pyridine hydrochloride were formed, and the supernatant had a light brown color. The reaction mixture was poured on ice–water and stirred for a few minutes. The milky solution was extracted with ether. The organic layer was washed with dilute HCl to remove the pyridine. The ether was evaporated at room temperature. The residue was dissolved in methanol and left for crystallization to give a product yield of 9.0 g (65%), mp 49–50 °C.

1-(3,4-Dimethoxyphenyl)-2-(methylseleno)ethane (3). To dimethyl diselenide (2.23 g, 12 mmol) in THF, under nitrogen, sodium borohydride (1.9 g, 24 mmol) in ethanol was added dropwise until the solution decolorized. To this solution was added the tosyl derivative **2** (6.72 g, 20 mmol) in ethanol. After 30 min of stirring, water was added to the reaction mixture, and the mixture was extraced with chloroform. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated to leave 4 g (77%) of a pale yellow oil: NMR ($CDCl_3$) δ 6.73–6.83 (m, 3 H, ArH), 3.87 (s, 6 H, 2 OCH_3), 2.76–2.93 (m, 4 H, CH_2CH_2), 2.00 (s, 3 H, CH_3).

[2-(3,4-Dimethoxyphenyl)ethyl]dimethylselenonium Iodide (4). Methyl iodide (1.45 g, 10 mmol) was added to compound **3** (2.59 g, 10 mmol) and left at room temperature for 30 min. The yellow solid that formed was dissolved in absolute ethanol and left for crystallization. Yellow crystals (3 g, 75%) of the desired compound were obtained: mp 113–115 °C; NMR (D_2O) δ 6.95–7.05 (m, 3 H, ArH), 3.90 (s, 6 H, 2 OCH_3), 3.56–3.80 (t, 2 H, Ph-CH_2), 3.03–3.30 (t, 2 H, CH_2Se), 2.67 (s, 6 H, 2 CH_3); MS, *m/e* 260 (M for the cation – CH_3). Anal. ($C_{12}H_{18}O_2SeI$) C, H.

[2-(3,4-Dihydroxyphenyl)ethyl]dimethylselenonium Chloride (7). The selenide **3** (4 g, 16 mmol) was dissolved in CH_2Cl_2 and dried over anhydrous $MgSO_4$. The solution was filtered and transferred to a three-necked flask equipped with a condenser and dropping funnel. The system was placed under nitrogen and cooled to 0 °C. Boron trichloride (35 mL of 1 M solution in CH_2Cl_2, 35 mmol) was added. After the addition, the solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with methanol (50 mL), and the solvent was removed under vacuo to leave a white solid. Crystallization from methanol/acetone provided shiny crystals of compound **7** (3.5 g, 77%): mp 148–149 °C; NMR (D_2O) δ 6.85–7.02 (m, 3 H, ArH), 3.45–3.76 (t, 2 H, Ph-CH_2), 2.91–3.23 (t, 2 H, CH_2Se), 2.67 [s, 6 H, $Se(CH_3)$]; MS, *m/e* (M for cation – CH_3). Anal. ($C_{10}H_{15}O_2SeCl$) C, H.

Radioactive Synthesis. To selenious acid (1.29 mg, 10 μmol) in 0.1 mL of phosphate buffer (pH 6.0, 0.5 M), 3.5 mCi of $H_2{}^{75}SeO_3$ was added. The solution was stirred under argon, and sodium borohydride (1.14 mg, 30 μmol) in 0.1 mL water was added dropwise until a colorless solution was formed. To this solution, 0.2 mL of phosphate buffer (pH 6.0, 0.5 M) was added, followed by the addition of the tosyl derivative **2** (3.36 mg, 10 μmol) in 0.1 mL ethanol. Ethanol (0.5 mL) was added to the reaction mixture and stirred overnight. Then the mixture was extracted with ether, and the organic layer was left to evaporate at room temperature. The residue, diselenide **9** (3 mCi), in 0.2 mL of THF was transferred to a three-necked flask, and $NaBH_4$ (0.38 mg, 10 μmol) in 0.2 mL of 95% ethanol was added under argon, followed by the addition of CH_3I (2.9 mg, 20 μmol). After the solution was stirred for 15 min, 2 mL of water was added, and the solution was extraced with ether. The aqueous layer contained compound **4** (1.1 mCi), while the ether layer contained compound **3** (1.8 mCi). The ether layer was dried over anhydrous $MgSO_4$ and filtered, and the filtrate was evaporated to dryness by using a stream of nitrogen. The residue was dissolved in anhydrous CH_2Cl_2; to this solution, boron trichloride in CH_2Cl_2 was added under argon. After 5 h, excess BCl_3 was decomposed with methanol, and 0.5 mL of water was added. The solution was extracted with ether to remove the unreacted starting material. The aqueous layer contained 1.3 mCi of the desired salt **7**.

Tissue Distribution Studies. The tissue distribution of [^{75}Se]selenonium salts **4** and **7** was examined in female Sprague-Dawley rats (100–300 g). The rats were injected in a lateral tail vein with 0.2 mL of a saline solution containing 5–6 μCi of test compound. At different time periods after injection, groups of rats (five animals per group) were subjected to chloroform anesthesia and killed by cardioectomy. Samples of large organs (liver, lungs, small intestine, and muscle) were taken, and small organs (heart, kidneys, spleen, uterus, and adrenals) were taken intact, rinsed with saline, blotted dry, and weighed. The radioactivity in the samples was counted in a Beckman Automatic Gamma Counter (Model 9000), and the values were converted to percent of injected dose per gram of sample (% dose/g).

Registry No. 1, 7417-21-2; **2**, 75010-39-8; **3**, 85709-84-8; **3**-^{75}*Se*, 85709-85-9; **4**, 85709-86-0; **4**-^{75}*Se*, 85709-87-1; **7**, 85709-88-2; **7**-^{75}*Se*, 85709-89-3; **9**, 85709-90-6; TSCl, 98-59-9; $CH_3Se^-Na^+$, 37773-10-7; $H_2{}^{75}SeO_3$, 7783-00-8.

β_1-Selective Adrenoceptor Antagonists: Examples of the 2-[4-[3-(Substituted-amino)-2-hydroxypropoxy]phenyl]imidazole Class

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A series of 2-[4-[3-(substituted-amino)-2-hydroxypropoxy]phenyl]imidazoles is described. The compounds were investigated in vitro for β-adrenoceptor antagonism, and several examples were found to be selective for the β_1-adrenoceptor. The structure–activity relationship exhibited by this series of compounds is discussed. (*S*)-2-[*p*-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-(2-thienyl)imidazole [(*S*)-**13**] was over 100 times more selective than atenolol for the β_1-adrenergic receptor and has been selected for in-depth studies.

A substantial advance in the understanding of the adrenergic system occurred in 1948, when Ahlquist[1] proposed the existence of two discrete receptor types designated α and β. The introduction of pronethalol[2] and propranolol[3] reinforced this hypothesis and laid the foundation for the role of β-adrenoceptor antagonists in the management of various cardiovascular conditions, particularly angina pectoris, cardiac arrhythmias, and essential hypertension.[4] However, the use of such agents is occasionally associated with bronchospasms and Raynaud's phenomenon. An approach toward elimination of these side effects emerged with the discovery of practolol,[5] a cardioselective agent,

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(1) Ahlquist, R. P. *Am. J. Physiol.* **1948**, *154*, 586.
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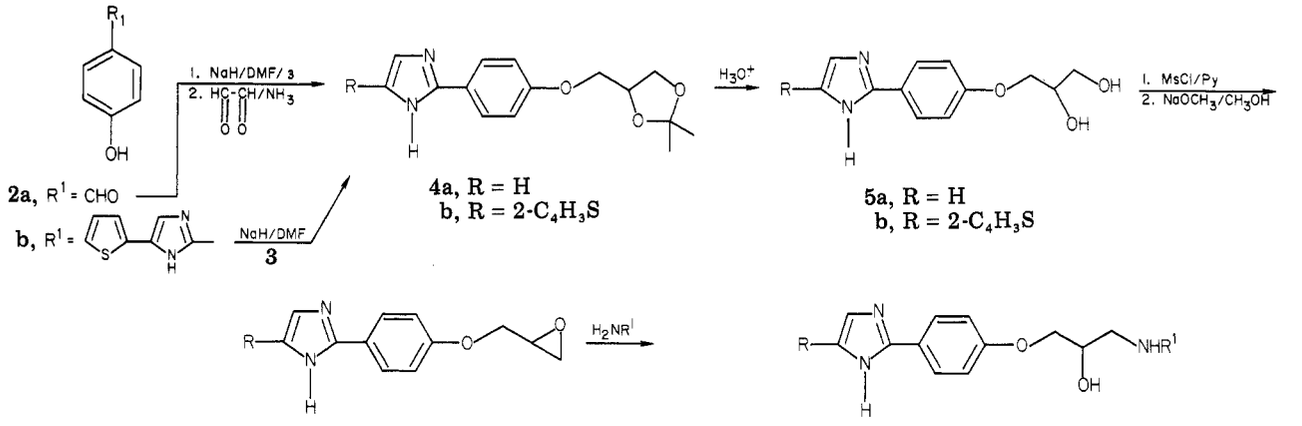
(3) Crowther, A. F.; Smith, L. H. *J. Med. Chem.* **1968**, *11*, 1009.
(4) (a) Black, J. W.; Stephenson, J. S. *Lancet* **1962**, *2*, 311. (b) Black, J. W.; Duncan, W. A. M.; Shanks, R. G. *Br. J. Pharmacol. Chemother.* **1965**, *25*, 577.

0022-2623/83/1826-0950$01.50/0

Scheme I



2a, R1 = CHO
b, R1 = 2-C4H3S

4a, R = H
b, R = 2-C4H3S

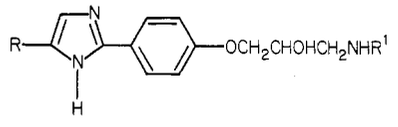
5a, R = H
b, R = 2-C4H3S

6a, R = H
b, R = 2-C4H3S

7, R = H; R1 = c-C3H5
8, R = H; R1 = CH2CH2-C6H3-3,4-(OCH3)2
9, R = 2-C4H3S; CH(CH3)CH2-C6H3-3,4-(OCH3)2
10, R = 2-C4H3S; R1 = C(CH3)2CH2-C6H3-3,4-(OCH3)2
(R)-13, R = 2-C4H3S; R1 = CH2CH2-C6H3-3,4-(OCH3)2

which discriminated between the cardiac β_1- and peripheral β_2-adrenoceptors. Although cardioselective agents, such as metoprolol, atenolol, and betaxolol, have been developed, they exhibit only modest separation between these subreceptor affinities (see Table II).

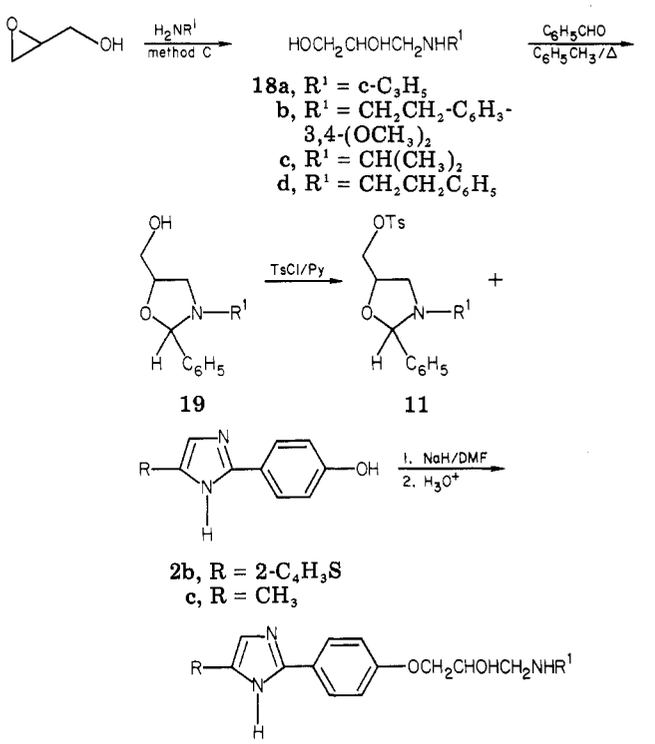
In this paper, we describe β_1-adrenoceptor antagonists in which the in vitro β_1-selectivity, for all practical purposes, borders on absolute specificity. In principal, such highly selective compounds should offer significant therapeutic advantages. Our specific approach in the design of such agents took advantage of the cardioselectivity observed for (*S*)-2-[*p*-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]-4-(trifluoromethyl)imidazole (**1a**)[6] and related compounds **1b–f**.[7] Specifically, the strategy centered on a two-point variation involving the imidazole 4-substituent and the *N*-*tert*-butyl moiety.



1a, R = CF_3; R^1 = $C(CH_3)_3$
b, R = CF_3; R^1 = c-C_3H_5
c, R = CF_3; R^1 = CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$
d, R = H; R^1 = $C(CH_3)_3$
e, R = CH_3; R^1 = $C(CH_3)_3$
f, R = 2-C_4H_3S; R^1 = $C(CH_3)_3$

Chemistry. The compounds synthesized during the course of this study are listed in Table I. Examples **1b** and **1c** were prepared from 2-[4-(2,3-epoxypropoxy)-phenyl]-4-(trifluoromethyl)imidazole[6] on reaction with cyclopropylamine and 2-(3,4-dimethoxyphenyl)ethylamine,[8] respectively (method A). Substituent variation at both R and R^1 was accomplished via the synthetic strategies outlined in Schemes I and II.

Scheme II



18a, R^1 = c-C_3H_5
b, R^1 = CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$
c, R^1 = $CH(CH_3)_2$
d, R^1 = $CH_2CH_2C_6H_5$

19 11

2b, R = 2-C_4H_3S
c, R = CH_3

12, R = 2-C_4H_3S; R^1 = c-C_3H_5
13, R = 2-C_4H_3S; R^1 = CH_2CH_2-C_6H_3-3,4$(OCH_3)_2$
14, R = 2-C_4H_3S; R^1 = $CH(CH_3)_2$
15, R = 2-C_4H_3S; R^1 = $CH_2CH_2C_6H_5$
16, R = CH_3; R^1 = c-C_3H_5
17, R = CH_3; R^1 = CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$

As shown in Scheme I (method B), the key intermediates **4a,b** were prepared by two different methods. For **4a**, the approach involved side-chain introduction, followed by imidazole ring construction; in the synthesis of **4b**, the reverse strategy was used, i.e., ring formation followed by incorporation of the side chain.

For the preparation of **7** and **8** from **4a**, acid hydrolysis of the acetonide protecting group yielded the diol **5a**. Treatment of **5a** with methanesulfonyl chloride gave the primary mesylate, which, after reaction with slightly less than an equivalent amount of $NaOCH_3$, generated the epoxide **6a**. Ring opening of the epoxide **6a** with either

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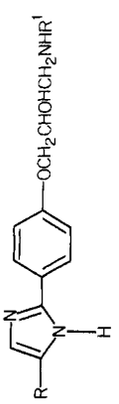
Table I



compd	R	R^1	method	mp, °C	reaction solvent	mol formula	anal.
1b	CF_3	c-C_3H_5	A	163.5–165	C_6H_5–C_6H_{12}	$C_{16}H_{18}F_3N_3O_2$	C, H, N
(S)-1b	CF_3	c-C_3H_5	D	169–171	CH_3CN	$C_{16}H_{18}F_3N_3O_2$	C, H, N
1c	CF_3	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	A	223–224	EtOH	$C_{23}H_{26}F_3N_3O_4{\cdot}2HCl$	C, H, N
7	H	c-C_3H_5	B	214–215	EtOH-MeOH-Et_2O	$C_{15}H_{19}N_3O_2{\cdot}2HCl$	C, H, N
8	H	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	B	233.5–235.5	EtOH-MeOH-Et_2O	$C_{22}H_{27}N_3O_4{\cdot}2HCl$	C, H, N
9	2-C_4H_3S	$CH(CH_3)CH_2$-C_6H_3-3,4-$(OCH_3)_2$	B	175–179	EtOH-Et_2O	$C_{27}H_{31}N_3O_4S{\cdot}2HCl$	C, H, N
10	2-C_4H_3S	$C(CH_3)_2CH_2$-C_6H_3-3,4-$(OCH_3)_2$	B	243–245	EtOH-MeOH-Et_2O	$C_{28}H_{33}N_3O_4S{\cdot}2HCl{\cdot}H_2O$	C, H, N
12	2-C_4H_3S	c-C_3H_5	C	241.5–243.5	EtOH	$C_{19}H_{21}N_3O_2S{\cdot}2HCl$	C, H, N
13	2-C_4H_3S	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	C	278–280	EtOH	$C_{26}H_{29}N_3O_4S{\cdot}2HCl$	C, H, N
14	2-C_4H_3S	$CH(CH_3)_2$	C	172–174	CH_3CN	$C_{19}H_{23}N_3O_2S$	C, H, N
15	2-C_4H_3S	CH_2CH_2-C_6H_5	C	274–276	EtOH-MeOH-Et_2O	$C_{24}H_{25}N_3O_2S{\cdot}2HCl$	C, H, N
16	CH_3	c-C_3H_5	C	244.5–245.5	EtOH	$C_{16}H_{21}N_3O_2{\cdot}2HCl$	C, H, N
17	CH_3	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	C	224–227	EtOH-Et_2O	$C_{23}H_{29}N_3O_4{\cdot}2HCl{\cdot}0.5H_2O$	C, H, N
(S)-8	H	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	D	223–225	*i*-PrOH-CH_3OH	$C_{22}H_{27}N_3O_4{\cdot}2HCl{\cdot}H_2O$	C, H, N
(S)-12	2-C_4H_3S	c-C_3H_5	C	238–241	EtOH-Et_2O	$C_{19}H_{21}N_3O_2S{\cdot}2HCl{\cdot}0.5H_2O$	C, H, N
(S)-13	2-C_4H_3S	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	C	269–271	EtOH	$C_{26}H_{29}N_3O_4S{\cdot}2HCl$	C, H, N
(R)-13	2-C_4H_3S	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	B	270–272	EtOH	$C_{26}H_{29}N_3O_4S{\cdot}2HCl$	C, H, N

cyclopropyl or 2-(3,4-dimethoxyphenyl)ethylamine provided the 4-unsubstituted imidazoles **7** and **8**, respectively.[9] The syntheses of the thienyl-substituted derivatives **9** and **10** from **4b** were accomplished in an analogous manner to that used for **7** and **8**. Compound **9**, having two chiral centers, was determined to be an equal mixture of diastereomers. Using 300-MHz ^1H NMR, the methyl signal at δ 1.2 appeared as two finely split doublets.

As outlined in Scheme II, compounds **12–17** were prepared by direct introduction of the aminohydroxypropyl group through the reaction of the oxazolidine tosylate **11** with the preformed imidazoles **2b** and **2c** (method C).[7] In the preparation of **12**, for example, the sodium salt of 2-(*p*-hydroxyphenyl)-4-(2-thienyl)imidazole (**2b**) was allowed to react with the tosylate of 2-phenyl-3-cyclopropyl-5-(hydroxymethyl)oxazolidine (**11a**), which, after deprotection, provided **12**. Varying the amino group of **11** and the substituent in the 4-position of the imidazole ring provided the remaining examples **13–17**.

The chiral center in (*S*)-**8**, (*S*)-**13**, and (*R*)-**13** was established via the diacetonide of D-mannitol (**20**) (method D).[10] Sequential treatment of **20** with $Pb(OAc)_4$, excess 2-(3,4-dimethoxyphenyl)ethylamine, and $NaBH_4$ and acid deprotection yielded (*S*)-3-[[2-(3,4-dimethoxyphenyl)-ethyl]amino]-1,2-propanediol [(*S*)-**18b**]. The glycolamine (*S*)-**18b** was converted to the tosylate (*S*)-**11b** in two steps by utilizing previously described chemistry.[6,7] Reaction of the sodium salt of *p*-hydroxybenzaldehyde (**2a**) with (*S*)-**11b**, followed by deprotection, provided (*S*)-4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]benzaldehyde (**21**) (method E). Compound **21** was then converted to (*S*)-**8** via condensation with glyoxal and NH_3. Similarly, reaction of either chiral oxazolidines (*S*)-**11a** or (*S*)-**11b** with 2-(*p*-hydroxyphenyl)-4-(2-thienyl)imidazole (**2b**) provided, after deprotection, the imidazoles (*S*)-**12** and (*S*)-**13**, respectively. It should be pointed out that intermediate **11** is a mixture of diastereomers with the configuration at C-5 of the oxazolidine ring fixed as *S*. The *R* enantiomer of **13** was prepared by treatment of the diacetonide of D-mannitol (**20**) with $Pb(OAc)_4$, followed by $NaBH_4$ reduction to give (*S*)-glycerol 1,2-acetonide (**22**).[11] Reaction of (*S*)-**22** with methanesulfonyl chloride yielded the mesylate (*R*)-**3**. The use of (*R*)-**3** in place of **3**, as described in Scheme I, allowed for the synthesis of (*R*)-**13** containing approximately 5–10% of the *S* enantiomer. Substitution *p*-toluenesulfonyl chloride in this sequence yielded enantiomerically pure (*R*)-**13**.

Optical purity was determined by ^1H NMR spectroscopy by using the chiral shift reagent tris[3-(heptafluorobutyryl)-α-camporate]europium. For (*S*)-**8**, (*S*)-**13**, and (*R*)-**13**, assay conditions were obtained by studying the effect of addition of the lanthanide reagent on racemic material. The methoxy resonances of **8** and **13** were used as analytical signals with separation of 8–15 Hz for each methoxy in the presence of 0.1 and 0.5 molar equiv of lanthanide. This technique did not differentiate clearly any signals in the racemic mixture of **12** due to significant line broadening in the presence of chiral shift reagent. Thus, the chiral purity of (*S*)-**12** is based on analogy and rotation.

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Data Analysis. The data were analyzed by calculating the mean isoproterenol-induced relaxation of the tracheal chain (five to seven doses) for 6–12 tracheal chain preparations, and in the case of the atria, the mean isoproterenol-induced chronotropic response (seven to eight doses) for eight atrial preparations were determined. This was done for the isoproterenol concentration–response in the absence of antagonist and in the presence of antagonist. The concentration–response relationship was analyzed by nonlinear symmetrical curve fitting routines to yield a calculated EC_{50}. If only a single concentration of antagonist was being studied, the data resulting from the analysis were used to calculate a "local pA_2" as proposed by MacKay[12] and applied by O'Donnell and Wanstall.[13] The "local pA_2" was calculated from the following equation:

$$pA_2 = \log [(B - A)/A]/P$$

where A = EC_{50} of agonist in the absence of antagonist, B = EC_{50} of agonist in the presence of antagonist, and P = concentration of antagonist. If more than one concentration of antagonist was used in the study, the individual data were further analyzed by the method of Schild[14] to produce a multiconcentration "system pA_2". The system pA_2 was calculated by unweighted linear regression analysis of the line of best fit by the method of least squares. The pA_2 was the positive value of the intercept of the line derived by plotting log (CD − 1) vs. log antagonist concentration with the abscissa. All computations were performed on a DEC MINC-11 computer.

Results and Discussion

We have previously reported that the trifluoromethylimidazole derivative **1a** lowered mean arterial blood pressure in the spontaneously hypertensive rat (SHR) and exhibited vasodilating and β_1-selective adrenoceptor antagonism in the dog.[6] The observed selectivity was on the order of that seen with practolol (Table II). Variation of the trifluoromethyl group of **1a** yielded specific examples that demonstrated enhanced β_1 selectivity (compounds **1d–f**, Table II).[7] In a separate structural study, replacement of the N-terminal *tert*-butyl moiety of **1a** with cyclopropyl and 2-(3,4-dimethoxyphenyl)ethyl moieties also provided examples that exhibited high β_1 selectivity (compunds **1b** and **1c**, Table II). Therefore, our approach toward cardiospecific agents was to simultaneously incorporate those structural features that in the two single variant studies enhanced β_1-selectivity.

The in vitro evaluation of compounds **1**, **7–10**, and **12–17** is summarized in Table II. The interaction with the β_1-receptor was determined via inhibition of the positive chronotropic actions of isoproterenol is isolated guinea pig atrial preparations. β_2 potency was determined by using isolated guinea pig tracheal chains contracted with $PGF_{2\alpha}$ and by measuring inhibition of isoproterenol-induced relaxation.

In the single-point study, substitution of the trifluoromethyl group of **1a** by hydrogen and methyl decreased both β_1 and β_2 pA_2 values with a tendency toward greater β_1 selectivity. Replacement of the *N-tert*-butyl group by cyclopropyl and 2-(3,4-dimethoxyphenyl)ethyl moieties induced a negative effect primarily on β_2 antagonism, thus providing a greater increase in β_1 selectivity.

Variation of both the 4-trifluoromethyl group with hydrogen and methyl and the *N-tert*-butyl substituent with cyclopropyl and 2-(3,4-dimethoxyphenyl)ethyl moieties resulted in a further increase in the cardioselectivity ratio. For example, compounds **7**, **8**, **16**, and **17** exhibited a separation between β_1 and β_2 affinities of 2.5 to 3.5 log units higher than that observed for **1a**. In these examples, the preference for the β_1- and β_2-receptors appeared to be reduced from that observed for the trifluoromethyl series. This reduction in potency was much more pronounced for the β_2-receptor pA_2 value.

In a similar SAR study for the 4-(2-thienyl) derivatives **1f**, **12** and **13** β_1 potency was not reduced by variation of the *N-tert*-butyl substituent but remained on the order of that observed for the 4-(trifluoromethyl)imidazole **1a**. However, the β_2 pA_2 values were depressed. The most interesting feature of this subclass was the approach toward absolute specificity for the β_1-receptor with the 2-(3,4-dimethoxyphenyl)ethyl derivative **13**. This effect was primarily due to a decreased pA_2 value for the β_2-receptor.

Several reports on known β-adrenoceptor antagonist[15–17] have demonstrated that the *S* enantiomers are more efficient at inhibiting the effects of isoproterenol stimulation. For this reason, the *S* isomers of **1b**, **8**, **12**, and **13** were prepared and evaluated. In this study (Table II), the *S* enantiomers exhibited similar pA_2 values comparable to the corresponding racemates. A more accurate system pA_2 via Schild plot was determined for (*S*)-**13**; a cardioselectivity ratio of 8709 was computed. In the Schild plot, the slope for the regression function was less than 1. However, the 95% confidence limits for the slope encompass 1, indicating competitive antagonism. The deviation from 1 occurred with concentration ratios above 20; at lower concentrations, the deviation was less pronounced. This property of the compound may be related to its unusually high lipid solubility. For these reasons, it is not yet possible to state unequivocally that the antagonism observed is competitive. For comparison, (*R*)-**13** was also synthesized and studied. In this example, both β_1 and β_2 pA_2 values for (*R*)-**13** were markedly reduced from that observed for **13** and (*S*)-**13**.

In the 4-(2-thienyl)imidazole series, the introduction of α-methyl substituents on the 2-phenylethyl side chain of **13**, as in examples **9** and **10**, resulted in compounds exhibiting high cardioselectivity. Replacement of the 2-(3,4-dimethoxyphenyl)ethyl group of **13** by cyclopropyl and isopropyl (examples **12** and **14**) increased affinity for the β_2-receptor,, with a resulting loss in cardioselectivity. Finally, removal of the 3,4-dimethoxy substituents of **13** provided compound **15**, which exhibited a diminution in the β_1 pA_2 value without a concomitant loss in affinity for the β_2-receptor. Thus, the 3,4-dimethoxy groups of **13** appear critical for β_1-receptor affinity. In a similar end-group study in the 1-amino-3-(*m*-tolyloxy)-2-propanol series,[8] this variation had no apparent effect on β_1 and β_2 potency as measured in vitro with atria and trachea from guinea pig against isoproterenol stimulation.

Compound (*S*)-**13** has been chosen for in-depth evaluation. The results of these studies will be published elsewhere.

Experimental Section

^1H NMR spectra were determined in the indicated solvent on a Varian T-60 or an EM390 spectrometer with tetramethylsilane as an internal standard. Optical rotation measurements were obtained on a Perkin-Elmer 141 polarimeter. Melting points were determined on a Thomas-Hoover apparatus, in open capillary tubes, and are uncorrected. Microanalyses are within 0.4% of

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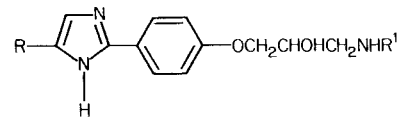
Table II. Comparative Pharmacology for Test Compounds and Standards with in Vitro pA_2 Values Obtained from Guinea Pig Tissue



compd	R	R¹	pA_2[e] β_1[a]	pA_2[e] β_2[b]	ratio[c]
(*S*)-1a	CF_3	$C(CH_3)_3$	9.05 ± 0.070 (8.88-9.22)	8.05 ± 0.029 (7.98-8.12)	10
1b	CF_3	c-C_3H_5	9.07 ± 0.102 (8.81-9.33)	6.84 ± 0.088 (6.64-7.04)	170
(*S*)-1b	CF_3	c-C_3H_5	8.72 ± 0.068 (8.56-8.88)	7.24 ± 0.071 (6.94-7.55)	30
1c	CF_3	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	8.27 ± 0.054 (8.14-8.40)	5.89 ± 0.058 (5.74-6.03)	240
1d	H	$C(CH_3)_3$	7.22 ± 0.068 (7.04-7.39)	6.21 ± 0.077 (6.03-6.39)	10
7	H	c-C_3H_5	6.17 ± 0.058 (6.03-6.31)	3.97 ± 0.055 (3.84-4.10)	158
8	H	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	7.97 ± 0.073 (7.78-8.16)	4.46 ± 0.047 (4.34-4.57)	3 236
(*S*)-8	H	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	7.68 ± 0.072 (7.50-7.85)	4.53 ± 0.072 (4.36-4.70)	1 412
1e	CH_3	$C(CH_3)_3$	7.22 ± 0.052 (7.09-7.35)	6.25 ± 0.032 (6.16-6.34)	9
16	CH_3	c-C_3H_5	7.22 ± 0.123 (6.93-7.52)	4.57 ± 0.077 (4.17-4.97)	447
17	CH_3	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	7.62 ± 0.058 (7.48-7.76)	3.73 ± 0.082 (3.33-4.13)	7 762
1f	2-C_4H_3S	$C(CH_3)_3$	8.80 ± 0.080 (8.60-9.01)	7.48 ± 0.088 (7.27-7.69)	21
12	2-C_4H_3S	c-C_3H_5	8.20 ± 0.070 (8.03-8.38)	5.60 ± 0.080 (5.20-6.00)	398
(*S*)-12	2-C_4H_3S	c-C_3H_5	8.21 ± 0.067 (8.05-8.37)	6.06 ± 0.086 (5.86-6.27)	141
14	2-C_4H_3S	$CH(CH_3)_2$	8.92 ± 0.061 (8.78-9.06)	6.88 ± 0.151 (6.39-7.36)	110
10	2-C_4H_3S	$C(CH_3)_2CH_2$-C_6H_3-3,4-$(OCH_3)_2$	8.04 ± 0.120 (7.73-8.34)	4.44 ± 0.075 (4.05-4.79)	3 981
9	2-C_4H_3S	$CH(CH_3)CH_2$-C_6H_3-3,4-$(OCH_3)_2$	8.22 ± 0.134 (7.88-8.57)	4.91 ± 0.058 (4.78-5.05)	2 042
13	2-C_4H_3S	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	8.36 ± 0.190 (7.96-8.76)	4.32 ± 0.077 (3.92-4.72)	10 965
(*S*)-13	2-C_4H_3S	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	9.07 ± 0.107[d] (8.86-9.28)	5.13 ± 0.187[d] (4.74-5.51)	8 709
(*R*)-13	2-C_4H_3S	CH_2CH_2-C_6H_3-3,4-$(OCH_3)_2$	7.27 ± 0.086 (6.87-7.67)	<3.5	>5 000
15	2-C_4H_3S	CH_2CH_2-C_6H_5	6.73 ± 0.110 (6.47-6.99)	4.34 ± 0.068 (4.18-4.51)	245
			Standards		
practolol			6.98 ± 0.028 (6.92-7.03)	5.35 ± 0.054 (5.22-5.48)	43
atenolol			7.62 ± 0.087 (7.41-7.83)	5.93 ± 0.027 (5.87-5.99)	49
metoprolol			7.83 ± 0.105 (7.58-8.08)	6.79 ± 0.040 (6.70-6.88)	11
betaxolol			8.76 ± 0.082 (8.56-8.95)	6.98 ± 0.044 (6.88-7.08)	60
propranolol			8.76 ± 0.138 (8.45-9.07)	8.52 ± 0.156 (8.15-8.87)	2
timolol			9.44 ± 0.074 (9.28-9.61)	9.62 ± 0.102 (9.38-9.86)	0.66

[a] β_1 pA_2 values were determined with guinea pig atria that have an enriched population of β_1-receptors. [b] β_2 pA_2 values were determined with guinea pig trachea that have an enriched population of β_2-receptors. [c] The cardioselectivity ratio was obtained by taking the antilog of ($pA_{2(\beta_1)} - pA_{2(\beta_2)}$). [d] System pA_2 values. [e] Mean plus or minus SEM. 95% confidence limits in parentheses.

theoretical values when indicated by symbols of the elements. Silica gel 60 (E. Merck, Darmstadt) was used for column chromatography. Organic solutions were dried over Na_2SO_4 and filtered, and the filtrates were concentrated to dryness on a Buchi rotary evaporator under water-aspirator pressure (20 mm).

Method A. The synthesis of **1b** is presented as an example of the synthetic method. Compound **1c** was prepared by using essentially the same procedure by substituting 2-(3,4-dimethoxyphenyl)ethylamine for cyclopropylamine.

2-[4-[3-(Cyclopropylamino)-2-hydroxypropoxy]phenyl]-4-(trifluoromethyl)imidazole (1b). A solution of 2-[4-(2,3-epoxypropoxy)phenyl]-4-(trifluoromethyl)imidazole[6] (4.0 g, 0.014 mol) and cyclopropylamine[18] (1.0 g, 0.018 mol) in CH_3CN (25 mL) was heated at reflux for two 3-h periods separated by 16 h at ambient temperature. The solution was then concentrated, and the residue was chromatographed on silica gel. The product was eluted with 10% CH_3OH–$CHCl_3$ and then recrystallized from $C_6H_5CH_3$–C_6H_{12} to yield 2.5 g (52%) of **1b**, mp 163.5–165 °C.

Method B. The preparation of **7** is presented as an example of the synthetic method. Compounds **8–10** and (*R*)-**13** were obtained by essentially the same procedure. The following amines were either obtained from commercial sources or by known literature procedures: 2-(3,4-dimethoxyphenyl)ethylamine,[18] 3-(3,4-dimethoxyphenyl)-2-propylamine,[19] and 3-(3,4-dimethoxyphenyl)-2-methyl-2-propylamine.[20]

3-[*p*-(2-Imidazolyl)phenoxy]-1,2-propanediol Acetonide (4a). A solution of **2a** (28 g, 0.23 mol) in DMF (150 mL) was added dropwise under N_2 at 70 °C to a suspension of NaH (60% oil dispersion, 10 g, 0.25 mol) in DMF (50 mL). After 15 min at 70 °C a solution of **3** (45.5 g, 0.22 mol) in DMF (50 mL) was added dropwise. After the solution was heated on a steam bath for 18 h, H_2O was added, and the solution was extracted with EtOAc (3 times). The combined extracts were washed with H_2O (2 times) and saturated NaCl, dried, and filtered, and the filtrate was concentrated. The residue was treated with CH_3OH (500 mL), 40% glyoxal (100 mL), and 28% concentrated NH_4OH (150 mL). After the mixture was stirred overnight at ambient temperature, the CH_3OH was removed under reduced pressure, H_2O was added to the residue and the solution was extracted with $CHCl_3$ (4 times). The combined extracts were dried and filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel, and the product was eluted with 10% CH_3OH–$CHCl_3$. The product was crystallized from toluene–ligroin to yield 13 g (22%) of **4a**: mp 148–150 °C; ^1H NMR (Me_2SO-d_6) δ 1.35 (6 H, d), 4.0 (5 H, m), 6.95 (2 H, d, J = 9 Hz), 7.05 (2 H, s), 7.8 (2 H, d, J = 9 Hz). Anal. ($C_{15}H_{18}N_2O_3$) C, H, N.

2-[*p*-[3-(Cyclopropylamino)-2-hydroxypropoxy]phenyl]-imidazole Dihydrochloride (7). A solution of **4a** (5.9 g, 0.022 mol) in 3 N HCl (45 mL) and acetone (45 mL) was heated at reflux. After 0.5 h, the acetone was removed under reduced pressure, and the resulting aqueous layer was basified, saturated with solid K_2CO_3, and filtered to yield 5.2 g (100%) of **5a**: mp 165.5–167 °C; ^1H NMR (Me_2SO-d_6) δ 3.5 (2 H, m), 3.9 (3 H, m), 6.65 (3 H, br s, exch), 6.95 (2 H, d, J = 9 Hz), 7.05 (2 H, s), 7.85 (2 H, d, J = 9 Hz).

A mixture of **5a** (15.2 g, 0.065 mol), C_5H_5N·HCl (8.2 g, 0.07 mol), and C_5H_5N (125 mL) was cooled to 0–4 °C and stirred while methanesulfonyl chloride (7.5 g, 0.065 mol) was added dropwise over 15 min. After the addition, the mixture was stirred at ambient temperature for 1.5 h, basified with K_2CO_3 (9.0 g, 0.065 mol) in H_2O (30 mL), and concentrated. The residue was triturated with a solution of K_2CO_3 (9.0 g) in H_2O (50 mL) and filtered, and the filtrate was dried to yield 18.3 g (90%) of mesylate. The product was suspended in CH_3OH (215 mL) and CH_2Cl_2 (215 mL), and the solution was cooled to 0–4 °C while a solution of $NaOCH_3$ (3.5 g, 0.065 mol) in CH_3OH (40 mL) was added over 10 min. After 1.5 h at 0–4 °C, H_2O (100 mL) was added, and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2, the combined organic extracts were dried and filtered, and the filtrate was concentrated to yield 10.3 g (73%) of **6a**: ^1H NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.7 (2 H, m), 3.25 (1 H, m), 4.1 (2 H, m), 6.9 (2 H, d, J = 9 Hz), 7.0 (2 H, s), 7.75 (2 H, d, J = 9 Hz).

A mixture of **6a** (4.95 g, 0.023 mol) in cyclopropylamine (50 mL) was heated at 60 °C. After 30 h, the mixture was concentrated, and the residue was chromatographed on silica gel. The product was eluted with 10% CH_3OH–$CHCl_3$ saturated with NH_3 to yield 1.2 g (19%) of free base **7**. The product was converted to the dihydrochloride salt with EtOH–HCl and crystallized from EtOH–MeOH–Et_2O to yield **7**: ^1H NMR (Me_2SO-d_6) δ 0.9 (4 H, m), 2.8 (1 H, m), 3.2 (2 H, m), 4.25 (3 H, m), 7.25 (2 H, d, J = 9 Hz), 7.75 (2 H, s), 8.35 (2 H, d, J = 9 Hz), 9.5 (2 H, br, exch).

Method C. The synthetic sequence used to prepare 2-[*p*-[3-(cyclopropylamino)-2-hydroxypropoxy]phenyl]-4-(2-thienyl)-imidazole dihydrochloride (**12**) is presented as an example of this method. Compounds **13–17** were obtained by essentially the same process. The use of 2-(3,4-dimethoxyphenyl)ethylamine, isopropylamine, and 2-phenylethylamine in place of cyclopropylamine yielded the oxazolidines **19b–d**. Use of chiral oxazolidines **19a** and **19b** yielded the chiral compounds (*S*)-**12** and (*S*)-**13**, respectively.

2-[*p*-[3-(Cyclopropylamino)-2-hydroxypropoxy]-phenyl]-4-(2-thienyl)imidazole Dihydrochloride (12). A solution of glycidol (50.0 g, 0.67 mol) in 2-propanol was added dropwise with stirring at 45 °C to a solution of cyclopropylamine (95.2 g, 1.67 mol) in 2-propanol (240 mL). After heating at 70 °C for 1.5 h, the solution was stirred at ambient temperature for 15 h and concentrated, and the residue was distilled at 116–119 °C at 1.6 mm to yield 88 g (79%) of **18a**: ^1H NMR ($CDCl_3$) δ 0.45 (4 H, m), 2.15 (1 H, m), 2.8 (2 H, m), 3.6 (6 H, m, 3 exch).

A mixture of **18a** (67 g, 0.52 mol), benzaldehyde (200 mL, 1.98 mol), benzoic acid (3 g), and toluene (110 mL) was heated at reflux for 3 h while collecting the azeotroped H_2O. The solution was then cooled, washed with saturated $NaHCO_3$ and saturated NaCl, dried, and filtered, and the filtrate was concentrated. The excess benzaldehyde was removed under high vacuum at 0.2 mm, and the product was distilled at 130–135 °C at 0.2 mm to yield 54 g (47%) of **19a**: ^1H NMR ($CDCl_3$) δ 0.3 (4 H, m), 1.95 (1 H, m), 2.85 (1 H, s, exch), 3.15 (2 H, m), 3.7 (2 H, m), 4.25 (1 H, m), 5.1 and 5.15 (1 H, 2 s), 7.15 (5 H, br s).

A mixture of **19a** (6.8 g, 0.03 mol) in C_5H_5N (12 mL) was cooled at 0–4 °C, and *p*-toluenesulfonyl chloride (5.9 g, 0.03 mol) was added portionwise while keeping the temperature below 25 °C. After 3 h at 25 °C, a cold solution of K_2CO_3 (4.3 g, 0.03 mL) in H_2O (25 mL) was added, and the mixture was extracted with $CHCl_3$ (3 times). The extracts were washed with H_2O, dried, and filtered, and the filtrate was concentrated first at 20-mm pressure and then at 1 mm while keeping the temperature below 50 °C to yield 11.3 g (97%) of **11a**: ^1H NMR ($CDCl_3$) δ 0.3 (4 H, m), 1.8 (1 H, m), 2.41 (3 H, s), 3.1 (2 H, m), 4.15 (3 H, m), 5.1 (1 H, s), 7.45 (9 H, m).

To a solution of **2b** (7.0 g, 0.03 mol) in DMF (50 mL) was added, under N_2 at 60 °C, NaH (50% oil dispersion, 1.4 g, 0.03 mol). After 0.5 h, a solution of **11a** (11.3 g, 0.03 mol) in DMF (45 mL) was added, and the mixture was heated at reflux for 16 h. The cooled reaction mixture was then poured into H_2O, and the solution was extracted with Et_2O (3 times). The combined organic layers were extracted with cold 1 N HCl (3 × 75 mL), the acid layer was added to NaOAc (18.5 g, 0.23 mol), and the solution was stirred at ambient temperature for 5 h.[21] The solution was extracted with Et_2O (2 times), basified with saturated Na_2CO_3, and extracted with 10% CH_3OH–$CHCl_3$ (3 times). The organic layers were dried and filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel, and the product was eluted with 5% CH_3OH–$CHCl_3$ saturated with NH_3 to yield 0.43 g (4%) of free base. The product was converted to the dihydrochloride salt (**12**) with EtOH–HCl: ^1H NMR (Me_2SO-d_6) δ 0.75 (4 H, m), 2.55 (2 H, m), 2.8 (1 H, br m), 3.2 (2 H, br m), 4.4 (4 H, m), 7.3 (3 H, dd), 7.75 (1 H, d, J = 4.5 Hz), 8.1 (2 H, s), 8.5 (2 H, d, J = 9 Hz), 9.5 (2 H, br s, exch).

The preparation of (*S*)-2-phenyl-3-[2-(3,4-dimethoxyphenyl)-ethyl]-5-(hydroxymethyl)oxazolidine *p*-toluenesulfonate (**11b**) is

(18) Commercially available from Aldrich Chemical Co.
(19) Shepard, E. R.; Noth, J. F.; Porter, H. D.; Simmans, C. K. *J. Am. Chem. Soc.* **1952**, *74*, 4611.
(20) Kober, J. *Szeged*; *Tanarkepso Foiskola Tud. Koz.* **1970**, 203; *Chem. Abstr.* **1970**, *77*, 151841*r*.
(21) Previous attempts to hydrolyze the oxazolidine intermediate were carried out in 1 N HCl, and gross mixtures were obtained. Utilization of dilute acetic acid to effect hydrolysis afforded **12**.

presented as an example. Use of cyclopropylamine in place of 2-(3,4-dimethoxyphenyl)ethylamine in this sequence yielded oxazolidine (*S*)-**11a**.

(*S*)-3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-1,2-propanediol (18b). To an ice cooled solution of **20** (128.7 g, 0.49 mol) in THF (650 mL) was added portionwise, with stirring, dry $Pb(OAc)_4$ (220 g, 0.5 mol) while maintaining the temperature below 10 °C. The solution was stirred for 30 min at 0–4 °C and then for 30 min at ambient temperature. The mixture was filtered through Super-Cel, the pad was washed with THF (500 mL), and the cooled yellow solution was treated with 2-(3,4-dimethoxyphenyl)ethylamine (331 g, 1.8 mol). After the addition, the thick suspension was stirred for 1 h at ambient temperature and then cooled to 0–4 °C, and a solution of $NaBH_4$ (38 g, 1 mol) in 4% NaOH (600 mL) was added with vigorous stirring while keeping the temperature below 10 °C. After the additon, the solution was stirred for 0.5 h at 0–4 °C and then for 1.5 h at ambient temperature, and then the pH was adjusted to 9.4 with solid NH_4Cl. The organic solvents were removed under reduced pressure, and the resulting solution was extracted with $CHCl_3$ (3 times). The combined extracts were dried and filtered, and the filtrate was concentrated. The residue was treated with cold 2 N HCl (1 L) and stirred at ambient temperature. After 18 h, the solution was neutralized with solid K_2CO_3 and extracted with EtOAc, and the extract was saturated with NaCl. The aqueous solution was then continuously extracted for 5 days with $CHCl_3$, and the organic layer was concentrated to yield 360 g of a mixture of starting amine and **18b**. The residue was chromatographed on silica gel and eluted first with 5% CH_3OH–$CHCl_3$ saturated with NH_3 to yield 138 g (90% recovery of excess starting amine) and then with 10% CH_3OH–$CHCl_3$ saturated with NH_3 to give 195 g (77%) of **18b**: trituration with hexane; mp 52–56 °C; $[\alpha]^{25}_D$ −16.5° (*c* 1.946, 1 N HCl); ^1H NMR ($CDCl_3$) δ 2.7 (6 H, m), 3.0 (3 H, br s), 3.6 (2 H, br s), 3.8 (7 H, 2 s, m), 6.7 (3 H, br s). Anal. ($C_{13}H_{21}NO_4$) C, H, N.

(*S*)-2-Phenyl-3-[2-(3,4-dimethoxyphenyl)ethyl]-5-(hydroxymethyl)oxazolidine *p*-Toluenesulfonate (11b). A solution of **18b** (195 g, 0.76 mol), benzoic acid (3.0 g), benzaldehyde (270 mL), and C_6H_6 (180 mL) was heated at reflux while collecting the azeotroped water. After 2.5 h, the theoretical amount of H_2O (13 mL) was collected, and the solution was cooled and washed with saturated Na_2CO_3. The aqueous layer was further extracted with $CHCl_3$, the combined $CHCl_3$ layers were dried and filtered, and the filtrate was concentrated first at 20-mm pressure and then a 1 mm to remove excess benzaldehyde to yield **19b** (205 g): ^1H NMR ($CDCl_3$) δ 2.6 (6 H, m), 3.4 (2 H, m), 3.75 (7 H, 2 s, m), 4.3 (1 H, m), 4.75 + 4.80 (1 H, 2 s), 6.7 (3 H, m), 7.4 (5 H, br s).

To a solution of **19b** (34.3 g, 0.1 mol) in C_5H_5N (45 mL) cooled to 0–5 °C was added portionwise *p*-toluenesulfonyl chloride (19.3, 0.1 mol) while maintaining the temperature below 30 °C. After 3 h at 0–5 °C, $CHCl_3$ was added, and the solution was washed with saturated Na_2CO_3. The aqueous layer was then extracted with $CHCl_3$ (2 times), the combined extracts were dried and filtered, and the filtrate was concentrated first at 20-mm pressure and then at 1 mm while keeping the temperature below 50 °C to yield 49.7 g (100%) of **11b**: ^1H NMR ($CDCl_3$) δ 2.35 (3 H, s), 2.55 (6 H, br s), 3.75 (3 H, s), 3.8 (3 H, s), 4.15 (3 H, m), 4.7 and 4.75 (1 H, 2 s), 6.65 (3 H, br s), 7.5 (9 H, m). The compound was used directly in the next step without further purification as described in method D.

Method D. The synthesis of (*S*)-**8** is presented as an example of the synthetic method. Reaction of **2a** with (*S*)-**11a** yielded (*S*)-*p*-[3-(cyclopropylamino)-2-hydroxypropoxy]benzaldehyde (**22**). Imidazole formation utilizing trifluoromethylglyoxal[7] with **22** yielded compound (*S*)-**1b** in essentially the same manner.

(*S*)-2-[*p*-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]imidazole Dihydrochloride (8). To a suspension of NaH (60% oil dispersion, 1.2 g, 0.07 mol) in DMF (20 mL) was added at 70 °C under N_2 a solution of **2a** (3.7 g, 0.03 mL) in DMF (30 mL). After the mixture was stirred for 15 min at 70 °C, a solution of (*S*)-**11b** in DMF (50 mL) was added dropwise. After the addition, the mixture was heated at 120 °C for 18 h. The solution was then poured into H_2O and extracted with EtOAc (3 times). The organic extracts were washed with H_2O (2 times) and saturated NaCl (1 time), dried, and filtered, and the filtrate was concentrated. The residue was treated with H_2O (250 mL) and AcOH (25 mL) and stirred overnight at room temperature. The solution was extracted with EtOAc (2 times), neutralized with saturated Na_2CO_3, and extracted with $CHCl_3$ (4 times). The organic extracts were dried and filtered, and the filtrate was concentrated to yield 8.5 g of **21**: ^1H NMR ($CDCl_3$) δ 2.7 (6 H, m), 3.75 (3 H, s), 3.85 (3 H, s), 4.1 (3 H, m), 6.7 (3 H, br s), 6.95 (2 H, d, *J* = 9 Hz), 7.75 (2 H, d, *J* = 9 Hz).

A mixture of **21** (8.5 g, 0.024 mol), CH_3OH (50 mL), 40% aqueous glyoxal (10 mL, 0.07 mol), and 28% concentrated aqueous NH_3 (15 mL) was allowed to stir at ambient temperature. After 18 h, the CH_3OH was removed under reduced pressure, and H_2O was added. The resulting aqueous layer was extracted with $CHCl_3$ (4 times), the organic layer was dried and filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel, and the product was eluted with 2% CH_3OH–$CHCl_3$ saturated with NH_3 to yield 3.0 g of free base. The material was converted to the dihydrochloride salt with HCl–EtOH to yield 1.3 g (11%) of (*S*)-**8**: $[\alpha]^{25}_D$ −6.94° (*c* 0.562, H_2O); ^1H NMR (Me_2SO-d_6) δ 3.2 (6 H, m), 3.75 (3 H, s), 3.85 (3 H, s), 4.2 (3 H, m), 6.9 (3 H, m), 7.25 (2 H, d, *J* = 9 Hz), 7.75 (2 H, s), 8.35 (2 H, d, *J* = 9 Hz), 9.35 (2 H, br s, exch).

Pharmacology. To determine in vitro β_1-adrenoceptor activity, female Duncan–Hartley guinea pigs (200–300 g body weight) were killed by cervical dislocation. The extirpated hearts were placed in warm Krebs buffer solution, and the left and right intact atria were isolated from the ventricles and major blood vessels. The left atrium was sutured to a glass mounting rod, and the right atrium was attached to the force-displacement transducer. The preparations were set up in water-jacketed, 10-mL, isolated tissue baths with a modified Krebs buffer (pH 7.2, mM): NaCl, 106.1; KCl, 4.63; $CaCl_2$, 2.51; $MgSO_4$, 1.2; NaH_2PO_4, 0.88; $NaHCO_3$, 11.9; Dextrose, 5.6; and ascorbic acid, 0.051. The temperature of the baths was maintained at 37 °C, and the buffer was continuously aerated with 95% O_2 and 5% CO_2. The initial tension of 1 g was applied to the atria following their attachment to the force transducer. The tissues were washed at 0 and 15 min. Fifteen minutes after the second wash, isoproterenol was added to the bath. Seven cumulative doses were given at 1-min intervals in volumes of 0.1 mL each. At the end of the first concentration–response, the tissues were washed at 0 and 15 min and allowed to recover for 30 min, at which time the isoproterenol concentration–response series was repeated. The atria were again washed, and the antagonist being tested was added to the bath at 0 and 15 min with a wash in between. At the end of 30 min, isoproterenol was added to the bath but at 5 times the original series concentration; i.e., instead of 1×10^{-9} M, it was added at 5×10^{-9} M in the presence of the antagonist.

For the determination of in vitro β_2-adrenoceptor blockade, female Duncan–Hartley guinea pigs (200–400 g body weight) were also used. They were killed by a blow to the head, and the trachea was excised and placed in a petri dish containing normal saline. The extraneous tissue was trimmed away, and the tracheal tube was cut lengthwise through the cartilage opposite the line of smooth muscle. Segments of trachea were cut approximately 2 to 3-mm wide. One segment from each of the four guinea pigs per assay was used in each tracheal chain. Segments were placed end to end and tied securely taking care not to tie any of the smooth muscle in the knots. One end of the chain was attached to a glass tissue holder and the other end to a force displacement transducer. The tracheal chains were then placed in 10-mL, water-jacketed organ baths containing a modified Krebs buffer solution at 37 °C containing (mM): NaCl, 106.1; KCl, 4.63; $CaCl_2$, 1.89; $MgSO_4$, 1.16; NaH_2PO_4, 1.0; $NaHCO_3$ 25.0; dextrose, 11.1; ascorbic acid, 0.051; indomethacin, 0.0014; and $PGF_{2\alpha}$, 0.0014. The baths were constantly aerated with 95% O_2 and 5% CO_2. An initial 2.0-g tension was applied to each of the chains for exactly 5 min, after which the tension was lowered to 1.0 g. The chains were washed several times and allowed to stabilize for 60 min. After the chains had gained a degree of tension over the 60-min period, cumulative concentrations of the agonist (isoproterenol) were added to the baths at 5-min intervals. After the concentration-response curve was established, the tracheal chains were washed and then washed again 15 min later and allowed to stabilize for a total time of 30 mins. The concentration-response curve was repeated, the tissues were washed, and the antagonist was added to the bath. The chains were washed after 15-min

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.

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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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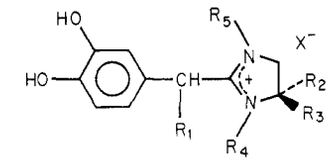
The optical isomers and deoxy form of 2-(3,4,α-trihydroxybenzyl)imidazoline hydrochloride were examined for their α-adrenergic activity on rat aorta. The rank order of stimulant activity was deoxy (**2**) ≃ (*R*)-(−)-**1** > (*S*)-(+)-**1**. This is in contrast to catecholamines in which the order of 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^-

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