exposure to the antagonist, which was then readministered to the bath for a total exposure of 30 min. A concentration-response curve was repeated in the presence of the antagonist.

Acknowledgment. The authors are indebted to P. K. Lumma for synthetic assistance, to Dr. B. H. Arison, Dr. D. W. Cochran and Ms. J. S. Murphy for ^{1}H NMR and ^{1}H NMR chiral shift reagent studies, to Ms. A. A. Morris and Mr. D. Weitz for the in vitro determination using guinea pig tissue, to Mr. K. B. Streeter, Ms. J. Stranick, Mr. Y. C. Lee and Mr. J. B. Moreau for analytical determination and Ms. T. H. Brunner for preparation of this manuscript.

Registry No. (*S*)-**1a**, 60990-47-8; (±)-**1b**, 85613-25-8; (*S*)-**1b**, 85648-06-2; **1c**, 85613-49-6; **1c**·2HCl, 85613-26-9; **1d**, 60963-65-7; **1e**, 60963-79-3; **1f**, 60963-72-6; **2a**, 123-08-0; **2b**, 70552-22-6; (±)-**3**, 34331-40-3; **4a**, 85613-27-0; **5a**, 85613-28-1; **5a** (mesylate), 85613-29-2; **6a**, 85613-45-2; **7** (base), 85613-31-6; **7**, 85613-30-5; (±)-**8**, 85613-50-9; (±)-**8**·2HCl, 85613-43-0; (*S*)-**8** (base), 85648-11-9; (*S*)-**8**, 85648-08-4; **9** (isomer 1), 85613-51-0; **9** (isomer 1) 2HCl, 85613-32-7; **9** (isomer 2), 85613-58-7; **9** (isomer 2) 2HCl, 85613-57-6; **10**, 85613-52-1; **10**·2HCl, 85613-33-8; **11a**, 85613-34-9; (2*S*,5*S*)-**11b**, 85613-47-4; (2*R*,5*S*)-**11b**, 85613-59-8; (±)-**12** (base), 85613-36-1; (±)-**12**, 85613-35-0; (*S*)-**12**, 85648-12-0; (*S*)-**12**·2HCl, 85648-07-3; (±)-**13**, 85613-53-2; (±)-**13**·2HCl, 85613-44-1; (*S*)-**13**, 85648-13-1; (*S*)-**13**·2HCl, 85648-09-5; (*R*)-**13**, 85648-14-2; (*R*)-**13**·2HCl, 85699-85-0; **14**, 85613-37-2; **15**, 85613-54-3; **15**·2HCl, 85613-38-3; **16**, 85613-55-4; **16**·2HCl, 85613-39-4; **17**, 85613-56-5; **17**·2HCl, 85613-40-7; **18a**, 85613-41-8; (*S*)-**18b**, 85648-10-8; **19a**, 85613-46-3; (2*S*,5*S*)-**19b**, 85613-48-5; (2*R*,5*S*)-**19b**, 85613-60-1; **20**, 1707-77-3; **21**, 85613-42-9; 2-[4-(2,3-epoxypropoxy)phenyl]-4-(trifluoromethyl)imidazole, 62911-13-1; cyclopropylamine, 765-30-0; 2-(3,4-dimethoxyphenyl)ethylamine, 120-20-7; 3-(3,4-dimethoxyphenyl)-2-propylamine, 120-26-3; 3-(3,4-dimethoxyphenyl)-2-methyl-2-propylamine, 75561-47-6; isopropylamine, 75-31-0; 2-phenylethylamine, 64-04-0; glycidol, 556-52-5; *p*-toluenesulfonyl chloride, 98-59-9; benzaldehyde, 100-52-7.

Optically Active Catecholimidazolines: A Study of Steric Interactions at α-Adrenoreceptors

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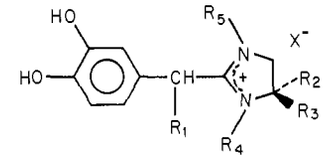
The optical isomers and deoxy form of 2-(3,4,α-trihydroxybenzyl)imidazoline hydrochloride were examined for their α-adrenergic activity on rat aorta. The rank order of stimulant activity was deoxy (**2**) ≃ (*R*)-(−)-**1** > (*S*)-(+)-**1**. This is in contrast to catecholamines in which the order of activity is (*R*)-(−)-epinephrine > (*S*)-(+)-epinephrine = epinine (deoxyepinephrine). The relative order of potency for the isomers of 2-(3,4,α-trihydroxybenzyl)imidazoline is different than that predicted by the Easson–Stedman theory for stereoisomers of catecholamines. Also, substitution of the deoxy compound **2** with substituents, methyl or benzyl, in the 4-position lowers the α-adrenergic agonist activity, and differences observed between optical isomers were small.

Imidazolines are an important class of drugs that interact with α-adrenergic receptors.[1-10] In contrast to phenethanolamines, few studies have appeared in which the actions of optically active imidazolines have been examined for their pharmacological activity.[6,11-13]

The Easson–Stedman theory has provided an important means of explaining the steric structure–activity relationships for the interaction of asymmetric phenethanolamines with the adrenoreceptors.[1] However, no studies have been carried out with optically active imidazolines to test the validity of the Easson–Stedman theory. In the present study, we have prepared the optical isomers of 2-(3,4,α-trihydroxybenzyl)imidazoline hydrochloride [3,4,α-trihydroxytolazoline (**1**)], and its deoxy form, 2-(3,4-dihydroxybenzyl)imidazoline hydrochloride [3,4-dihydroxytolazoline (**2**)], in order to investigate their α-adrenergic activity with regard to the Easson–Stedman theory.

Earlier findings indicated that the addition of substituents to the α-adrenergic agonist, naphazoline, converted it to an antagonist.[6,14] Subsequently, we were interested in observing the effect of similar substituents on the catecholimidazoline, 3,4-dihydroxytolazoline hydrochloride (**2**). We prepared compounds **3**, **4**, **6**, and **7**, which provided an opportunity to examine the effects of 4-substituted catecholimidazolines on α-adrenoreceptors. Since only limited studies have been carried out with optically active imidazolines,[6,11,12,14] it was thought studies of such an important class of adrenergic drugs should add considerable new knowledge to the understanding of stereochemical



1, R_1 = OH; R_2 = R_3 = R_4 = R_5 = H; X = Cl^-
2, R_1 = R_2 = R_3 = R_4 = R_5 = H; X = Cl^-
3, R_1 = R_2 = R_4 = R_5 = H; R_3 = CH_3; X = Cl^-
4, R_1 = R_3 = R_4 = R_5 = H; R_2 = CH_3; X = Cl^-
5, R_1 = R_2 = R_3 = R_5 = H; R_4 = CH_3; X = Cl^-
6, R_1 = R_2 = R_4 = R_5 = H; R_3 = $CH_2C_6H_5$; X = Cl^-
7, R_1 = R_3 = R_4 = R_5 = H; R_2 = $CH_2C_6H_5$; X = Cl^-
8, R_1 = R_2 = R_3 = H; R_4 = R_5 = CH_3; X = BF_4^-

(1) Easson, L. H.; Stedman, E. *Biochem J.* **1933**, *27*, 1257. This has been reviewed by Patil, P. N.; Miller, D. D.; Trendelenburg, U. *Pharmacol. Rev.* **1974**, *26*, 323.
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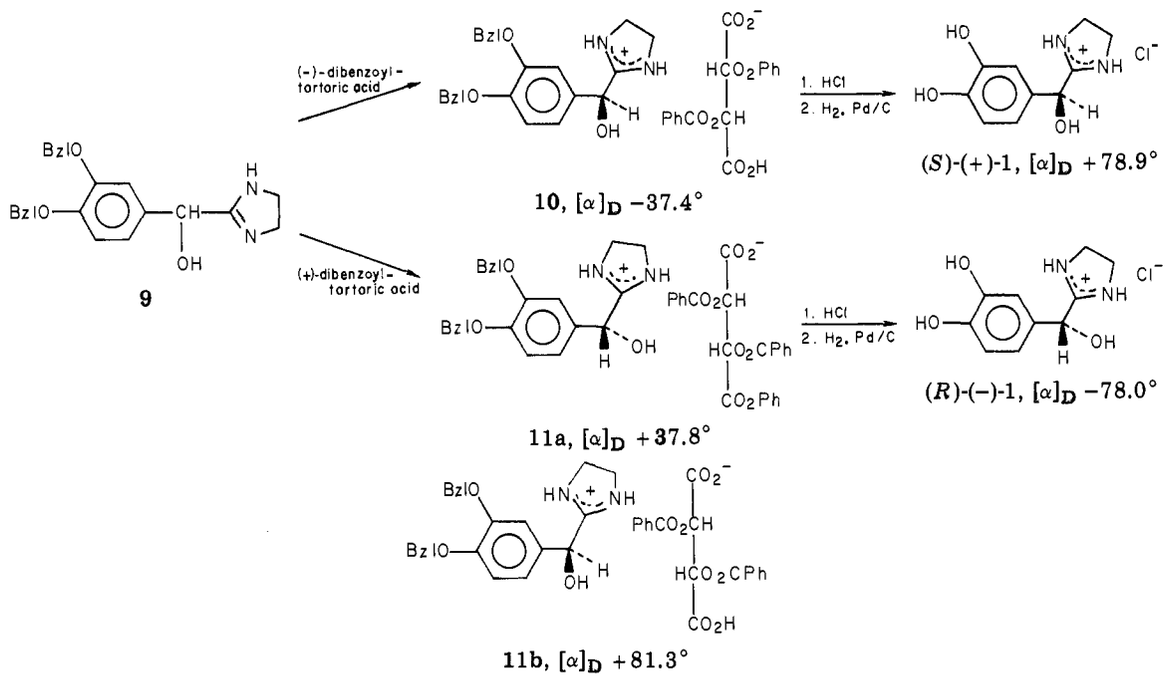
Scheme I



requirements of the imidazolines class of drugs with adrenoreceptors.

Chemistry. The synthesis of racemic 2-[3,4-bis(benzyloxy)-α-hydroxybenzyl]imidazoline (**9**) was carried out according to the procedure of Bristow.[15] After treatment of **9** with (+)-dibenzoyl-D-tartaric acid, a diastereoisomeric salt was isolated and recrystallized to give the salt **11a**. The salt **11a** was taken up in ethanol/ether, and gaseous hydrogen chloride was added, followed by pentane, to give the resulting HCl salt, which was in turn converted by catalytic reduction to the desired optically active catechol (−)-**1**. In a similar manner, (+)-**1** was obtained by using (−)-dibenzoyl-L-tartaric acid as illustrated in Scheme I.

In an attempt to determine the absolute configuration of the optical isomers of **1** we obtained circular dichroism curves in which (−)-**1** provided a negative cotton effect (CD $[\alpha]_{240}$ −5886°) and (+)-**1** gave the mirror-image cotton effect with methanol as a solvent. The *R*(−) isomer of norepinephrine has a CD curve with a negative cotton effect in methanol (CD $[\alpha]_{230}$ −3178°). It has been reported that the (−)isomer of 2-(α-hydroxybenzyl)imidazoline hydrochloride has the *R* absolute configuration.[16]

To confirm the absolute configuration of the isomeric imidazolines, (+)-**1** and (−)-**1**, we first attempted to carry out an X-ray analysis of the HCl salt of (−)-**1** and the (+)-dibenzoyltartaric acid of the protected imidazoline **11a**. Neither of the compounds provided suitable crystals for X-ray analysis. However, we did obtain good results with the (+)-dibenzoyltartaric acid salt of the protected imidazoline **11b**. Based on the known absolute configuration of (+)-dibenzoyltartaric acid with both asymmetric centers having the *S* absolute configuration, it was determined that the asymmetric benzylic carbon of **11b** had the *S* absolute configuration as shown in Figure 1.

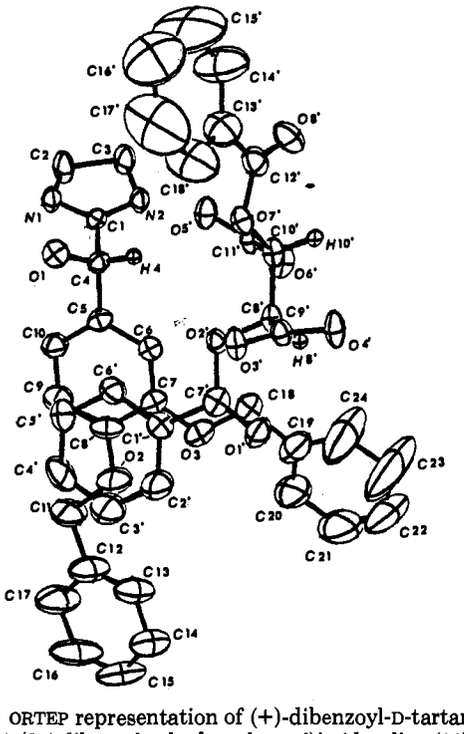


Figure 1. ORTEP representation of (+)-dibenzoyl-D-tartaric acid salt of (*S*)-2-(3,4-dibenzyl-α-hydroxybenzyl)imidazoline (**11b**) with hydrogen atoms shown only at asymmetric centers.

The preparation of the various substituted imidazoline analogues (**3**–**8**) shown in Scheme II utilized 3,4-bis(benzyloxy)phenylacetonitrile (**12**) as starting material. The nitrile (**12**) was converted to the ethyl imidate **13**, which was then directly converted to the various derivatives. Treatment of **13** with 1,2-diaminoethane gave **14**, which

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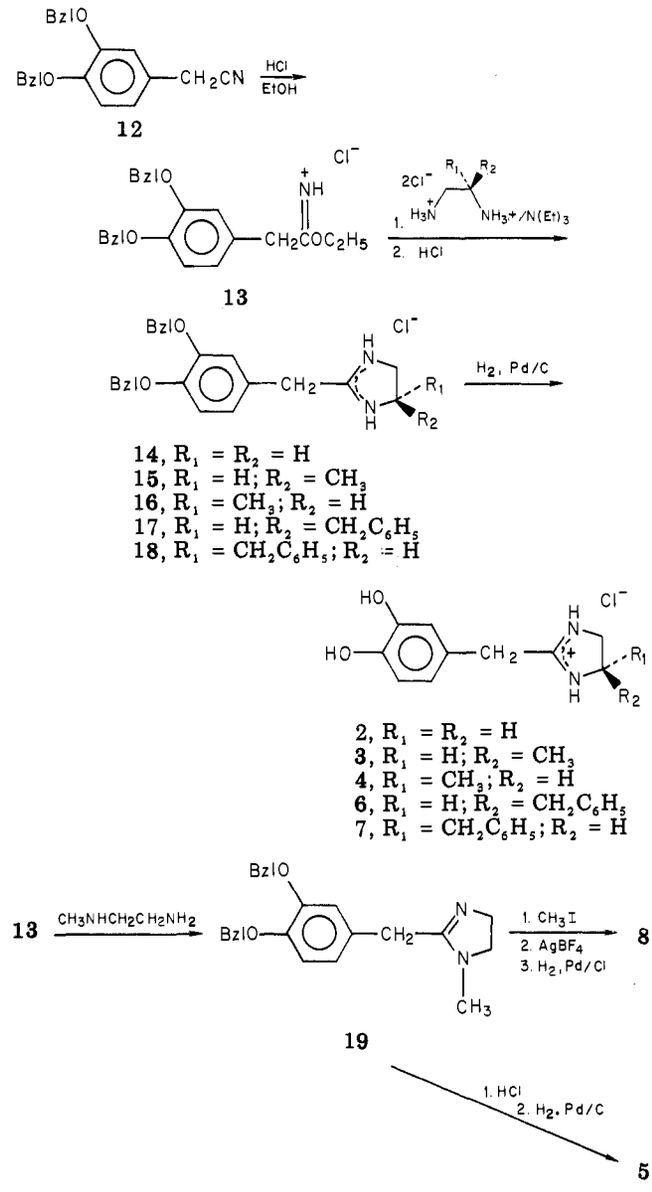
(14) Hsu, F.; Hamada, A.; Booher, M. E.; Fuder, H.; Patil, P. N.; Miller, D. D. *J. Med. Chem.* **1980**, *23*, 1232.
(15) Bristow, N. W. *J. Chem. Soc.* **1957**, 513.
(16) Neilson, D. G.; Peters, D. A. V.; Roach, L. H. *J. Chem. Soc.* **1962**, 2272.

Scheme II



was then reduced to the parent compound **2**. The synthesis of the 4-substituted 3,4-dihydroxytolazolines, **3**, **4**, **6**, and **7**, was carried out by treatment of the *R* and *S* isomers of 1,2-diaminopropane[6], or 1,2-diamino-3-phenylpropane,[14] with **13** to give **15–18**, respectively. The benzyl protecting groups were then removed via catalytic hydrogenation to give the desired *R* and *S* isomers of 4′-methyl-3,4-dihydroxytolazoline, **3** and **4**, and the *R* and *S* isomers of 4′-benzyl-3,4-dihydroxytolazoline, **6** and **7**.

The *N*-methyl derivative of 3,4-dihydroxytolazoline (**5**) was prepared by treatment of **13** with *N*-methyl-1,2-diaminoethane to give **19**. The HCl salt was isolated and the benzyl protecting groups were removed via catalytic hydrogenation to give **5**.

Treatment of **19** with methyl iodide gave a quaternary salt that decomposed upon standing at room temperature. Attempts at catalytic reduction of the quaternary salt failed, but treatment with $AgBF_4$ in anhydrous methanol, followed by catalytic reduction, gave the desired stable quaternary salt **8**.

Biological Results and Discussions

Substances were tested on rat aorta, a tissue known to contain both α_1- and α_2-adrenoreceptors.[17] The dose–response curves for the catecholimidazolines (*R*)-(−)-**1**, (*S*)-(+)-**1** and **2** are shown in Figure 2. When compared at ED_{50} concentrations, the potency of deoxy compound **2** is equal to (−)-**1**, which in turn is tenfold more active than (+)-**1**. Results with the isomers of epinephrine on rat aorta are illustrated in Figure 3. ED_{50} values are summarized in Table I. It is known that the relative rank order of activity of the isomers of epinephrine or norepinephrine for the activation of α-adrenoreceptors is in accord with the Easson–Stedman theory and is (−)-epinephrine > (+)-epinephrine = epinene.[1]

The Easson–Stedman theory[1] has provided the most important means of explaining the structure–activity relationship studies performed with optically active phen-

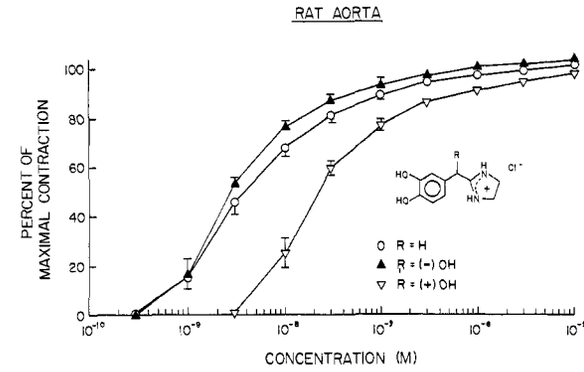


Figure 2. α-Adrenoreceptor stimulant activity of 2-(3,4-dihydroxybenzyl)imidazoline hydrochloride (**2**) and the *R*(−)- and *S*(+) isomers of 2-(3,4,α-trihydroxybenzyl)imidazoline hydrochloride (**1**) on isolated rat aorta. Each curve represents an average of four to six separate experiments.

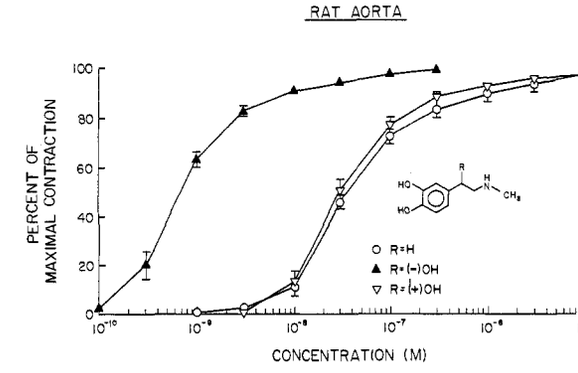


Figure 3. α-Adrenoreceptor stimulant activity of (*R*)-(−)- and (*S*)-(+)-epinephrine and epinine on isolated rat aorta.

Table I. Summary of Negative Log Molar ED_{50} Values of the Substances Reported in the Text

compd	pED_{50}[a] ± SEM	IA[b]
(−)-**1**	8.59 ± 0.06	1.00
(+)-**1**	7.67 ± 0.05	1.00
2	8.59 ± 0.11	1.00
3	6.29 ± 0.12	0.74
4	6.32 ± 0.14	1.00
6	4.44 ± 0.16	0.91
7	4.33 ± 0.11	1.00
5	5.84 ± 0.15	0.85
8	5.54 ± 0.10	0.81

[a] pED_{50} = negative log molar ED_{50}. [b] IA = relative value for maximum contraction (10^{-5} M = 1.00, phenylephrine). Number of separate observations (n) = 4–6 per compound

(17) Ruffolo, Jr., R. R.; Waddell, J. E.; Yaden, E. L. *J. Pharmacol. Exp. Ther.* **1982**, *221*, 309.

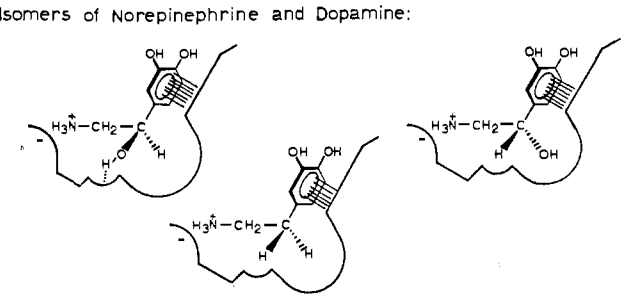


Figure 4. Illustration depicting the interaction of the isomers of norepinephrine and dopamine with the hypothetical α-adrenoreceptor. (*R*)-(−)-Norepinephrine has a three-point attachment to the receptor, while (*S*)-(+)-norephinephrine and dopamine are shown with a two-point attachment.

ethanolamines on tissues containing both α_1- and α_2-adrenoreceptors.[18] The theory proposes that in a molecule possessing an asymmetric center such as (*R*)-(−)-epinephrine, three of the four groups attached to the asymmetric carbon atom are involved in the attachment to the adrenoreceptor. These groups are (a) the basic amino group (b) the aromatic ring (with catechol group) and (c) the benzylic hydroxy group. With the *S*(+) isomer of epinephrine, only a two point interaction with the receptor is expected. This view of the interaction of the isomers of epinephrine is strengthened by the fact that the deoxyepinephrine (epinine), which lacks the hydroxy group, is equiactive with (*S*)-(+)-epinephrine on α-adrenoreceptors. Thus, the structure–activity relationship for a set of optical isomers and the corresponding deoxy form of any of the phenethanolamines, e.g., norepinephrine, epinephrine, and isoproterenol, is found to be *R*(−) > *S*(+) ≃ deoxy form (Figures 3 and 4). The rank order potency for the activation of α-adrenoreceptors by **2**, (−)-**1**, and (+)-**1** in other tissues, such as rabbit fundus and rabbit ileum, is the same as that observed for rat aorta.[19] This is a significant finding, since the imidazolines do not follow the same order as phenethanolamine (catecholamine) derivatives on α-adrenoreceptors, and the order of activity of the imidazolines cannot be explained by the classical Easson–Stedman theory. This study is in agreement with the report by Ruffolo et al.[9,10] in which they observed a higher pD_2 value for 3-hydroxytolazoline as compared to racemic 3,α-dihydroxytolazoline. The benzylic hydroxy group of (*R*)-(−)-phenethanolamines appears to be important for binding to α-adrenoreceptors in the aorta; a similar group does not appear to be equally important for binding of imidazolines to adrenoreceptors. These findings are consistent with earlier work with imidazolines on α-adrenergic tissues.[21,22] Both Ruffolo et al.[9] and Miller et al.[20] have independently indicated that the Easson–Stedman theory does not fully explain how imidazolines interact with α-adrenoreceptors, although the theory is very useful in explaining the results with phenethanolamine.[1] Thus, imidazolines and catecholamines must be interacting with

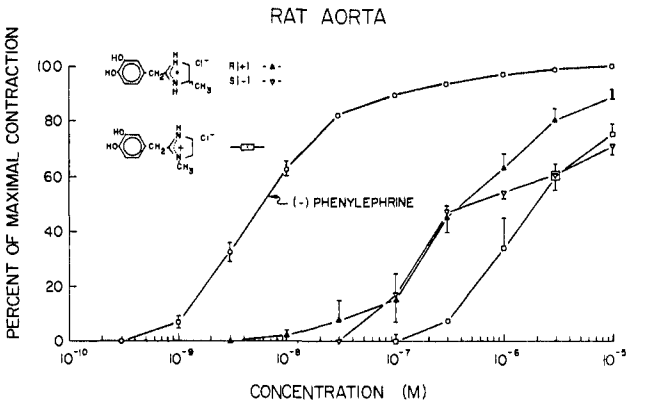


Figure 5. α-Adrenoreceptor stimulant activity of rat aorta of (*R*)-(+)- and (*S*)-(−)-4-methyl-2-(3,4-dihydroxybenzyl)imidazoline hydrochloride (**3** and **4**) and *N*-methyl-2-(3,4-dihydroxybenzyl)-imidazoline (**5**) with the standard α-adrenergic agonist phenylephrine.

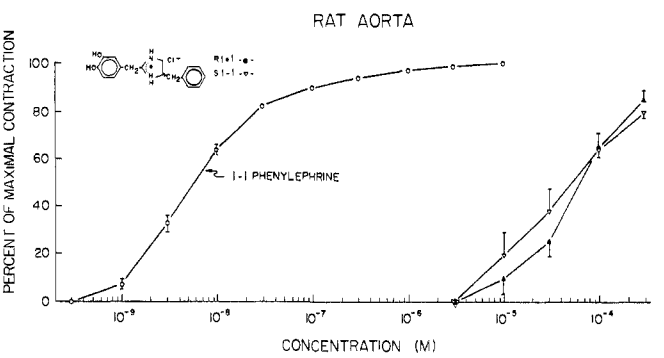


Figure 6. α-Adrenergic activity of (*R*)- and (*S*)-4-benzyl-2-(3,4-dihydroxybenzyl)imidazoline hydrochloride (**6** and **7**) in relationship to the standard α-adrenergic agonist phenylephrine.

(1) possibly one or two common sites on the α-adrenoreceptor, (2) different sites on the α-adrenoreceptor, or (3) different types of adrenoreceptors.

Since 3,4-dihydroxytolazoline is a potent α-adrenergic agonist, we decided to examine derivatives in which addition of a methyl group at the 4-position gave optical isomers **3** and **4**, the *N*-methyl derivative **5**, and the 1,3-dimethyl derivative **8**. All of the methyl analogues are less potent than the parent molecule **2** (see Figure 5 and Table I). Phenylephrine, which we use as the standard in this set of experiments on the rat aorta, is very similar to the parent molecule **2**. In order to investigate the effect of larger groups at the 4-position and to see if a larger group might show stereoselectivity, we examined (*R*)- and (*S*)-4-benzyl-2-(3,4-dihydroxybenzyl)imidazoline (**6** and **7**) on rat aortic tissue (see Figure 6). In all instances, the addition of a methyl group or a benzyl group provides compounds with less agonist activity. Our earlier findings[6,14] showed that nonphenolic imidazoline agonists were converted to antagonists, while in the present report it appears catecholimidazolines retain agonist activity, although weaker than the parent molecule, when a methyl or benzyl group is added to the imidazoline ring in the 4-position. In conclusion, we have found (1) catecholimidazoline derivatives, such as (*R*)-(−)-**1**, (*S*)-(+)-**1**, and **2**, do not follow the Easson–Stedman hypothesis; (2) methyl or benzyl substitution on the imidazoline ring lowers α-adrenergic agonist activity; and (3) substitution on the nitrogen of the imidazoline ring system gives compounds with lower α-agonist activity. However, with respect to the latter finding, **8** shows agonist activity, and this appears to indicate that the amine portion of the molecule can be and

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possibly should be in the cationic form when interacting with α-adrenoreceptors.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. IR spectral data were obtained with a Perkin-Elmer 257 or Beckman 4230 infrared spectrophotometer, and NMR spectral data were obtained with a Varian A-60A (60 MHz) or Bruker HX-90E NMR spectrometer (90 MHz) in the pulse mode. Mass spectra were obtained with a Dupont Model 21-491 double-focusing mass spectrometer. The optical rotations were obtained by using a Perkin-Elmer 240 polarimeter. X-ray analysis was carried out on a Syntex P$\bar{1}$ diffractometer. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Analytical results for elements indicated were within ±0.4% of the theoretical values.

Resolution of 2-[3,4-Bis(benzyloxy)-α-hydroxybenzyl]-imidazoline (9). To a solution of 100 mL of hot ethanol were added 9.5 g (24.4 mmol) of **9**[15] and 9.3 g (24.7 mmol) of (-)-dibenzoyl-L-tartaric acid monohydrate. The resulting solution was allowed to stand at room temperature overnight and filtered to give 16.2 g of the salt, which was recrystallized four times from a minimum amount of methanol, followed by two recrystallizations from MeOH–EtOH (1:1) to give 7.05 g (77.2% yield) of **10**, which was dried overnight at 1 mmHg and at room temperature: temperature: dec pt 128–130 °C; $[\alpha]_D$ -37.4°. The mother liquor was set aside as solution A.

To a suspension of 4.0 g of **10** in 15 mL of EtOH and 15 mL of ether was added gaseous HCl until the solution became clear. After the addition of 15 mL of pentane, the resulting solution was kept in the refrigerator to give a white solid, which was recrystallized from $CHCl_3$–ether to give 2.11 g (95% yield) of the imidazoline hydrochloride salt: mp 170–172 °C; $[\alpha]_D$ +36.4°. Hydrogenation of 1.0 g of the imidazoline hydrochloride salt in 30 mL of MeOH with 50 mg of 10% Pd/C for 1 h gave a mixture, which was filtered. The ethanol solution was concentrated to about 2 mL, and 10 mL of CH_2Cl_2 was added to give an oil. The solvent was decanted from the oil, and the oil was dried under reduced pressure to give 0.55 g (95.5% yield) of (*S*)-(+)-**1**: dec pt 82–85 °C; $[\alpha]_D$ +78.9°; ^1H NMR (D_2O) δ 7.0–7.1 (m, 3 H), 5.54 (s, 1 H), 3.95 (s, 4 H). Anal. ($C_{10}H_{13}N_2O_3Cl$) C, H, N.

Solution A was evaporated in vacuo to give 10.1 g of the imidazoline tartaric acid salt, which was treated with 3 g of NaOH in 200 mL of water and extracted with 300 mL of $CHCl_3$, the $CHCl_3$ layer was dried (Na_2CO_3) and filtered, and to the filtrate was added 4.7 g (13.1 mmol) of (+)-dibenzoyl-D-tartaric acid. The resulting mixture was allowed to stand at room temperature for 1 h, and the solvent was evaporated to give a viscous liquid, which was dissolved in MeOH. The solution was kept at room temperature overnight to yield 8.5 g of the (+)-**11a**, which was recrystallized three times from MeOH and twice from MeOH–EtOH (1:1) to give 5.6 g (61.4% yield) of the imidazoline (+)-dibenzoyl-D-tartartic salt **11a**: dec pt 122–126 °C; $[\alpha]_D$ +37.8°.

To a suspension of 3.0 g of imidazoline (+)-dibenzoyl-D-tartaric salt **11a** in 15 mL of EtOH and 15 mL of ether was added gaseous HCl until the solution turned clear. After the addition of 15 mL of pentane, the resulting solution was kept in the refrigerator to give a white solid, which was recrystallized from $CHCl_3$–ether to give 1.59 g (95.4% yield) of the imidazoline hydrochloride salt: mp 169–171 °C; $[\alpha]_D$ -36.5°. Hydrogenation of 1.0 g of the imidazoline hydrochloride salt in 30 mL of MeOH with 50 mg of 10% Pd/C for 1 h at 40 psi gave a mixture, which was filtered, the ethanol solution was concentrated to about 2 mL, and 10 mL of CH_2Cl_2 was added to give an oil. The solvent was decanted from the oil, and the oil was dried under reduced pressure to give 0.51 g (90.2% yield) of solid (*R*)-(-)-**1**: dec pt 82–85 °C; $[\alpha]_D$ -78.0°; ^1H NMR (D_2O) δ 7.0–7.1 (m, 3 H), 5.54 (s, 1 H), 3.95 (s, 4 H). Anal. ($C_{10}H_{13}N_2O_3Cl$) C, H, N.

In a similar process, 10 g (257 mmol) of **9** in 100 mL of MeOH and 9.3 g (25.9 mmol) of (+)-dibenzoyl-D-tartaric acid were mixed together and allowed to stand at room temperature to give 13.5 g of a solid (**11a**), and the resulting mother liquor was concentrated to give 5.8 g of a solid material. The 5.8 g of solid material was taken up in a minimum amount of 1:1 (MeOH, EtOH), and after two crystallizations, a total of 1.57 g of solid was isolated. The mother liquor from this latter crystallization was then concentrated, and a total of 1.4 g of solid was isolated. This latter solid was recrystallized from EtOH to give 279 mg of a solid, and the resulting mother liquor was concentrated to give 295 mg of solid **11b**: dec pt 161–162 °C; $[\alpha]_D$ +81.3°.

A small sample of 130 mg of **11b** was converted to the HCl salt as previously described, and it gave 59 mg of solid HCl salt, which matched the HCl salt prepared from **10**.

X-ray Analysis of 11b. Crystals of sufficient size and quality for X-ray structural analysis were prepared by cocrystallizing (+)-2-[3,4-bis(benzyloxy)-α-hydroxybenzyl]imidazoline with (+)-dibenzoyl-D-tartaric acid from ethanol. The two molecules crystallized in space group $P2_1$ with a = 7.499 (2), b = 18.050 (4), c = 14.309 (4) Å, β = 94.24 (2)°, and V = 1931 (2) Å.[3] Each asymmetric unit contained one imidazoline and one tartaric acid molecule. The calculated and measured densities are d_x = 1.283 g/cm^3 (-122 °C) and d_m (CCl_4/pentane) = 1.28 g/cm^3 (24 °C), respectively. A slightly yellow, irregular pentagonal prism was selected for data collection. All measurements were made with Mo $K\alpha$ graphite-monochromatized radiation ($\lambda(K\alpha_1)$ = 0.70926 Å) at -122 °C on a Syntex P$\bar{1}$ four-circle automated diffractometer.

Data collection was carried out with an $\omega - 2\theta$ scan technique with $4° \leq 2\theta \leq 50°$. One full quadrant was collected using a variable scan rate between 2 and 24°/min. Eight check reflections were monitored after every 100 reflections measured and indicated a small rate of decay. A total of 3533 unique reflections was measured, with 2891 having $I > 3\sigma(I)$.

Initial data processing and the final structure refinements were carried out with the CRYM crystallographic computing system.[23] The intensity data were corrected for decay, Lorentz, polarization, and absorption (μ = 0.87 cm^{-1}) effects.

The direct methods program MULTAN80[24] was successful in finding a molecular fragment containing 15 of the 55 non-hydrogen atoms in the asymmetric unit. The remaining non-hydrogen atoms were located by successive structure factor and Fourier calculations by the SHELX-76 system.[25]

Structural parameters were refined by least-squares minimization of the function $\sum W^2|F_o^2 - F_c^2|^2$, where $W = 1/\sigma(F_o^2)$. Atomic scattering factors were those compiled by Cromer and Waber.[26] The positions of most of the hydrogens were calculated based on the geometry of the non-hydrogen atoms. The positions of the hydrogens attached to N1 and O1 were located in a difference electron density map. All non-hydrogen atoms were refined anisotropically. Owing to the number of parameters involved, it was necessary to block each molecule in the asymmetric unit separately during least-squares refinement. The final R factors, as based on F^2 refinement on all 3533 reflections and a total of 503 variables, converged to R_1 = 0.056 and R_w = 0.099

$$R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$$

$$R_w = [\sum W^2(|F_o|^2 - |F_c|^2)^2 / \sum W^2|F_o|^4]^{1/2}$$

where a final difference Fourier synthesis showed no significant features with a maximum peak height of 0.18 eÅ^{-3}.

Based on the known configuration about the asymmetric carbons of the tartaric acid, the absolute configuration for the asymmetric hydroxy carbon in the imidazoline molecule is *S*. An ORTEP drawing of the two molecules shows the configuration around the asymmetric centers. Final positional parameters for non-hydrogen atoms are given in Table II. Details of the structure

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Table II. Positional Parameters of Non-Hydrogen Atoms for 11b (see Figure 1)

atom	x[a]	y	z	atom	x	y	z
C1	155 350 (41)	81 729 (19)	53 485 (20)	C1'	83 800 (45)	72 816 (20)	28 907 (24)
N1	162 996 (36)	87 927 (14)	56 303 (20)	C2'	79 440 (75)	73 820 (26)	19 542 (29)
C2	181 973 (46)	86 745 (21)	59 257 (29)	C3'	81 732 (97)	80 624 (29)	15 415 (32)
C3	182 961 (49)	78 206 (21)	59 731 (28)	C4'	87 798 (70)	86 508 (25)	20 805 (31)
N2	165 851 (37)	76 015 (14)	54 754 (20)	C5'	91 816 (56)	85 574 (21)	30 228 (29)
C4	136 484 (42)	81 059 (18)	48 770 (21)	C6'	90 163 (51)	78 828 (21)	34 237 (24)
O1	124 491 (27)	86 010 (13)	52 673 (15)	C7'	81 326 (44)	65 366 (21)	32 849 (24)
C5	136 958 (43)	81 686 (21)	38 262 (22)	O1'	74 851 (35)	60 196 (14)	28 541 (17)
C6	134 378 (50)	75 235 (18)	32 983 (24)	O2'	87 283 (27)	64 843 (12)	42 065 (14)
C7	133 635 (57)	75 442 (22)	23 411 (26)	C8'	84 631 (42)	57 579 (17)	45 866 (22)
C8	135 599 (61)	82 194 (28)	18 909 (25)	C9'	64 849 (41)	56 107 (18)	46 983 (22)
C9	138 630 (66)	88 643 (24)	24 065 (28)	O3'	60 552 (28)	49 493 (12)	47 681 (17)
C10	139 211 (53)	88 313 (20)	33 782 (24)	O4'	54 478 (26)	61 556 (12)	47 408 (16)
O2	134 410 (51)	81 884 (20)	9 224 (18)	C10'	95 413 (40)	56 889 (18)	55 096 (22)
C11	131 509 (79)	88 521 (28)	4 290 (29)	C11'	113 977 (41)	60 261 (18)	54 640 (23)
C12	127 583 (65)	86 453 (32)	−5 920 (28)	O5'	118 916 (30)	65 736 (13)	58 836 (17)
C13	118 710 (64)	80 114 (30)	−8 477 (29)	O6'	123 114 (27)	56 440 (13)	48 844 (17)
C14	114 908 (66)	78 515 (31)	−17 925 (33)	O7'	85 897 (28)	60 329 (13)	62 294 (15)
C15	120 281 (64)	83 228 (39)	−24 836 (30)	C12'	91 331 (50)	58 203 (20)	71 134 (26)
C16	128 742 (75)	89 516 (42)	−22 245 (32)	O8'	103 617 (38)	54 026 (15)	72 804 (18)
C17	132 526 (80)	91 484 (34)	−12 749 (33)	C13'	80 522 (62)	61 646 (27)	78 211 (30)
O3	130 747 (43)	69 451 (17)	17 737 (18)	C14'	64 620 (77)	65 158 (38)	75 908 (36)
C18	128 905 (60)	62 556 (23)	22 224 (29)	C15'	87 326 (78)	61 245 (41)	87 582 (36)
C19	125 815 (64)	56 635 (28)	15 096 (34)	C16'	63 669 (148)	68 589 (61)	92 196 (56)
C20	129 866 (105)	57 581 (34)	6 057 (40)	C17'	56 033 (108)	68 658 (57)	83 098 (59)
C21	126 278 (146)	51 521 (53)	− 364 (51)	C18'	79 019 (132)	64 588 (67)	94 299 (49)
C22	119 235 (138)	45 113 (52)	3 124 (62)				
C23	120 136 (133)	50 019 (46)	17 745 (51)				
C24	117 192 (168)	44 195 (55)	11 857 (74)				

[a] Fractional coordinate values are multiplied by 10^5. The values given in parentheses are estimated standard deviations.

will be published in a forthcoming crystal structure paper.

2-[3,4-Bis(benzyloxy)benzyl]imidazoline Hydrochloride (14). HCl gas was bubbled into the suspension of nitrile **12** (5.0 g, 15.2 mmol) in EtOH (1.0 g, 21.7 mmol) and benzene (10 mL) with cooling in an ice bath. The mixture turned pale green, then gradually to pale dark green. HCl gas was added until ca. 0.6 g of HCl had been absorbed. The mixture was allowed to stand at room temperature for 30 min and then kept in the refrigerator overnight.

The resulting mixture was filtered through glass wool and then poured into 300 mL of anhydrous ether and stored in the refrigerator for 2 h. Filtration and washing with 50 mL of ether gave 6.0 g (96% yield) of white solid ethyl imidate **13**: dec pt 98 °C. Ethylenediamine (2.0 g, 33.33 mmol) was added dropwise for 5 min to a solution of the imidate (5.0 g, 12.15 mmol) in 10 mL of CH_2Cl_2 with stirring and cooling in an ice bath, and the mixture was allowed to come to room temperature and kept at this temperature for 15 h. To the resulting mixture were added 50 mL of CH_2Cl_2 and 100 mL of water, and the organic layer was washed with 50 mL of water, dried (Na_2CO_3), and filtered. Evaporation of the solvent afforded 4.2 g (92.9%) of a pale yellow solid of the free base **14** (mp 109–111 °C), which was recrystallized from *n*-hexane–CH_2Cl_2 to give white crystals (mp 109–111 °C). HCl gas was bubbled into a suspension of the imidazoline (2.0 g) in 10 mL of ether, 5 mL of benzene, and 3 mL of CH_2Cl_2 at room temperature. The bubbling of HCl gas was stopped at the point when viscous material attached to the wall of the vessel began to solidify; then stirring was continued vigorously until all viscous liquid had turned to a solid. Ether (20 mL) was added to the resulting mixture, which was then filtered to give a white solid, which was washed with 20 mL of ether to afford 2.16 g (98.3% yield) of the HCl salt **14**: mp 149–151 °C. Recrystallization from CH_2Cl_2–benzene gave colorless crystals: (mp 151–152 °C); ^{1}H NMR ($CDCl_3$) δ 10.60 (s, 2 H), 7.4–7.6 (m, 13 H), 5.20 (s, 2 H), 4.00 (s, 2 H), 3.93 (s, 2 H), 3.57 (s, 4 H); IR (KBr) 1620 cm^{-1}. Anal. ($C_{24}H_{25}O_2N_2Cl$) C, H, N.

2-(3,4-Dihydroxybenzyl)imidazoline Hydrochloride (**2**). A mixture of 3.2 g of **14** and 0.2 g of palladium in 80 mL of methanol was hydrogenated at 40 psi for 2.5 h at room temperature. The resulting mixture was filtered, and the solvent was removed to afford a solid, which was recrystallized from EtOH–CH_2Cl_2–pentane to give 1.75 g of colorless crystals, mp 60–71 °C. The crystals obtained (1.4 g, 78.3% yield) were dried at 4 mmHg at 100 °C for 2 days: mp 154–156 °C; ^{1}H NMR (D_2O) δ 7.1–6.7 (m, 3 H), 3.95 (s, 4 H), 3.83 (s, 2 H); IR (KBr) 3460, 3370 1650 cm^{-1}. Anal. ($C_{10}H_{13}N_2O_2Cl$) C, H, N.

1-Methyl-2-[3,4-bis(benzyloxy)benzyl]imidazoline Hydrochloride (**19**). To a solution of 3.3 g (8.0 mmol) of **13** in 15 mL of CH_2Cl_2 was added 1.8 g (24.3 mmol) of *N*-methylethylenediamine over a 5-min period in an ice bath. The resulting solution was stirred for 4 h at room temperature. To the resulting mixture was added 35 mL of CH_2Cl_2 and 50 mL of 1% NaOH solution, and the organic layer was separated and washed twice with 50 mL of H_2O, dried (Na_2CO_3), and evaporated to give 2.95 g (95%) of an oil. The oil was converted to an HCl salt and crystallized from $CHCl_3$–hexane–benzene to give crystalline **19**: mp 180–182 °C; ^{1}H NMR ($CDCl_3$, free base) δ 7.5–6.8 (m, 13 H), 5.07 (s, 2 H), 5.01 (s, 2 H), 3.88–2.88 (m, 4 H), 3.43 (s, 2 H), 2.48 (s, 3 H). Anal. ($C_{25}H_{27}N_2O_2Cl$) C, H, N.

1-Methyl-2-(3,4-dihydroxybenzyl)imidazoline Hydrochloride (**5**). To 50 mL of MeOH was added 1.4 g of **19** and 140 mg of 10% Pd/C, and the mixture was hydrogenated at 40 psi for 3 h. The mixture was filtered, and the solvent was removed in vacuo and taken up in MeOH–hexane to give crystalline **5** mp 169–170 °C. Anal. ($C_{11}H_{15}N_2O_2Cl$) C, H, N.

1,3-Dimethyl-2-(3,4-dihydroxybenzyl)imidazoline Tetrafluoroborate (**8**). To a solution of 3.6 g of the free base of **19** in 10 mL of ethyl acetate cooled in an ice bath was added 1.4 g (9.86 mmol) of methyl iodide in 2 mL of ethyl acetate over a 10-min period. When the viscous product appeared, 10 mL of CH_2Cl_2 was added to the reaction mixture, and resulting solution was stirred vigorously with cooling in an ice bath. After the solution was stirred for an additional 80 min, another 20 mL of ethyl acetate was added, and the mixture was stirred for another 30 min. The resulting white solid was isolated by filtration and washed with ethyl acetate to give 4.7 g of the methyl iodide product, mp 128–130 °C. The material decomposes if allowed to stand at room temperature, and suitable C, H, and N analysis could not be obtained. A suspension of 1.8 g of the methyl iodide salt in 10 mL of anhydrous methanol was treated with 0.7 g of silver tetrafluoroborate and stirred at room temperature for 1 h. The resulting silver iodide was removed by filtration and washed with $CHCl_3$. The organic layers were combined and evaporated to give a residue, which was taken up in 50 mL of $CHCl_3$ and washed with water. The organic layer was dried (Na_2SO_4) and evaporated to give a solid, which was recrystallized from

Table III. Physical Constants for Optically Active Imidazoline Derivatives

compd	final crystn solvent	mp, °C	yield, %	$[\alpha]^{28}$, deg Na_{589}	Hg_{578}
3	CH_2Cl_2-ether	70-72	93	+58.4	+61.1
4	CH_2Cl_2-ether	69-72	94	-56.6	-58.2
6	EtOH-ether	120-122	89	+90.3	+94.9
7	EtOH-ether	121-123	85	-92.3	-97.2
15	CH_2Cl_2-ether	102-104	70	+30.2	+32.1
16	CH_2Cl_2-ether	100-102	66	-30.9	-32.2
17	CH_2Cl_2-ether	68-70[a]	43	+47.3	+49.6
18	CH_2Cl_2-ether	67-69[a]	47	-46.0	-48.0

[a] The hydrates for these compounds had a melting point of 101-103 (17) and 100-102 (18); when dried at 1 mmHg at 70 °C for 1 day, we obtained the melting point reported above.

$CHCl_3$-ether and dried at 80 °C (0.1 mm) overnight to give 1.32 g (89% yield) of crystalline tetrafluoroborate salt, mp 121–123 °C. Anal. ($C_{26}H_{29}N_2O_2BF_4$) C, H, N.

To 1 g of 1,3-dimethyl-2-[3,4-bis(benzyloxy)benzyl]imidazoline tetrafluoroborate salt in 30 mL of MeOH was added 100 mg of 10% Pd/C, and the mixture was reduced under hydrogen at 40 psi for 3 h. Filtration of the reaction mixture, followed by concentration of the resulting solution, gave a total of 0.59 g (93.5% yield) of solid catechol 8, mp 87–90 °C. Anal. ($C_{12}H_{17}N_2OBF_4$) C, H, N.

General Procedure for the Preparation of Compounds 2–7. The imidazolines were prepared via a modification of the procedure of King and Acheson.[27] A typical example was as follows. To an ice-cooled solution of optically active 1,2-diamine dihydrochloride[6,14] (5 mmol) and $N(Et)_3$ (1.11 g, 11 mmol) in anhydrous MeOH (10 mL) was added 2.06 g (5 mmol) of ethyl 1-[3,4-bis(benzyloxy)phenyl]iminoacetate hydrochloride (13). The resulting mixture was stirred at room temperature for 5 h. The solvent was removed, and the resulting residue was treated with a diluted NaOH solution and extracted into $CHCl_3$. The organic layers were combined, dried (Na_2CO_3), and evaporated to give an oil, which was converted to a HCl salt. The HCl salts were isolated (see Table III) and converted to catechols by catalytic hydrogenation as described for the isomers of 1 and 2. (See Table III for physical constants.)

Pharmacology. Substances were tested in the isolated rat aortic strip[28] prepared according to the modifications suggested by Herlihy.[29] Male Charles River Wistar rats weighing 175 to 300 g were killed by a blow to the head, followed by cervical dislocation. The thoracic aorta from the aortic arch to the diaphragm was excised and then placed in physiological salt solution (PSS) at room temperature, and the adventitia was removed with fine forceps. Since it has been reported that α-adrenoreceptors may not be homogeneously distributed along the length of the aorta,[30] the 2-cm segment distal to the first intercoastal artery was always used. This aortic tube was placed on a stainless-steel needle and cut at an angle of 75 to 80° relative to the lumen of the vessel; this angle was reported by Herlihy[29] to parallel the muscle fibers of the tissue and to permit the greatest response. The tissue was mounted in a jacketed physiological chamber maintained at 37 °C and aerated with 95% oxygen/5% carbon dioxide.

PSS was prepared in double distilled water and contained the following (mM): NaCl (118.07), KCl (4.69), $CaCl_2 \cdot 2.2H_2O$ (2.52), $MgSO_4$ (0.57), $NaHCO_3$ (25.01), NaH_2PO_4 (1.01), and dextrose (11.00). PSS was aerated with 95% oxygen/5% carbon dioxide and was maintained at room temperature.

The aortic strips were attached to a Grass FTOC force-displacement transducer connected to a Grass Model 7 polygraph. Tissues were adjusted to 2-g tension and allowed to equilibrate for 1 h, subsequently exposed to a half maximal concentration of phenylephrine, and allowed to reequilibrate for 1 h prior to the test.

Cumulative concentration–effect curves were constructed by increasing the bath concentration of drug by approximately threefold.[31] The tissue response was allowed to reach a constant level before the drug concentration was increased. After the completion of each concentration–effect curve, the drug was washed from the preparation, and at least 1 h separated consecutive curves.

Concentration–effect curves were analyzed by computer with a statistical analysis system.[32] ED_{50} values represent the concentration to produce 50% of the maximum contraction of the tissue.

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Registry No. (*S*)-(+)-1, 75847-72-2; (*S*)-1 (base), 85232-93-5; (*R*)-(−)-1, 75847-71-1; (*R*)-1 (base), 85232-94-6; 2, 85612-41-5; 2 (base), 72143-18-1; 3, 85612-42-6; 3 (base), 85612-61-9; 4, 85612-43-7; 4 (base), 85612-62-0; 5, 85612-44-8; 5 (base), 85612-65-3; 6, 85612-45-9; 6 (base), 85612-63-1; 7, 85612-46-0; 7 (base), 85612-64-2; 8, 85612-54-0; 8 (dibenzyl derivative), 85612-72-2; (±)-9, 85612-47-1; 10, 85647-95-6; 10·HCl, 85647-96-7; 11a, 85647-98-9; 11a·HCl, 85647-99-0; 11b, 85648-00-6; 12, 1699-60-1; 13, 85612-50-6; 14, 85612-48-2; 14 (base), 85612-49-3; 15, 85612-55-1; 15 (base), 85612-66-4; 16, 85612-56-2; 16 (base), 85612-67-5; 17, 85612-57-3; 17 (base), 85612-68-6; 18, 85612-58-4; 18 (base), 85612-69-7; 19 (base), 85612-51-7; 19, 85612-52-8; 19·MeI, 85612-70-0; (*R*)-1,2-diaminopropane, 6852-78-4; (*S*)-1,2-diaminopropane, 15967-72-3; (*R*)-1,2-diamino-3-phenylpropane, 85612-59-5; (*S*)-1,2-diamino-3-phenylpropane, 85612-60-8; ethylenediamine, 107-15-3; *N*-methylethylenediamine, 109-81-9.

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