Conformationally Defined Adrenergic Agents. 2.[1] Catechol Imidazoline Derivatives: Biological Effects at α_1 and α_2 Adrenergic Receptors

John F. DeBernardis,*† John J. Kyncl,† Fatima Z. Basha,† David L. Arendsen,† Yvonne C. Martin,‡ Martin Winn,† and Daniel J. Kerkman†

Division of Cardiovascular Research and Computer-Assisted Molecular Design Division, Abbott Laboratories, Abbott Park, Illinois 60064. *Received March 7, 1985*

The synthesis and pharmacology of 2-(5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthyl)imidazoline (A-54741, 4), a very potent α-adrenergic agonist, are described. The change in biological activity resulting from variation of the carbocyclic ring size of 4 from four through seven members (2–5) is presented, as well as an explanation that accounts for this change in activity by considering the "exactness of fit" of these compounds to both the α_1- and α_2-adrenergic receptors. Compound 4 was found in vitro to be a full agonist with greater potency at the α_2 receptor (ED_{50} norepinephrine (NE)/ED_{50} 4 = 188 ± 22) than at the α_1 receptor (ED_{50} NE/ED_{50} 4 = 13 ± 2).

Chemical modification of the neurotransmitter catecholamines has been an active and productive research endeavor dating from the time these substances were first chemically characterized over half a century ago. Most significant to the advance of the field was the classification[2] of adrenergic receptors into α and β types. Further subclassifications of the adrenergic receptors into β_1 and β_2[3,4] as well as α_1 and α_2[5-7] subtypes served as the basis for new developments. Recently,[8-10] evidence for the existence of a heterogeneous class of postsynaptic α receptors in vascular smooth muscle has been obtained, opening up additional avenues for drug development.

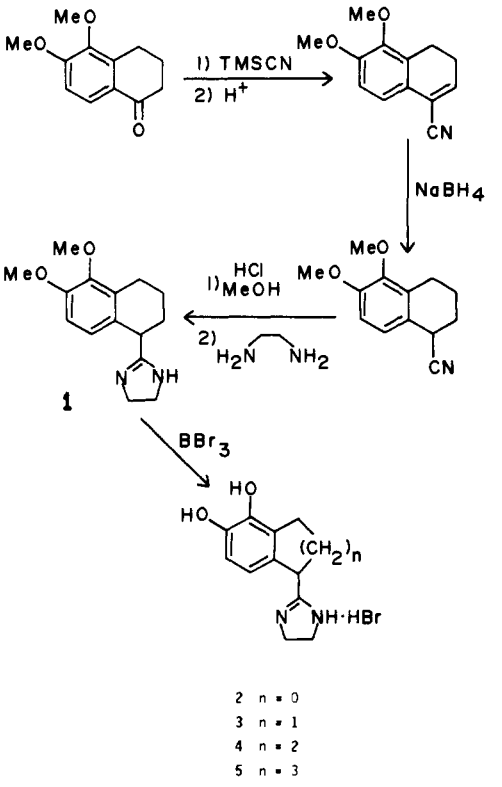
Our own investigations involving the design of compounds that interact selectively at adrenergic receptor sites have led us to the preparation of a series of imidazoline tetrahydronaphthalene derivatives. These investigations were aimed primarily at designing compounds that interact selectively at α-adrenergic sites. This paper describes the synthesis and pharmacological characterization of 2-(5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthyl)imidazoline (A-54741, 4), a very potent α-adrenergic agent, as well as the change in biological activity resulting from a variation of the carbocyclic ring size of 4 from four through seven members.

Chemistry. A general scheme for the preparation of these compounds is outlined in Scheme I. With use of the known 5,6-dimethoxytetralone[11] as the starting material, the trimethylsilyl cyanohydrin was prepared by using trimethylsilyl cyanide (TMSCN) with Lewis acid catalysis.[12] Acid-catalyzed deprotection and dehydration of the trimethylsilyl cyanohydrin afforded the unsaturated nitrile, which was subsequently reduced with sodium borohydride to the aliphatic nitrile. The corresponding carboximidate was formed after dissolving the nitrile in a 2:1 diethyl ether/methanol solution followed by HCl (g) addition at 0 °C for several hours. Evaporation of the volatiles afforded the imidate, which was then dissolved in ethanol and stirred with ethylenediamine, resulting in the formation of 1. The aromatic ethers could be easily cleaved with use of BBr_3 in excess followed by a methanol quench and removal of the boron as the trimethylborate/methanol azeotrope to yield the corresponding catechol.

Biological Results and Discussion

The α_1-adrenergic activity of these catechol imidazolines was measured with isolated rabbit aortic tissue. Stimulation of the α-adrenergic receptors in this tissue produces an increase in the force of contraction, which is blockable by α_1 antagonists such as prazosin. The potency of each test compound was expressed as a molar ED_{50}, and an index number[13] was obtained by calculating the ratio of

Scheme I



† Division of Cardiovascular Research.
‡ Computer-Assisted Molecular Design Division.

(1) For part 1, see: DeBernardis, J. F.; Kerkman, D. J.; Winn, M.; Bush, E. N.; Arendsen, D. L.; McClellan, W. J.; Kyncl, J. J.; Basha, F. Z. *J. Med. Chem.* **1985**, *28*, 1398.
(2) Ahlquist, R. P. *Am. J. Physiol.* **1948**, *153*, 586.
(3) Furchgott, R. F. *Ann. N.Y. Acad. Sci.* **1967**, *139*, 553.
(4) Lands, A. M.; Arnold, A.; McAuliff, J. P.; Luduena, F. P.; Brown, T. G. *Nature (London)* **1967**, *214*, 597.
(5) Starke, K.; Endo, T. *Gen. Pharmacol.* **1976**, *7*, 307.
(6) Starke, K.; Endo, T.; Taube, H. D. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1975**, *291*, 55.
(7) Langer, S. Z. *Br. J. Pharmacol.* **1977**, *60*, 481.
(8) Timmermans, P. B. M. W. M.; Kwa, H. Y.; van Zwietan, P. A. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1979**, *310*, 189.
(9) Docherty, J. R.; McGrath, J. C. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1980**, *312*, 107.
(10) Kobinger, W.; Pichler, L. *Eur. J. Pharmacol.* **1980**, *65*, 393.
(11) Oka, Y.; Motohashi, M.; Sugihara, H.; Miyashita, O.; Itoh, K.; Nishikawa, M.; Yurugi, S. *Chem. Pharm. Bull.* **1977**, *25*, 632.
(12) For a review of the reactions of TMSCN, see: Groutas, W. C.; Felkner, D. *Synthesis* **1980**, 861.

0022-2623/86/1829-0463$01.50/0

Table I. Indices and ED_{50} Values for Compounds 2–5 in the Rabbit Aorta (α_1)

compd no.	index[a,b] (ED_{50} NE/ED_{50} CPD)	n	E_{max}, %	ED_{50} NE ($\times 10^7$)[a]	ED_{50} CPD ($\times 10^7$)[a]
2	0.4 ± 0.07	6	98 ± 2	0.52 ± 0.05	1.3 ± 0.2
3	12 ± 3	8	124 ± 2	2.2 ± 0.7	0.17 ± 0.03
4	13 ± 2	31	114 ± 2	1.4 ± 0.2	0.17 ± 0.06
5	inactive	5		1.4 ± 1.0	

[a] Mean of n experiments ± SEM. [b] See ref 13.

Table II. Indices and ED_{50} Values for Compounds 2–5 in the PBZ-Pretreated Dog Saphenous Vein (α_2)

compd no.	index[a,b]	n	E_{max}, %	ED_{50} NE ($\times 10^7$)[a]	ED_{50} CPD ($\times 10^7$)[a]
2	1.8 ± 0.17	2	67 ± 7	7.1 ± 1.5	4.0 ± 1.8
3	22 ± 8	4	102 ± 3	7.6 ± 1.7	0.48 ± 0.14
4	188 ± 22	8	102 ± 2	5.8 ± 0.6	0.03 ± 0.01
5	0.03 ± 0.005	2	31 ± 8	9.8 ± 1.3	350 ± 7

[a] Mean of n experiments ± SEM. [b] See ref 13.

Table III. Radioligands Binding Affinities for Compounds 2–5

	α_1				α_2			
compd no.	K_1,[a] nM	n	HC[b]	IC_{50},[c] nM	K_i,[a] nM	n	HC[b]	IC_{50},[c] nM
2	1100 (760–1500)	3	1.00 ± 0.03	4400 (3900–4900)	46 (37–58)	3	0.71 ± 0.17	49 (46–52)
3	350 (310–380)	4	0.92 ± 0.03	1570 (1520–1620)	3.1 (1.9–5.3)	4	0.58 ± 0.13	3.3 (2.6–4.1)
4	400 (340–470)	8	0.89 ± 0.17	2500 (2200–2900)	6.5 (5.6–7.7)	6	0.53 ± 0.10	7.0 (6.5–7.5)
5	13000 (8000–22000)	3	0.92 ± 0.08	56000 (50000–62000)	4000 (3200–4800)	2	0.82 ± 0.04	4200 (4000–4300)
NE	390 (370–410)	6	0.83 ± 0.11	1620 (1560–1700)	37 (35–39)	6	0.52–0.08	33 (29–37)

[a] Geometric mean of n duplicate determinations with 90% confidence limit shown in parentheses. See ref 1, notes 15 and 16. [b] Mean pseudo Hill coefficient of n duplicate determinations ± SDM. See ref 16. [c] Geometric mean of n duplicate determinations with 95% confidence limits shown in parentheses.

the ED_{50} of norepinephrine (NE) to that of the test compound (CPD). The larger the index number, the more potent the compound (relative to NE).

α_2-Adrenergic activity was measured in the dog saphenous vein which had been pretreated for 30 min with phenoxybenzamine (PBZ, 100 nM).[14] At the end of the PBZ pretreatment, the tissues were thoroughly washed and a control cumulative dose–response curve was obtained for NE. Following washout of the NE, the tissues were equilibrated and a cumulative dose–response curve was obtained for the test compound. As in the case of the α_1 activities, an index number (ED_{50} NE/ED_{50} CPD)[13] for the α_2 potency of the compounds was calculated.

Information pertaining to the affinity of the compounds for α_1- or α_2-adrenergic receptors was obtained from radioligand binding assays with rat liver and [^{3}H]prazosin (α_1) or rat cortex and [^{3}H]rauwolscine (α_2). The values are expressed as an equilibrium affinity constant (K_i), with lower K_i values reflecting better affinities for the respective adrenergic receptors.

Table I shows the results of testing compounds 2–5 in the rabbit aorta. As can be seen from the index values for compounds 3 and 4, both are extremely potent α_1 agonists, being 12 and 13 times more potent than NE, respectively. These two compounds were also effective full agonists eliciting a maximal contraction of the aorta greater than that achievable with NE.

In the case of compound 2, the potency was approximately one-half that of NE. As the carbocyclic ring size was increased to seven members, i.e., 5, the flexibility of the molecule increased as well as its steric bulk. Regardless of which was the detrimental effect, 5 was inactive at the α_1 site. The overall conformational/steric effect imparted to the molecule by incorporation of a five- or six-membered carbocyclic ring clearly results in a favorable interaction at the α_1 receptor since both compounds 3 and 4 were more active than NE.

Shown in Table II are the results from the PBZ-pretreated dog saphenous vein. As can be seen, all the compounds except for 5 show α_2 effects. Compounds 3 and 4 are both full agonists,[15] being 23 and 188 times more potent than NE, respectively. Comparisons of the α-subtype selectivities of 3 and 4 indicate that even though both are very potent α agonists, 3 is nonselective while 4 shows a 14-fold perference for α_2 activity in these in vitro assays.

Comparison of the K_i values for 2–5 obtained from radioligand binding assays (Table III) reveals that both 3 and 4 show good affinities for the α_1 and α_2 receptors, both being about equal to NE at the α_1 receptor but showing better affinity than NE for the α_2 receptor. In the functional assays (Tables I and II) 3 was a nonselective α agonist, but when the radioligand binding data are considered, 3 demonstrates α_2 selectivity as does 4. However, Timmermans et al.[17] have recently reported that even some of the known α_1-selective agents such as cirazoline show preference for the α_2 receptor on the basis of radioligand binding affinities. Thus, some caution is needed when interpreting "selectivities" of compounds using radioligand binding assays.

(13) Because the ED_{50} NE and the ED_{50} CPD were both determined in the same tissue (see Experimental Section for details), these values are "paired", and the index must be calculated for each experiment and then summed to produce a mean. It is not appropriate to divide the mean ED_{50} NE by the mean ED_{50} CPD since these are not independent observations. For a discussion of paired comparisons, see: Mainland, D. "Elementary Medical Statistics"; W. B. Saunders, Co.: Philadelphia, PA, 1963; p 202.

(14) Kyncl, J. J.; Buckner, S. A.; Bush, E. N.; DeBernardis, J. F.; Lin, C. T.; Warner, R. B. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1985**, *44*, 1466.

(15) Fowler, P. J.; Grous, M.; Price, W.; Matthews, W. D. *J. Pharmacol. Exp. Ther.* **1984**, *229*, 712.

(16) Calculations of K_i values from data that gives a Hill coefficient less than 1 has been reported; see: Perry, B. D.; U'Prichard, D. C. *Eur. J. Pharmacol.* **1981**, *76*, 461.

(17) Timmermans, P. B. M. W. M.; Matthews, W. D.; DeMarinis, R. M.; Hieble, J. P.; Mathy, M. J.; Doods, H. N.; Thoolen, M. J. M. C.; DeJonge, A.; Wilffert, B.; van Zwieten, P. A. *Eur. J. Pharmacol.* **1984**, *101*, 45.

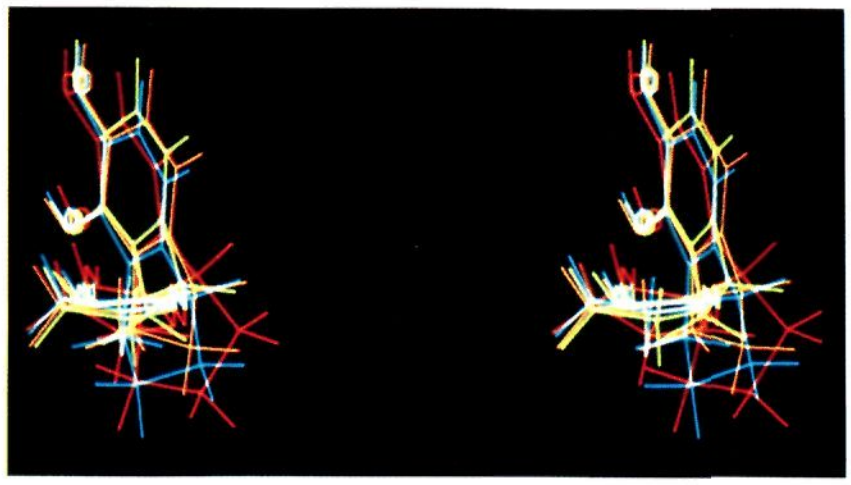


Figure 1. A stereoview of low-energy conformations of **2** (green), **3** (amber), **4** (blue), and **5** (red) superposed so that the best match of the catechol and imidazoline functional groups is achieved.[32]

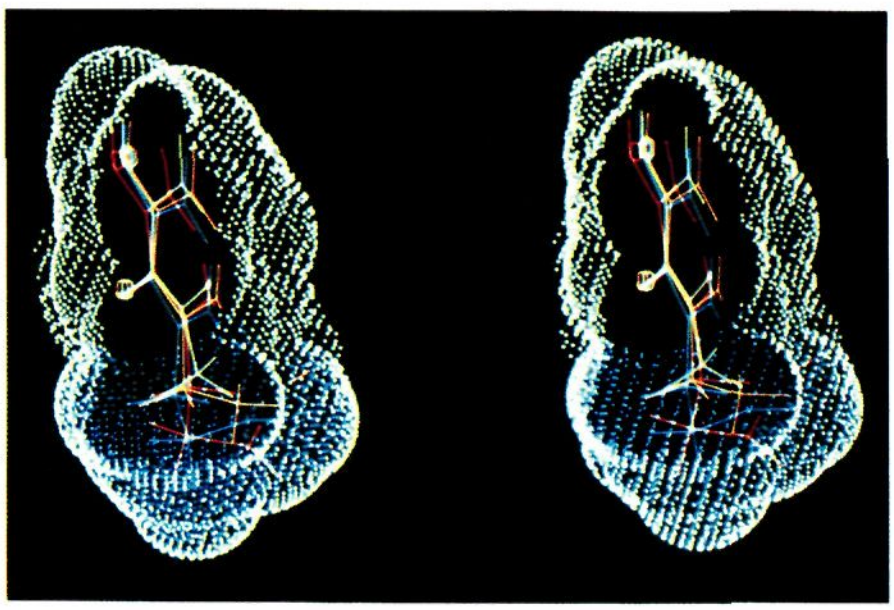


Figure 2. As in Figure 1 except that the composite water accessible surface of **2**–**4** is shown as green dots and the volume left unfilled by **2** is shown as blue dots. The front and back planes of these structures have been sliced off to highlight the important differences.[32]

When the biological activity of the different carbocyclic ring systems was reviewed, we found that maximal biological activity was observed when the carbocyclic ring was six-membered, i.e., **4**; however, the five-membered ring compound **3** also showed considerable activity. The four-membered derivative **2** was much less active than either **3** or **4** while the seven-membered ring derivative **5** showed virtually no α-adrenergic effects. As an explanation for these differences we discuss below the interaction of these compounds with α_1- and α_2-adrenergic receptors.

From electrostatic considerations of the similarity of these compounds to the natural agonist norepinephrine, we expect that the aromatic catechol and the imidazoline functional groups play a major role in influencing the orientation in which these compounds bind to and stimulate the α_1 and α_2 receptors (Figure 1). However, the overal "exactness of fit" of these compounds to the receptors has a profound effect on their potency. We suggest that the London dispersion forces[18] that govern this interaction are at their maximum in the case of the six-membered ring compound **4**. As the carbocyclic ring is made smaller (i.e., **3** and **2**), this attractive force is decreased since there are fewer atoms to participate in the interaction, and in the case of the smaller carbocyclic ring (**2**), the methylene units are further away from the receptor (Figure 2).[19] In the case of the seven-membered ring

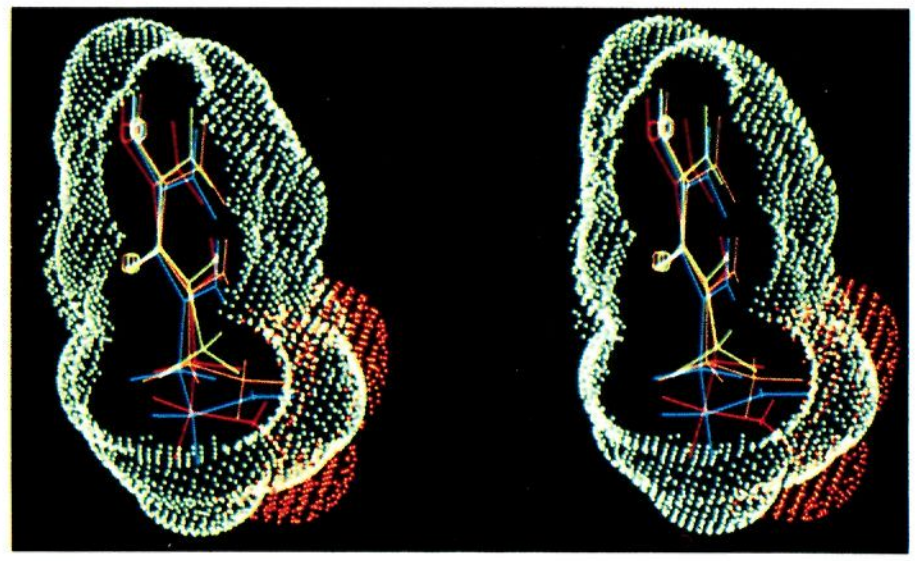


Figure 3. As in Figure 2 except that the extra volume occupied by **5** is shown as red dots.[32]

compound **5**, the larger ring size results in a repulsive steric interaction with the α-adrenergic receptors so that effective binding cannot be achieved (Figure 3). We are currently involved in the synthesis of other modifications of these structures to further probe the characteristics of the α_1- and α_2-adrenergic receptors.

In summary, we have prepared potent α-adrenergic agents, **3** and **4**. In various test systems, it has been shown that these compounds are much more active than the natural neurotransmitter NE. Both **3** and **4** are quite potent at α_1- and at α_2-receptor sites, with **4** showing more (in vitro) selectivity for the α_2-receptor subtype.

Experimental Section

α_1 Activities Using Isolated Rabbit Aorta. Female rabbits, weighing 2–5 kg, were sacrificed by cervical dislocation. The thoracic cavity was immediately opened and the descending aorta was removed and placed in a petri dish containing Krebs buffer aerated with 95% O_2 and 5% CO_2. The Krebs buffer solution was prepared as follows: (mM concentrations) NaCl 119, $NaHCO_3$ 25, KCl 4.7, $MgSO_4$ 1.5, KH_2PO_4 1.2, $CaCl_2$ 2.5, glucose 11, NaEDTA 0.03, and ascorbic acid 0.3. The buffer was prepared daily from a concentrated stock solution and was adjusted to a pH of 7.4.

A helical strip of aorta was mounted in a 10-mL tissue bath containing Krebs buffer and was attached to a force transducer (Grass or Statham) so that an initial tension of 2 g was applied. The tissue was allowed to equilibrate for 1 h during which time the tissue was washed four times and the tension reset to 2 g until it had stabilized. A mixture of 95% O_2 and 5% CO_2 was continuously bubbled through the tissue bath and reservoir. Stirring in the bath was provided by vigorous bubbling of the gas mixture. The temperature of the tissue bath was maintained at 37 ± 0.5 °C by means of a constant temperature bath that circulated approximately 8 L/min of warmed water through the water jacket of the tissue bath. Standard weights were hung on the force transducers to calibrate them. Contractions, measured by the force transducers, were recorded on a Grass Model 7 polygraph, and periodic samples of the data were acquired by an on-line computer system that included a PDP 11/45 and DEC 10 computer.

A cumulative dose–response curve of contraction was produced with the standard agonist norepinephrine from 1×10^{-8} to 1×10^{-3} M doses. Drugs were administered by means of an adjustable microliter pipet in volumes usually from 10 to 100 μL. The response to each dose of standard or test compound was allowed to plateau before the administration of the next dose. Following the dose–response series for norepinephrine, the tissue was washed with aliquots of buffer every 10–15 min for 60–90 min until the tension returned to base line or reached a plateau near the base

(18) For a discussion of hydrophobic interactions and leading references, see: Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969; Chapter 8.

(19) There is an inverse relationship between distance and the strength of the London dispersion interaction: see ref 18, p 412.

line level. The tension of the tissues was readjusted until it stabilized at 2 g before the dose–response series of the test compound was obtained.

α_2 Activities Using PBZ-Pretreated Dog Saphenous Vein. Rings (3–4 mm wide) of lateral saphenous veins excised from beagle dogs of either sex were suspended in 10-mL tissue baths containing bicarbonate buffer of the following mM composition: NaCl 119, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.5, KH_2PO_4 1.2, $NaHCO_3$ 20, dextrose 11, ascorbic acid 0.3, NaEDTA 0.03, cocaine 0.03, hydrocortisone hemisuccinate 0.04, and propranolol 0.004. The solution was gassed with 95% O_2 and 5% CO_2 at 37 °C, pH 7.45. Isometric contractions of the tissues, preloaded with a tension of 2 g, were measured with Grass FT03 strain gauges and recorded on a Grass Model 7 polygraph.

Following an equilibration period of 15–20 min and maximal contraction by norepinephrine (1×10^{-4} M), the tissues were washed for 60 min at which time they were exposed to phenoxybenzamine (PBZ) (1×10^{-7} M) for 30 min. At the end of the PBZ treatment a thorough washout followed for 60 min. Tissues were then adjusted to 2-g tension, and a control cumulative dose–response curve was obtained for the standard agonist norepinephrine. After washout of norepinephrine (45–60 min), tissues were again equilibrated, and a cumulative dose–response curve of the tested agonist was obtained.

Radioligand Binding Assays. Tissue Preparation. Twenty male Sprague–Dawley rats weighing 250–350 g were anesthetized with pentobarbital sodium (50 mg/kg, ip), and the brains and livers were quickly removed and placed in assay buffer (Tris-HCl, 50 mM, pH 7.7, at 25 °C) at 4 °C. Cerebral cortices were separated from the remainder of the brains, and tissues were pooled prior to homogenization. The organs were weighed, and pooled tissues were separately homogenized in 20 volumes of preparation buffer (Tris-HCl, 50 mM pH 7.7, at 25 °C containing 5 mM EDTA), using a Tekmar SDT homogenizer at full speed for two 10-s bursts. The homogenates were centrifuged at 50000*g* (4 °C) for 10 min, and the supernatant was discarded. The pellets were resuspended by homogenization as above in 20 volumes of preparation buffer and recentrifuged for 10 min, and the supernatant was again discarded. The final pellet was resuspended in 6.25 volumes of assay buffer, flash-frozen in liquid nitrogen, and stored at −70 °C until the day of the experiment. Tissues were thawed at room temperature and thereafter maintained at 4 °C.

Assay Methods. All assays were performed in a light-subdued laboratory, with a total incubation volume of 1.0 mL. Four hundred and fifty microliters of radioligand [either [^{3}H]prazosin (sp act. 23 Ci/mmol, Amersham, Arlington Heights, IL) for α_1 assays or [^{3}H]rauwolscine[20] (sp act. 79 Ci/mmol, New England Nuclear, Boston, MA) for α_2 assays] in assay buffer was incorporated with 50 μL of 0.3 mM ascorbic acid, containing phentolamine (10^{-5} M, nonspecific binding), varying concentrations of test compounds, or no addition (total binding). Incubation commenced upon the addition of 500 μL of membrane homogenate in assay buffer, resulting in a final protein concentration of 50–150 μg/mL, determined by the method of Bradford.[21]

Equilibrium binding was evaluated after a 50-min incubation at 25 °C for α_1 assays or a 2-h incubation period at 4 °C for α_2 assays. Receptor-bound radioligand was separated from free ligand by filtration under ~180 mmHg vacuum through Whatman 934AH filters, which were dried in a hot air oven at 60 °C. Three milliliters of Ready-Solv NA (Beckman) was added and the solubilized ligand was counted to a 4.5% 2σ error level in a Beckman LS3800 liquid scintillation counter at ca. 63% counting efficiency. The "added" radioligand tubes were not filtered, but 0.1 mL was dried on a filter, combined with 3 mL of Ready-Solv, and counted. Quenching was determined by the H# method.

In saturation binding experiments, eight concentrations of radioligand between 10^{-11} and 10^{-8} M were utilized. Total (buffer control) and nonspecific (10^{-5} M phentolamine) binding were determined in triplicate at each concentration of radioligand. The radioligand affinity (K_D) and apparent receptor density (B_{max}) were evaluated, using the method of Scatchard.[22] Total and nonspecific binding data were also analyzed via the SCAFIT program of Munson and Rodbard,[23] to determine if the data could be best described by either a one- or two-site model.

In the competition binding assays, total and nonspecific binding were each determined with five replicates. Specific binding was the arithmetic difference between total binding and nonspecific binding. Affinities of each of the tested compounds were evaluated by measuring the percent inhibition of specific binding, using at least four concentrations between 10^{-10} to 10^{-3} M, with duplicate determinations at each concentration. The concentration at which 50% inhibition of specific binding was observed and the pseudo-Hill coefficient were calculated from the linear relationship between logit % specific bound [log [%/(1 − %)]] vs. log concentration. The dissociation constant (K_i) was derived according to the equation of Cheng and Prusoff:[24]

$$K_i = (IC_{50}/1 + [L]/K_D)$$

The ligand concentration (L) used in this calculation was the arithmetic difference between the total ligand added to each incubation tube as determined from the counts in the "added" tubes and the radioligand bound at the IC_{50} concentration. The ligand affinity for the receptors (K_D) was held constant for each radioligand.

Chemistry. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian T-60 or Varian XL-100 instrument using Me_4Si as an internal standard. Mass spectra were obtained on a Varian CH7 spectrophotometer. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 521 spectrophotometer. Elemental analyses were done in house and determined values are within 0.4% of theoretical values.

1-Cyano-3,4-dimethoxybenzocyclobutene (1, *n* = 0). 3-(6-Bromo-2,3-dimethoxyphenyl)propionitrile (10 g, 35 mmol) was added in three equal portions to a suspension of $NaNH_2$ (9 g, 230 mmol) in liquid NH_3 (ca. 300 mL) at −78 °C. Upon complete addition, the reaction was allowed to warm to −33 °C under nitrogen. The reaction mixture underwent color changes from gray to light yellow to brown during 10 min, at which point the reaction was stirred an additional 15 min. After the mixture was cooled to −78 °C NH_4Cl (15 g, 280 mmol) was *cautiously* added in portions. Following complete addition, the reaction was allowed to warm to room temperature and afforded, after NH_3 evaporation, a tan residue. This was taken up in a CH_2Cl_2/H_2O mixture (4:1), and the organic layer was separated, washed with H_2O (100 mL), dried ($MgSO_4$) and evaporated, affording a cream solid, 6.5 g recrystallized from Et_2O, mp 109–110 °C.

General Procedure for the Synthesis of the Unsaturated Nitriles (*n* = 1–3). To a suspension of the corresponding keto compound (10 mmol) in 5 mL of benzene was added TMSCN (12 mmol) and a catalytic amount of $AlCl_3$. The reaction mixture was stirred at 70 °C, which afforded a solution. Stirring was continued at 70 °C until the reaction was complete as indicated by TLC (1–4 h). The solvent was stripped and the oily residue was taken up in ethanolic HCl (ca. 50 mL) and stirred at room temperature for 30 min. The solvent was evaporated in vacuo, and the crystalline residue was washed with H_2O and with MeOH and dried, affording 85–90% of the corresponding unsaturated nitrile as a crystalline solid.

General Procedure for the Synthesis of Saturated Nitriles (*n* = 1–3). To a suspension of unsaturated nitrile (5.0 g) in EtOH (100 mL) was added $NaBH_4$ (2.0 g). The reaction mixture was refluxed for 30 min, and then the solvent was evaporated and the residue partitioned between 1:1 ether/CH_2Cl_2 and H_2O. The organic layer was separated, washed with 0.5 N HCl and brine, dried ($MgSO_4$), filtered, and stripped to afford the corresponding saturated nitrile in 90–95% yield.

General Procedure for the Synthesis of the Imidazolines (*n* = 0–3). A solution of saturated nitrile (ca. 5.0 g) in a mixture of ether/CH_2Cl_2/MeOH (4:4:2) at 0 °C was saturated with HCl gas. The solution was kept at room temperature (except for the

(20) The use of the α_2-antagonist [^{3}H]rauwolscine as a radioligand for α_2-agonist binding has been reported; see ref 16.
(21) Bradford, M. M. *Anal. Biochem.* **1976**, *72*, 248.
(22) Scatchard, G. *Ann. N.Y. Acad. Sci.* **1949**, *51*, 660.
(23) Munson, P. J.; Rodbard, D. *Anal. Biochem.* **1980**, *107*, 220.
(24) Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.

case where $n = 0$, which was kept at 4 °C) for 15 h. The solvent was evaporated and the solid residue was triturated with ether/CH_2Cl_2 to afford the crystalline imino ether. To a suspension of the imino ether (ca. 15 mmol) in EtOH (40 mL) was added an excess of ethylenediamine (2 mL). The reaction mixture was allowed to stir for 3 h at room temperature. The solvent was evaporated and the oily residue was partitioned between H_2O and CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered, and evaporated to afford the desired compound.

General Procedure for the Dimethyl Ether Cleavage. The imidazoline hydrochloride (2.6 mmol) was suspended in dry methylene chloride (25 mL) and cooled to −78 °C under nitrogen. Boron tribromide (1.0 mL) in methylene chloride (5 mL) was added via a syringe and the reaction was allowed to warm to room temperature and was stirred for 2 h. After this time, the reaction was cooled to −78 °C and quenched by the dropwise addition of methanol (5 mL). After the reaction was allowed to warm to room temperature, ether (20 mL) was added and the crystalline residue collected by decanting the supernatant. The solid was washed with ether and a small amount of 2-propanol to afford on drying the corresponding catechol derivatives.

1-(2-Imidazolino)-3,4-dihydroxybenzocyclobutene Hydrobromide (2). Following the general procedure for dimethyl ether cleavage described above using 0.70 g (2.6 mmol) of the 1-(2-imidazolino)-3,4-dimethoxybenzocyclobutene hydrochloride gave 0.65 g (87%) of **2**: mp 225 °C dec; IR (KBr) 3300, 1600 cm^{-1}; mass spectrum, m/e 204 (M^+); ^1H NMR (Me_2SO-d_6) 3.36, 3.48 (2 H, ddd, J = 14, 3, 7 Hz), 3.42 (1 H, dd, J = 3, 7 Hz), 3.80 (4 H, s), 6.60 (1 H, d, J = 8 Hz), 6.72 (1 H, d, J = 8 Hz). Anal. ($C_{11}H_{12}N_2O_2 \cdot HBr \cdot 1^1/_2H_2O$) C, H, N.

1-(2-Imidazolino)-4,5-dihydroxyindan Hydrobromide (3). Following the general procedure for dimethyl ether cleavage described above using 1.20 g (4.2 mmol) of 1-(2-imidazolino)-4,5-dimethoxyindan hydrochloride gave 0.98 g (78%) of **3**: mp 239–240 °C; IR (KBr) 3200, 1600 cm^{-1}; mass spectrum, m/e 218 (M^+); ^1H NMR (Me_2SO-d_6) 2.0–2.6 (2 H, m), 2.6–3.16 (2 H, m), 3.80 (4 H, s), 4.26 (1 H, t, J = 8 Hz), 6.30 (1 H, d, J = 8 Hz), 6.70 (1 H, d, J = 8 Hz). Anal. ($C_{12}H_{14}N_2O_2 \cdot HBr$) C, H, N.

1-(2-Imidazolino)-5,6-dihydroxytetralin Hydrobromide (4). Following the general procedure for dimethyl ether cleavage described above using 1.05 g (4.1 mmol) of **1** as the hydrochloride gave 1.0 g (79%) of **4**: mp 268 °C dec; IR (KBr) 3300, 1600 cm^{-1}; mass spectrum, m/e 232 (M^+); ^1H NMR (Me_2SO-d_6) 1.3–2.0 (4 H, m), 2.3–2.6 (2 H, m), 3.70 (4 H, s), 6.25 (1 H, d, J = 8 Hz), 6.60 (1 H, d, J = 8 Hz). Anal. ($C_{13}H_{16}N_2O_2 \cdot HBr$) C, H, N.

1-(2-Imidazolino)-6,7-dihydroxybenzocycloheptene Hydrobromide (5). Following the general procedure for dimethyl ether cleavage described above using 1.73 g (5.6 mmol) of 1-(2-imidazolino)-6,7-dimethoxybenzocycloheptene hydrochloride gave 1.62 g (89%) of **5**: mp 264–265 °C; mass spectrum, m/e 246 (M^+); ^1H NMR (Me_2SO-d_6) 1.15–2.0 (6 H, m), 2.3–2.6 (2 H, m), 3.70 (4 H, s), 4.16 (1 H, m), 6.50 (1 H, d, J = 8 Hz), 6.66 (1 H, d, J = 8 Hz). Anal. ($C_{14}H_{18}N_2O_2 \cdot HBr$) C, H, N.

Molecular Modeling and Molecular Graphics. Since no one molecular modeling method is appropriate for both the imidazoline and the fused-ring catechol portions of the molecules, we employed a three-phase procedure. First, the imidazoline fragment was prepared by MNDO[25] optimization of imidazoline. Concurrently, the various ring puckers of each fused-ring catechol structure were minimized with MM2.[26] Second, the imidazoline and the fused-ring catechol (every low-energy pucker of each compound) were joined with a bond length of 1.50 Å. Finally, a rigid rotation in 10° increments about this same C–C bond was performed in CHEMLAB[27] using steric parameters of Scheraga[28] and MNDO point charges.[25] The conformations chosen for display were selected from the various low-energy structures (within 0.5 kcal of the global minimum) to provide the best match of volumes[29] and four heteroatoms to each other. The surfaces and exluded volumes were calculated by an algorithm written by us.[29] The photographs were taken from an Evans & Sutherland display generated by GRAMPS/CMD.[30,31]

Acknowledgment. We thank Arthur Hancock for helpful discussions; Elizabeth Danaher, Dusanka Stanisic, and Robert Warner for technical assistance; and Cynthia Davis and Joan Doerrer for typing this manuscript.

Registry No. **2**, 100449-00-1; **2** (free base), 100449-01-2; **2** (free base–dimethyl ether), 100449-02-3; **3**, 100449-03-4; **3** (free base), 100449-04-5; **3** (free base–dimethyl ether), 100449-05-6; **4**, 100449-06-7; **4** (free base), 100449-07-8; **4** (free base-dimethyl ether), 100449-08-9; **5**, 100449-09-0; **5** (free base), 100449-10-3; **5** (free base–dimethyl ether), 100449-11-4; 3-(6-bromo-2,3-dimethoxyphenyl)propionitrile, 83996-74-1; 4,5-dihydroxyindanone, 6342-80-9; 5,6-dihydroxytetralone, 24039-89-2; 6,7-dimethoxybenzocycloheptanone, 54130-94-8; 1-cyano-3,4-dimethoxybenzocyclobutane, 81615-24-9; 3-cyano-6,7-dimethoxyindene, 100449-12-5; 4-cyano-7,8-dimethoxy-1,2-dihydronaphthalene, 89047-59-6; 5-cyano-8,9-dimethoxy-2,3-dihydro-1*H*-benzocycloheptene, 100449-13-6; 1-cyano-4,5-dimethoxyindan, 100449-14-7; 1-cyano-5,6-dimethoxytetralin, 97352-15-3; 1-cyano-6,7-dimethoxybenzocycloheptane, 100449-15-8; 3,4-dimethoxy-1-formylbenzobutane methyl oxime, 100449-16-9; 1-formylindan methyl oxine, 100449-17-0; 1-formyltetraline methyl oxime, 100449-18-1; 1-formylbenzocycloheptane methyl oxime, 100449-19-2.

(25) Thiel, W.; Dewar, M. J. *QCPE:428 MNDO* **1981**, 1.
(26) Allinger, N. L.; Yuh, Y. H. *QCPE:395 MM2* **1980**, 1.
(27) The Chemical Modeling Laboratory Revision 83.2P, Molecular Design Limited, Hayward, CA.
(28) Momany, F. A.; Carruthers, L. M.; McQuire, R. F.; Scheraga, H. A. *J. Phys. Chem.* **1974**, *78*, 159.
(29) Sanathanan, L.; Martin, Y. C., unpublished results.
(30) O'Donnell, T. J.; Olson, A. J. *Computer Graphics* **1981**, *15*, 133.
(31) Martin, Y. C.; Kim, K. H.; Koschmann, T.; O'Donnell, T. J. In "Computer Applications in Chemistry"; Heller, S. R., Potenzone, R.; Eds.; Elsevier: Amsterdam, 1983; pp 285–301.
(32) An inexpensive "Folding Plastic Stereoscope", #2005, $3.95 ea., or "Fold-Flat Stereoprint Viewer" (cardboard), #2007, $2.95 ea., is available from Reel 3D Enterprises, P.O. Box 35, Duarte, CA 910100035.