examination of **1** (*R* enantiomer), as well as racemic **3** and **4**, in these tests are tabulated in Table I. The cis isomer **4** shows clear D-1 activity, being 6 times more potent than dopamine in the [^{3}H]fenoldopam binding assay and 8 times more potent in the adenylate cyclase assay. However, like most other benzazepine derivatives, it is a partial agonist, giving only 62% of the dopamine response. Since **4** shows only slight activity in the spiroperidol binding assay, it may be classified as highly selective toward the D-1 receptor subtype. In contrast, the trans isomer **3** is inactive at the D-2 receptor and shows only weak activity at the D-1 receptor.

Conformational Analysis. Molecular Mechanics. In an effort to evaluate the possible interactions of the various spacially oriented phenyl substituents with a complementary binding site on the surface of the D-1 (DA_1) subtype of dopamine receptors, a study of the conformational preferences of these compounds by theoretical as well as physical methods was undertaken. In molecular modeling studies the deshydroxy analogues of **3** and **4** were built with the SYBYL Molecular Modeling System (TRIPOS Associates) and were minimized by using Hopfinger's CHEMLAB (systematic search with rapid torsional minimization) and SIMPLEX (V. 3.2 of SYBYL). Hydroxyl groups were omitted for simplicity as preliminary studies indicated these substituents have little conformational influence on the seven-membered ring and its substituents. The results of this study are presented in Table II. The conformations of the isomers appear to be determined primarily by two factors: (a) the chair conformation of the ring system is more favorable than the twist and (b) the axial arrangement of the 4-phenyl group, in agreement with earlier molecular modeling studies with 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol (fenoldopam),[14] is more favorable than the equatorial, due in part to decreased van der Waals interactions. These observations suggest that the conformer with both the chair conformation and the axial orientation of the phenyl is the most stable; the twist-axial and chair-equatorial conformers are similar; and the twist-equatorial conformer is least stable. The cis isomer has two major conformers of essentially equal energy, i.e., twist-axial (Figure 2a) and chair-equatorial (Figure 2b). The trans isomer also has two major conformers, namely, chair-axial (Figure 2c) and twist-equatorial (Figure 2d), i.e., the most (3.03 kcal/mol) and least (4.05 kcal/mol) favored forms, respectively. These figures depict the isomers with the 4-phenyl group in an abolute *R* configuration as it is in the dopaminergic enantiomer of other phenyl-substituted benzazepines.[6,7,14] This molecular modeling study indicating the preferred chair-axial conformation for the *trans*-4-phenyl-substituted ethano-bridged benzazepine (Figure 2c) is in almost complete agreement with the structure of the *trans*-6,7-dimethoxy derivative **12a** which was determined by single-crystal X-ray analysis (Figure 1).

It is of interest that single-crystal X-ray analysis[6] of the *N,N*-dimethyl quaternary salt analogue of the dimethyl ether of **1** determined that it exists in the phenyl equatorial twist conformation while **1** hydrochloride exists in a chair conformation. Similar studies with the hydrobromide salt of (*R*)-fenoldopam, the 6-chloro-1-(4-hydroxyphenyl) analogue of **1**, showed that it also exists in the chair conformation with the phenyl equatorial.[14]

Configurational and Conformational Analysis. NMR. The relative stereochemistries for the ethano-bridged tetrahydrobenzazepines **12a** and **12b** were determined by analysis of their high-field NMR spectra. Observation of specific nuclear Overhauser enhancements (NOE's), evaluation of several vicinal coupling constants in the seven-membered rings, and the presence of certain weak couplings (long range) permitted both the determination of the relative configurations at the ring fusions and the following proposal of conformations for the seven-membered rings.

Table III. ^{1}H NMR Data

assignment	ppm	coupled to	long range
12a			
H1(ax)	2.90	H1(eq), H9a	
H1(eq)	3.25	H1(ax)	H4
H3(ax)	3.39	H3(eq)	H4
H3(eq)	3.98	H3(ax), H4	
H4	4.57	H3(eq)	H3(ax), H5
H5	6.54		H8(ax), OCH_3's
H8(ax)	2.86	H8(eq), H9(ax,eq)	H5
H8(eq)	2.92	H8(ax), H9(ax)	H9(eq)
H9(ax)	1.58	H9(eq), H8(ax,eq), H9a	
H9(eq)	2.25	H9(ax), H8(ax), H9a	H8(eq)
H9a	3.50	H1(ax), H9(ax,eq)	
12b			
H1(ax)	2.78	H1, H9a	
H1(eq)	3.42	H1, H9a	H4
H3(ax,eq)[a]	3.53, 3.6	H4	
H4	4.55	H3	H1(eq), H5
H5	5.80		H8, OCH_3's
H8(ax)	2.78	H8(eq), H9(ax,eq)	
H8(eq)	2.95	H8(ax), H9(ax,eq)	
H9(ax)	1.65	H9(eq), H8(ax,eq), H9a	
H9(eq)	2.33	H9(ax), H8(ax,eq), H9a	
H9a	3.74	H1(ax,eq), H9(ax,eq)	

[a] These shifts were observed in the mixed-solvent system. In Me_2SO-d_6–TFA they overlapped, leading to the observation of a triplet for H4 with an averaged coupling constant of 5 Hz, due to virtual coupling.

We have assigned **12a** as the isomer in which methine hydrogens at position 4 and 9a (see structure 4 for the numbering system) are disposed toward opposite faces of the seven-membered ring (trans) and **12b** as the isomer having its methine hydrogens on the same face (cis). The reasoning is outlined below. The compounds were studied as the trifluoroacetate salts, in Me_2SO-d_6, with excess TFA (4%), which maintained the protonation of the secondary ammonium center and shifted the interfering water signal to low field. For measurement of NOE's it was necessary to add $CDCl_3$ (Me_2SO–$CDCl_3$, 40/60) and increase the temperature from 19 to 45 °C, thereby decreasing the rotational correlation time for the salts from the region giving near-zero NOE's, into the range where positive NOE's are observed. The assignments of the tetrahydrobenzazepine ring protons were obtained via COSY 2D NMR experiments and are given in Table III. Weak couplings were detected by using a modified ("delayed") COSY experiment.

The proton spectrum of **12a** is characterized by a doubly benzylic proton (H4, 4.57 ppm) that appears as a slightly broadened doublet (J = 5.5 Hz), indicating that at least one of the H4–H3 dihedral angles is near 90°. The 5.5-Hz coupling implies a dihedral angle near 40–45° with the other H3. Together, these observations argue for an equatorial disposition for H4. Further, a strong NOE is observed at the aromatic singlet (H5) on irradiation of H4. This NOE is nearly as intense as that simultaneously elicited at the ortho aromatic signal in the attached 4-phenyl ring. This is further evidence for the equatorial disposition of H4. Since the strained tricyclic geometry of this system requires the bridgehead proton 9a to be axial, if the H4 methine is equatorial, a trans relationship between the hydrogens is implied. The 4-phenyl must then be axial.

The issue of whether the seven-membered ring has a crown-chair (such is illustrated in Figure 2c) or a twist-boat conformation (similar to Figure 2d) rests on the identification of the H3 protons. Specifically, is the H3 that is weakly coupled to H4 on the same face as phenyl group (cis) or the opposite (trans)? If it were trans-diaxial to the phenyl ring, model building suggests a chair conformer. A ring flip to a boat form that maintains the axial phenyl *and* the coplanarity of the C4–H4 and C5–H5 bonds requires the H3 cis to the phenyl group be weakly coupled to H4. This question is resolved by irradiating the H-(ortho) doublet from the aromatic ring. NOE's are induced at H4 and H9a (both consistent with the axial phenyl) and at the H3 that strongly couples to H4 (3.98 ppm). This H3 must be cis to the phenyl, and given the strong (5.5 Hz) coupling to H4, a crown-chair conformation for **12a** is indicated. In addition, H9a is coupled to only one of the H1 protons (no coupling to the other proton is detected even in the long-range COSY experiment). The required, near-90° angle, that the lack of an observable coupling indicates, can be obtained only in the chair conformer between H9a and H1(equatorial). The boat structure would give rise to significant couplings from both H1's to H9a.

The isomer **12b** shows substantial differences in the proton NMR spectrum, compared with **12a**. H5, the aromatic singlet, shows a dramatic upfield shift (5.80 ppm; 6.54 ppm in **12a**) presumably due to the shielding cone of the adjacent phenyl ring. H4 shows, as in **12a**, a very weak coupling to one of its vicinal H3 partners, but the stronger coupling is 10 Hz (5.5 Hz in **12a**), suggesting a trans-diaxial relationship between H4 and one of the H3's. The NOE difference spectra show significant differences as well. Irradiation of H4 gives rise to a enhancement of the H-(ortho) aromatic doublet as in **12a**, but the NOE to the H5 aromatic singlet is greatly diminished by comparison. Irradiation of H5, in turn, elicits an enhancement at the H(ortho) signal, as well as the expected NOE to the vicinal methoxyl group. These observations argue for an equatorial disposition for the 4-phenyl group, oriented, on average, such that H5 falls within its shielding cone (Figure 2b).

The equatorial 4-phenyl group requires the 4-methine to be axial. The observation of long-range coupling between H4 and H5 in the delayed COSY experiment supports this, in that this coupling is much larger for **12b** than for **12a**, as would be anticipated for a noncoplanar H5–C5–C4a–C4–H4 bond path in **12b**. This coupling is barely detectable in **12a**, which tends to confirm the nearly planar arrangement of H4 and H5 in **12a** suggested above. This experiment does not permit accurate estimates of the long-range coupling constants, but reveals in both **12a** and **12b** para benzylic couplings between H5 and the upfield of the two H8 protons, as well as between H5 and H1 (equatorial). This suggests similar overall geometries for both seven-membered rings (chair) (Figure 2b and 2c).

The data discussed thus far for **12b** could not definitively exclude a phenyl-axial boat nor a twisted boat conformer. However, a boat form should exhibit long-range ("*W*" type) coupling between H3(equatorial) and H1(equatorial) as has been observed in some other molecules in this class. The absence of such coupling in **12b** and in **12a**, although it is negative evidence at best, supports the notion of crown-chair conformers in both **12a** and **12b**. Another observation that corroborates the previously discussed disposition of the phenyl rings concerns the chemical shift of H9a. This proton experiences an upfield shift in the molecule that shows the "normal" shift for H5 (0.3 ppm upfield in **12b** compared to **12a**), which suggests that, in **12b**, it lies toward the face of the 4-phenyl ring. The overall rigidity of both molecules (relative insensitivity of chemical shifts and coupling constants to changes in temperature) helps to solidify the arguments based on NOE's and couplings and seem to argue against twist forms as significant contributors to the structures.

In summary, NMR studies have shown that in solution the trans isomer (**12a**) has a crown-chair conformation with the phenyl axial as depicted by Figure 2c, while the cis isomer (**12b**) has a equatorial phenyl and most probably also a crown-chair conformation as depicted by Figure 2b. These results are compatible with those of the molecular mechanics study that suggested a 1-kcal energy difference favoring the phenyl axial chair conformation for the trans isomer **3a** and only a 0.2-kcal difference favoring the twist-axial conformation for the cis isomer **4a**. Solvation at the nitrogen could easily shift the equilibrium to favor the observed conformation.

Discussion

The studies described in this paper neither clearly affirm nor refute the suggestion that D-1 dopamine receptor subtype selective agonists, e.g., **1** and **2**, owe their selectivity to binding to a unique site in the D-1 receptor subpopulation that can interact with an aryl group in an orientation approximately orthogonal to the catechol nucleus.[8] A priori, it might have been predicted that the isomer favoring a rigid axial orientation of the phenyl ring would be preferred. If this were the case the trans isomer **3**, in which such an orientation is favored, would have demonstrated greater potency and selectivity for the D-1 subpopulation of dopamine receptors. Many possible rationalizations[19] of the greater D-1 affinity of the cis isomer may be advanced. A simple explanation is that D-1 receptor binding is inhibited by an axial 1-phenyl group or enhanced by an equatorial 1-phenyl group. Another explanation is suggested by the well-established observation[20,21] that the dopaminergic pharmacophore requires that the side-chain nitrogen be nearly in the plane of the catechol nucleus for receptor binding. Examination of the preferred conformations of the cis (Figure 2a,b) and trans (Figure 2c,d) isomers determined by molecular modeling studies reveals that only the cis isomer with the tetrahydroazepine ring in a twist conformation places the phenyl group in an axial orientation while the nitrogen is approximately in the plane of the catechol ring. Thus, it is possible that it is this particular conformation, which by molecular mechanical calculations is energetically close to the phenyl equatorial chair conformation observed in the NMR experiments, that accounts for the binding of the cis isomer **4** to D-1, DA_1 receptors. Another possible explanation might be that the D-1 (and perhaps also the D-2) receptors are in a site accessible only to compounds that are able to obtain a relatively planar orientation, as has been observed generally for dopamine receptor agonists.[22] Precedent for this kind of explanation is found in the interpretation of certain substrate–enzyme interactions.[23] If this is the case, dopamine receptor agonists such as **4** (in a planar conformation) might be able to reach the active site where a conformer with the phenyl substituent in an axial (nonplanar) orientation could activate the D-1 receptor subpopulation. The decreased affinity of the trans isomer **3** might thus be rationalized by its inability to reach the D-1 dopamine receptor site.

Clearly, the work described in this paper has not unequivocally determined the required 1-phenylbenzazepine conformation necessary for potent D-1 receptor binding.

Experimental Section

Melting points were determined in open capillary tubes on a Thomas-Hoover Uni-Melt apparatus and were not corrected. Elemental analyses were performed in the Analytical, Physical and Structural Chemistry 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 (Perkin-Elmer 727 spectrophotometer), ^1H NMR (Perkin-Elmer R-24 or Bruker WM-360 spectrometer), and mass spectra (Hitachi Perkin-Elmer RMV-6E spectrometer) were determined for all compounds described in this section and were evaluated as being consistent with the assigned structures.

3-(2,3-Dimethoxyphenyl)propionic Acid (6). A mixture of 10 g (48 mmol) of 2,3-dimethoxycinnamic acid (**5**)[15] and 0.8 g of 10% Pd/C in a solution of 40 mL of HOAc and 120 mL of EtOH was hydrogenated at 35–40 °C at an initial H_2 pressure of 50 psi. After H_2 uptake was completed, the mixture was filtered. Concentration of the filtrate gave 10.1 g (100%) of a solid residue that was used for further reaction without additional purification.

4,5-Dimethoxy-1-indanone (7). A mixture of 17.5 g (83 mmol) of **6** and 200 g of polyphosphoric acid was stirred gently at 100 °C for 15 min. The homogeneous red product was poured into 1 L of ice–H_2O and the resulting solid was filtered and dissolved in Et_2O. The Et_2O solution was washed with H_2O, 5% aqueous $NaHCO_3$, and brine and then dried ($MgSO_4$) and concentrated. The residual solid was recrystallized from Et_2O to give 11.6 g (73%) of white crystals, mp 71–73 °C. Anal. ($C_{11}H_{12}O_3$) C, H.

3-Cyano-6,7-dimethoxy-1*H*-indene (8). To a stirred suspension of 2.1 g of ZnI_2 and 30.7 g (0.16 mol) of **7** in 650 mL of CH_2Cl_2 was added *slowly*, under N_2, 18.5 g (0.19 mol) of trimethylsilyl cyanide. After the stirred mixture was heated under reflux for 6 h, it was cooled to 20 °C and washed successively with H_2O and brine. The organic phase was dried ($MgSO_4$) and concentrated. The residue was taken into toluene and a small amount of unidentified insoluble material was filtered. TFA (43 mL) was added to the toluene solution and it was refluxed for 2 h. Et_2O was added to the solution and the mixture was washed successively with H_2O, 5% aqueous $NaHCO_3$ solution, H_2O, and brine. The organic solution was dried ($MgSO_4$) and concentrated. The residue was purified by "dry column" (SiO_2) chromatography. Elution with Et_2O–*n*–C_6H_{14} (3/2) gave 10.8 g (35%) of colorless crystals, mp 107–109 °C after recrystallization from EtOAc–*n*–C_6H_{14}. Anal. ($C_{12}H_{11}NO_2$) C, H, N.

1-Cyano-4,5-dimethoxyindan (9). Compound **9** was prepared by catalytic hydrogenation in the same manner described for reduction of **5** to **6**. The solid product (quantitative yield) melted at 68–70 °C after recrystallization from EtOH. Anal. ($C_{12}H_{13}NO_2$) C, H, N.

1-(Aminomethyl)-4,5-dimethoxyindan Hydrochloride (10). A solution of 9.0 g (44 mmol) of **9** in a mixture of Et_2O (200 mL) and THF (50 mL) was added dropwise to a suspension of 6.7 g (176 mmol) of $LiAlH_4$ in a mixture of Et_2O (200 mL) and THF (50 mL) at a rate sufficient to maintain gentle reflux. The mixture was stirred and refluxed for 6 h, and then, with *caution*, 7 mL of H_2O, 7 mL of 2.5 N NaOH, and 21 mL of H_2O were added successively. The mixture was filtered, the filtrate was concentrated, and a solution of the residue in MeOH was treated with HCl and Et_2O. Recrystallization of the solid product from MeOH gave 5.0 g (47%) of colorless crystals, mp 214–217 °C. Anal. ($C_{12}H_{17}NO_2$·HCl) C, H, N.

6,7-Dimethoxy-2,3,4,8,9,9a-hexahydro-4-phenyl-1*H*-indeno[1,7-*cd*]azepin-3-one (11). A stirred mixture of 4.75 g (23 mmol) of **10** and 3.8 g (23 mmol) of methyl mandelate was heated under N_2 for 16 h at 100 °C. The melt was suspended in CH_2Cl_2. A small amount of insoluble material was filtered, and the filtrate was concentrated. The residue was subjected to "dry column" chromatography (SiO_2), eluting with 3% MeOH in CH_2Cl_2. Concentration of the eluate gave a brown syrup, which was stirred gently with 100 g of PPA for 30 min at 100 °C. The mixture was poured into ice–H_2O. A solution of the resulting solid in CH_2Cl_2 was washed with H_2O and brine and then dried (Mg-

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SO_4). Concentration of the CH_2Cl_2 solution gave 2.4 g (32%) of white crystals, mp 204–208 °C after recrystallization from MeOH–EtOAc. Anal. ($C_{20}H_{21}NO_3$) C, H, N.

***trans*- and *cis*-6,7-Dimethoxy-2,3,4,8,9,9a-hexahydro-4-phenyl-1*H*-indeno[1,7-*cd*]azepine Hydrochlorides (12a and 12b).** A suspension of 2.3 g (7.1 mmol) of **11** in Et_2O (150 mL) and THF (50 mL) was added slowly to a stirred suspension of 1.1 g (30 mmol) of $LiAlH_4$ in 100 mL of Et_2O. The mixture was stirred and refluxed for 5 h and then with *caution* quenched by the sequential addition of H_2O (1 mL), 2.5 N NaOH (1 mL), and H_2O (3 mL). After the mixture was filtered, the filtrate was concentrated to give a viscous residue. TLC (silica gel, 5% MeOH in CH_2Cl_2) showed two spots, R_f 0.5, 0.6. The isomers were separated by "flash" chromatography (SiO_2), eluting with 12/1/400 MeOH–concentrated NH_4OH–CH_2Cl_2. The isomer with R_f 0.5 was converted into a hydrochloride (0.55 g, 22%), **12b**, mp 225 °C after recrystallization from MeOH–Et_2O. Similarly, the isomer with R_f 0.6 gave 0.4 g (15%) of **12a**, mp 240–242 °C.

^{1}H NMR Analysis of 12a and 12b. High-resolution ^{1}H NMR spectra of **12a** and **12b** were obtained with a Bruker Instruments WM 360 spectrometer operating at 360.13 MHz. COSY 2D spectra were measured at ambient temperatures on solutions of approximately 5 mg of **12a** and **12b** in 0.5 mL of Me_2SO-d_6 with 10% TFA added. The COSY spectra were measured with a standard Bruker "COSYN" command sequence, employing a 45° observation pulse; 128 1K spectra were collected for each increment. The data table was zero-filled to 256K and the sine-bell apodized prior to double Fourier transformation. In COSY spectra set to maximize long-range couplings, extra delays of 0.2 and 0.05 s were included before and after the observation pulse.

NOE difference spectra were measured with solutions of 5 mg of **12a** and **12b** dissolved in Me_2SO-d_6–$CDCl_3$–TFA (40/60/4; v/v/v) at 45 °C. Difference spectra were acquired by alternately adding, then subtracting, groups of 8 scans with low power irradiation on, then off, the resonance of interest. The irradiation period was 5.0 s, followed by a 2.0-ms delay before each acquisition.

Stereochemical assignments were based on ^{1}H NMR studies and were made by means of two-dimensional COSY spectra. Proton assignments for **12a** (Me_2SO-d_6–4% TFA): δ 1.58 (9 ax), 2.25 (9 eq), 2.86–2.92 (8 ax, 1 ax, 8 eq, overlapped), 3.25 (1 eq), 3.39 (3 ax), 3.50 (9a), 3.98 (3 eq), 4.57 (4), 6.54 (5) ppm (approximately). Proton assignments for **12b**: δ 1.65 (9 ax), 2.33 (9 eq), 2.78 (1 ax, 8 ax, overlapped), 2.95 (8 eq), 3.42 (1 eq), 3.53 (3 ax, eq), 3.74 (9a), 4.55 (4), 5.8 (5) ppm (approximately).

Single-Crystal X-ray Analysis of 12a. Crystals of the hydrochloride **12a** suitable for X-ray analysis were obtained by recrystallization from MeCN, followed by a second slow recrystallization from MeCN to which a few drops of 2-PrOH had been added. Crystal data: colorless acicula, 0.80 × 0.25 × 0.25 mm, space group $P4_2/n$, a = 21.774 (5) Å, c = 7.704 (2) Å, V = 3652.5 Å^3, Z = 8, ρ = 1.258 g/cm^3. Intensity data were collected on an Enrat-Nonius CAD-4 diffractometer at 293K using Mo Kα radiation and an ω–θ scan technique as suggested by peak-shape analysis. There was no evidence of crystal decay during data collection. Data were corrected for Lorentz–polarization effects, but not for absorption. Symmetry equivalent reflections due to the tetragonal lattice were averaged; the agreement factors were 3.4% on I and 2.4% on F_o. After averaging and removal of systematic absences, there were 4321 unique data. The structure was solved by direct methods with the MULTAN program package. Refinement proceeded smoothly through the isotropic and anisotropic stages. Hydrogen positions were located from difference Fourier maps and were refined along with isotropic temperature factors in the final cycles. All refinements were full matrix on F; the function minimized was $\sum w(|F_o| - |F_c|)^2$. A weighting scheme of the type $w = 1/\sigma(F_o)^2$ with $\sigma(F_o)^2$ given by the expression $[\sigma(I)^2 + (pF_o)^2]^{1/2}$ and p = 0.05 was used. There was no evidence for secondary extinction. Refinement converged to values of the standard crystallographic residuals R = 4.6% and R_w = 5.66% for 1829 observations with $I \geq 3\sigma(I)$. In the final least-squares cycle no parameter shifted by more than 0.02 times its estimated standard deviation. The goodness of the fit was 1.292. A final difference Fourier map was featureless; the maximum positive density was 0.191 e Å^{-3}. Values of the neutral atom scattering factors and anomalous dispersion were taken from ref 24. Hydrogen atom scattering factors were those of Stewart et al.[25]

***cis*-2,3,4,8,9,9a-Hexahydro-4-phenyl-1*H*-indeno[1,7-*cd*]azepine-6,7-diol Hydrobromide (4).** To a stirred solution of 0.24 g (0.78 mmol) of base derived from **12b** in 6 mL in 6 mL of CH_2Cl_2 at 0 °C was added a solution of 0.63 g (2.5 mmol) of BBr_3 in 3.2 mL of CH_2Cl_2. The solution was stirred at 0–25 °C for 2 h, then it was again brought to 0 °C, and MeOH (2 mL) was added dropwise. The solution was concentrated and the residue triturated with MeCN to give 0.25 g (89%) of white crystals, mp >290 °C after recrystallization from MeOH–Et_2O. Anal. ($C_{18}H_{19}NO_2$·HBr) C, H, N.

***trans*-2,3,4,8,9,9a-Hexahydro-4-phenyl-1*H*-indeno[1,7-*cd*]azepine-6,7-diol Hydrobromide (3).** Compound **3** was prepared from the base derived from **12a** in the same fashion as described for conversion of **12b** base to **4**. The initial product contained some ring-brominated material that was removed by catalytic hydrogenation in the presence of Pd/C. This gave white crystals (0.16 g, 57%), mp 210 °C after recrystallization from MeOH–Et_2O. Anal. ($C_{18}H_{19}NO_2$·HBr·0.5H_2O) C, H, N, Br.

Pharmacology. Competition for [^{3}H]Fenoldopam in Rat Striatum.[18] Homogenized and washed membrane preparations from rat caudate nuclei were utilized in this test that was performed as described previously. In each experiment the amount of [^{3}H]fenoldopam bound was determined in the absence (total) and presence (nonspecific) of 10^{-6} M (+)-butaclamol, the difference being specific [^{3}H]fenoldopam binding. The ability of each compound to compete with [^{3}H]fenoldopam (ca. 2.0 mM) was tested at concentrations of 10^{-7} and 10^{-6} M. If a compound displaced [^{3}H]fenoldopam by 50% at a concentration of 10^{-6} M, it was considered to have significant activity and was tested further to obtain an IC_{50} for competition against fenoldopam. The K_{Bind} of a compound was calculated from the equation $K_{Bind} = (IC_{50})/(1 + L/K_D)$, where L is the concentration of [^{3}H]fenoldopam and K_D is the equilibrium dissociation constant for fenoldopam, i.e., 2.3 ± 0.1 nM.

Stimulation of dopamine-sensitive adenylate cyclase was carried out as described previously.[18] EC_{50} values are the concentration of compound required to produce 50% of the maximum stimulation attainable with the compound.

Competition for [^{3}H]spiroperidol in bovine anterior pituitary was performed as described previously.[18] The ability of each compound to compete with [^{3}H]spiroperidol (ca. 0.25 nM) was tested at concentrations of 10^{-5} and 10^{-7} M. Compounds displacing [^{3}H]spiroperidol by 50% or more were tested further to obtain an IC_{50}. The K_{Bind} of a compound is $(IC_{50})/(1 + L/K_D)$, where L is the concentration of [^{3}H]spiroperidol and K_D is the dissociation constant for spiroperidol, i.e., 0.3 nM.

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Registry No. (*R*)-**1**, 62751-59-1; (±)-**3a**, 108346-59-4; (±)-**4a**, 108346-60-7; (±)-**3**·HBr, 108346-50-5; (±)-**4**·HBr, 108346-51-6; (±)-**4** (desphenyl), 108365-68-0; **5**, 7461-60-1; **6**, 10538-48-4; **7**, 6342-80-9; **8**, 100449-12-5; (±)-**9**, 108346-52-7; (±)-**10**·HCl, 108346-53-8; **11**, 108346-54-9; (±)-**12a**, 108346-55-0; (±)-**12a**·HCl, 108346-57-2; (±)-**12b**, 108346-56-1; (±)-**12b**·HCl, 108346-58-3; $(H_3C)_3SiCN$, 7677-24-9; (±)$C_6H_5CH(OH)CO_2CH_3$, 4358-87-6.

Supplementary Material Available: Tables of bond distances, bond angles, torsional angles, positional parameters, and general temperature factor expressions for **12a** (11 pages); tables of values of $10F_o$ and $10F_c$ for the single-crystal X-ray structure determination for **12a** (20 pages). Ordering information is given on any current masthead page.

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