mixed with 1.1 mmol of the acyl halide. The mixture was stirred at 25 °C for 2–4 h, after which time the crude product was precipitated by addition of Et_2O (50 mL) and collected. The crude salt either was purified directly by crystallization (*i*-PrOH–Et_2O or THF–Et_2O) or it was converted to the base for chromatographic purification (silica gel, 3% MeOH–$CHCl_3$). The product obtained from chromatographic purification was dissolved in dry THF and converted to the salt with HCl–Et_2O or HBr–Et_2O.

Method D. 3-Acetoxy-17-(pyrrole-2,5-dion-1-ylphenalkyl)morphinan (34–38). A mixture of the product obtained from method B (1.0 mmol) and maleic anhydride (1.2 mmol) was refluxed in THF (5 mL) for 2 h, cooled to 25 °C, and diluted with Et_2O. The crude maleamic acid which precipitated was collected by filtration, suspended in 2% NaOAc–Ac_2O (10 mL), and refluxed for 2 h. The solvent was removed in vacuo and the residue was partitioned between $CHCl_3$ and 10% $NaHCO_3$. After separation of the organic layer and removal of the $CHCl_3$ in vacuo, the residue was chromatographed on silica gel (3% MeOH–$CHCl_3$). The product was dissolved in dry THF and converted to the HCl salt with HCl–Et_2O.

Method E. 3-Hydroxy-17-(pyrrole-2,5-dion-1-ylphenalkyl)morphinan (39–42). A methanolic solution (25 mL) containing 1.0 mmol of the acetoxymaleimide hydrochloride and a catalytic amount of *p*-toluenesulfonic acid was refluxed for 0.5–4 h with monitoring by TLC. When the starting material had been consumed, the mixture was treated with $NaHCO_3$ (1.5 mmol) and the solvent was removed in vacuo. After the residue was partitioned between $CHCl_3$ and water, the organic phase was separated and dried (anhydrous Na_2SO_4), and the solvent was removed. The crude product then was chromatographed (silica gel, 5% MeOH–$CHCl_3$) and converted to the HCl salt by addition of HCl–Et_2O to a THF solution of the product.

Pharmacology. Male Swiss–Webster mice (Sasco or Biolab) weighing 20–25 g were used in all experiments. The test compounds were dissolved in 40% propylene glycol and the final concentration was made so that 10 mL/kg was injected sc at each dose level. Analgesic activity was determined by the method of D'Amour and Smith[17] which was modified for the mouse.[18] The ED_{50} values and the 95% confidence limits were estimated by the method of Litchfield and Wilcoxon.[19]

Inhibition of the binding of [^{3}H]naloxone to putative opiate receptors was determined by the method of Pert and Snyder[21] as modified by Pasternak et al.[20] The procedure included the preincubation step prior to the binding assay. Stereospecificity of the binding was determined by incubation with and without 1×10^{-6} M levallorphan. The concentration of [^{3}H]naloxone used was 1.5×10^{-9} M. The binding was also performed in the absence and presence of 100 mM NaCl in an attempt to discriminate the degree of agonistic and antagonistic properties contained in the drug.[8] The single-dose suppression test in morphine-dependent mice was carried out by the method of Takemori et al.[22]

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An Approach to Peripheral Vasodilator–β-Adrenergic Blocking Agents

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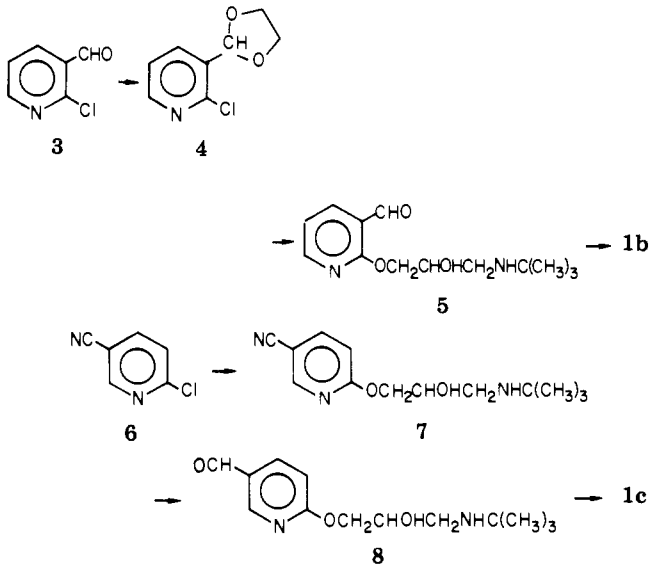
The syntheses of 2-phenyl- and 2-pyridyl-4-trifluoromethylimidazoles having a 3-*tert*-butylamino-2-hydroxypropoxy moiety attached to the aryl or heteroaryl substituent are described. Structure–activity relationships based on results from an evaluation of these compounds for antihypertensive, vasodilating, and β-adrenergic blocking activities are discussed.

Peripheral vasodilator drugs are of growing interest as agents for the treatment of moderate to severe hypertension.[1,2] Members of this class include sodium nitroprusside,[3,4] hydralazine,[5] diazoxide,[6] and minoxidil;[7] such agents lower blood pressure by decreasing peripheral resistance through direct action on the vascular smooth

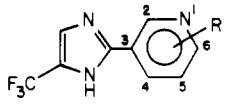
Scheme I



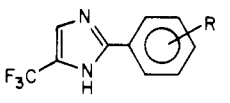
muscle. Clinical problems commonly associated with vasodilator therapy include tachycardia and fluid retention. These side effects may be attenuated by the concomitant administration of β-adrenergic blocking agents and diuretics.[8,9]

In an effort to overcome the tachycardia liability, we have incorporated functionality capable of conferring β-adrenergic blocking activity into a class of peripheral vasodilators. The class chosen for this study was the 2-aryl-4-trifluoromethylimidazoles.[10] These compounds have already been reported to possess xanthine oxidase inhibitory activity;[10] in this communication we report that several members of this series are also potent peripheral vasodilator–antihypertensive agents. The most active compound was found to be 2-(3-pyridyl)-4-trifluoromethylimidazole (**1a**). This compound, at 1 mg/kg orally, lowered the blood pressure of spontaneous hypertensive (SH) rats an average of 25 mmHg; when administered to renal hypertensive dogs at 4–16 mg/kg, the resulting decrease in blood pressure was associated with a reflex elevation in heart rate (+82 beats/min).

In order to attenuate the reflex tachycardia which was observed in laboratory animals, a β-adrenergic blocking side chain of the alkylaminohydroxypropoxy type was incorporated into **1a** and the 2-phenyl analogue **2a**.



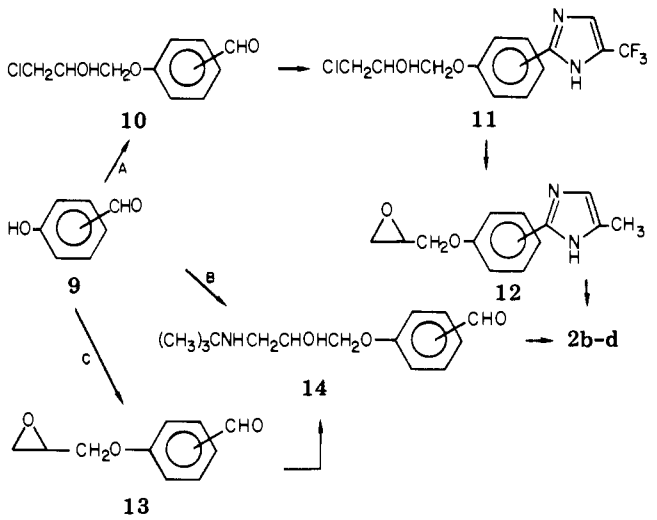
1a, R = H
b, R = 2-[$OCH_2CHOHCH_2NHC(CH_3)_3$]
c, R = 6-[$OCH_2CHOHCH_2NHC(CH_3)_3$]



2a, R = H
b, R = 2-[$OCH_2CHOHCH_2NHC(CH_3)_3$]
c, R = 3-[$OCH_2CHOHCH_2NHC(CH_3)_3$]
d, R = 4-[$OCH_2CHOHCH_2NHC(CH_3)_3$]

Chemistry. The pyridyl derivatives **1b** and **1c** were prepared as outlined in Scheme I. The aminohydroxypropoxy side chain was introduced through reaction of 2-chloronicotinaldehyde,[11] protected as the ketal **4**, with 2-phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine derived from mannitol according to the method of Weinstock.[12] Deprotection followed by condensation of **5** with ammonia and trifluoromethylglyoxal, generated from dibromotrifluoroacetone, yielded **1b** as the *S* isomer. Similarly, reaction of 6-chloronicotinonitrile[13] with the hydroxymethyloxazolidine gave **7** after mild acid hydrolysis. Reduction of the cyano group with diisobutylaluminum hydride yielded the aldehyde **8** which was converted to the trifluoromethylimidazole **1c**, having the *S* configuration.

Scheme II



The three aryl derivatives, **2b–d**, were prepared as illustrated in Scheme II. The ortho isomer **2b** was prepared by method C, the meta isomer **2c** by method A, and the para isomer **2d** by methods A–C. Methods A and C are similar to syntheses of other 1-amino-3-aryloxy-2-propanols in that a 1,2-epoxy-3-aryloxypropane is treated with an amine to generate the β-blocking side chain racemic around the chiral center. In method B the tosylate of 2-phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine was used to introduce the side chain intact and in optically pure form. Synthesis of **2d** in the *S* configuration was achieved through use of the oxazolidine derived from (*R*)-glyceraldehyde as described by Weinstock.[12] Synthesis of **2d** in the *R* configuration was achieved through use of the oxazolidine derived from (*R*)-3-*tert*-butylamino-1,2-propanediol obtained by resolution of the racemic glycolamine.[14] In the syntheses of (*R*)-**2d** and (*S*)-**2d** optical purity was determined on the intermediate para-substituted benzaldehyde **14** by NMR spectroscopy using the chiral shift reagent tris(3-heptafluorobutyryl-*d*-camphorato)europium(III). In the spectrum of the racemate, two peaks separated by 6 Hz were observed for the aldehyde proton; in the optically pure isomers only one was seen. By this method, optical purity was determined to be 99 ± 1%.

Discussion

The preliminary pharmacological data on the compounds prepared during this study are summarized in Table I. The results of blood flow studies in anesthetized dogs suggested that peripheral vasodilating activity may be involved in the mechanism of the antihypertensive activity of 2-(3-pyridyl)-4-trifluoromethylimidazole (**1a**). The introduction of an aminohydroxypropoxy side chain into the 2 position of the pyridine ring as in **1b** resulted in a substantial reduction of both antihypertensive activity in the rat and peripheral vascular effects in the dog with the introduction of only modest β-adrenergic blocking activity. When the side chain was introduced para to the trifluoromethylimidazolyl moiety as in **1c**, antihypertensive

Table I. Comparative Cardiovascular Effects of Compounds on Arterial Pressure of Spontaneously Hypertensive Rats and on Iliac Blood Flow and β-Adrenergic Blockade in Anesthetized Dogs

	Activity in SH rat					Activity in anesthetized dogs								
						Increase in iliac blood flow, mL/min ± SE						Blockade of isoproterenol-induced hypotension and tachycardia		
									After timolol dose, μg/kg iv[a]				Estd ED_{50}, μg/kg iv[d]	
Compd no.	Dose, mg/kg	Route[c]	No. of SHR	Max fall, mmHg ± SE in MAP	Duration (h) of effect	No. of dogs	Dose, μg ia[b]	Before timolol	320	800	2000	No. of dogs	MAP[f]	HR[g]
1a	1	po	7	21 ± 4	2	3	800	108 ± 20	99 ± 14					
	2	po	4	39 ± 6	6								NT[e]	NT
	8	po	8	48 ± 3	>6	3	800	93 ± 20		76 ± 17				
1b	20	ip	4	8–10		1	1600	4			9	1	125	250
	20	po	2	6–10										
1c	20	ip	2	40	>7	6	1600	103 ± 22		38 ± 11		3	58	2.5
	20	po	2	0										
2b	20	ip	2	32	<7	3	1600	35 ± 9			33 ± 4	2	100	300
	20	po	2	0										
2c	20	ip	1	40	>7		NT	NT				1	86	>1000
	20	po	2	5–10										
(*RS*)-2d	0.312	po	4	21 ± 4	7	5	8	52 ± 5			10 ± 7	4	36	9
	1.25	po	5	36 ± 8	18	5	16	58 ± 8			17 ± 7		(28–46)	(6–11)
	5	po	5	49 ± 8	18	5	32	63 ± 6			17 ± 7			
						3	1600	89 ± 8			15 ± 4			
(*R*)-2d	1.25	po	4	16 ± 3	2		NT	NT				4	>1000	102
	5	po	4	22 ± 4	6									(82–159)
	20	po	4	49 ± 3	8									
(*S*)-2d	0.312	po	6	24 ± 6	12–18	2	60	5			NT	4	38	7.6
	1.25	po	4	40 ± 6	18–24								(31–50)	(5–10)
	5	po	4	56 ± 9	>24									
Hydralazine	0.5	po	4	15 ± 5	4	3	400	78 ± 12			NT	NT	NT	NT
	1	po	6	30 ± 5	6	3	1600	66 ± 14						
	2	po	4	40 ± 3	>7	3	3200	53 ± 9						

[a] iv = intravenous administration. [b] ia = intraarterial administration. [c] ip = intraperitoneal administration. po = per os. [d] 95% confidence limits are given in parentheses. [e] NT = not tested. [f] MAP = mean arterial pressure. [g] HR = heart rate.

activity was retained in the SH rat and vasodilating activity was observed in the dog. This vasodilating activity was only partly attenuated by the prior administration of the potent β-adrenergic blocking agent, timolol, thus indicating that part, but not all, of the vasodilating activity could be attributed to intrinsic β-sympathomimetic activity. The doses of timolol employed in these experiments produced complete β-adrenergic blockade (see methods in the Experimental Section). It should also be pointed out that since the compounds were administered intraarterially, systemic changes in heart rate were not always observed. It was therefore not possible to determine whether timolol would also reduce in a parallel manner the effects of these compounds on heart rate. The profile of the β-adrenergic blocking activity of **1c** suggested that it was cardioselective; that is, this compound was more potent in blocking the β_1 receptors of the heart than the β_2 receptors of the peripheral tissue.

A similar structure–activity relationship was seen with the 2-aryl derivatives **2b–d**. The ortho and meta isomers **2b,c** were much less active as antihypertensive, vasodilating, and β-adrenergic blocking agents than the para isomer **2d**. The racemate, (*RS*)-**2d**, and the *S* isomer, (*S*)-**2d**, lowered blood pressure 25 mmHg or more at doses of 0.1 mg/kg po while (*R*)-**2d** was inactive at doses less than 20 mg/kg. As with **1c**, only a portion of the vasodilating activity observed with (*RS*)-**2d** could be ascribed to intrinsic β-agonist activity. That portion of the vasodilation not blocked by prior treatment with timolol is believed to be due to nonspecific relaxation of resistance vessels. The β-adrenergic blocking activity of (*RS*)-**2d** was due to the *S* enantiomorph as seen by the relative inactivity shown by (*R*)-**2d** as compared to (*S*)-**2d**. Cardioselectivity was seen in the β-adrenolytic activity with (*S*)-**2d**; this compound was six times more effective in blocking the cardiac β_1 receptors than the vascular β_2 receptors.

The finding that β-adrenergic blocking activity could be introduced into vasodilators of the 2-aryl-4-trifluoromethylimidazole class has encouraged further work in this area and in-depth pharmacological studies are being performed to establish the utility of these compounds as antihypertensive agents.

Experimental Section

Spectral data were obtained with the following instruments: IR, Perkin-Elmer Models 137 and 257 infrared spectrophotometers; NMR, Varian A-60 and T-60 using tetramethylsilane as internal standard; mass spectra, AEI MS-902; optical rotation measurements, Perkin-Elmer 141 polarimeter. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses are within 0.4% of theoretical values when indicated by symbols of the elements. Silica gel 60 (E. Merck, Darmstadt) and aluminum oxide 90 (of activity grade II, E. Merck, Darmstadt) were used for column chromatography. Concentrations of solutions were accomplished using a Büchi rotary evaporator under water aspirator pressure (20 mm).

2-Chloro-3-pyridinecarboxaldehyde Ethylene Acetal (4). A solution of **3**[11] (3.3 g, 0.023 mol), ethylene glycol (2 mL), *p*-toluenesulfonic acid (0.1 g), and C_6H_6 (30 mL) was refluxed under N_2 for 20 h with removal of H_2O in a Dean-Stark trap. The mixture was cooled, washed with saturated Na_2CO_3 solution, dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to yield a solid. The residue was triturated with C_6H_{14} and filtered to give **4** (4.0 g, 94%), mp 55–56 °C. This material was used in the next step without further purification.

(*S*)-3-Formyl-2-(3-*tert*-butylamino-2-hydroxypropoxy)pyridine (5). A stirred suspension of 57% NaH in mineral oil (1.0 g, 0.024 mol) in DMF (20 mL) was treated under N_2 with (*S*)-2-phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine (4.7 g, 0.02 mol). The mixture was stirred until H_2 evolution ceased (1 h), treated with **4** (4.0 g, 0.02 mol), and heated at 80 °C for 1 h. The mixture was cooled, poured onto ice, and extracted with Et_2O. The Et_2O extracts were washed with H_2O (2 × 20 mL) and then extracted with 1.2 N HCl (2 × 20 mL) and H_2O (20 mL). The combined aqueous extracts were heated on a steam bath for 0.5 h and then stirred at room temperature. After 16 h, the mixture was extracted with C_6H_6, basified with saturated Na_2CO_3 solution to pH 10, and extracted with EtOAc. The combined EtOAc extracts were washed with 50% saturated Na_2CO_3 solution, dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to yield **5** (4.9 g, 98%). The crude product was recrystallized from *i*-PrOH containing maleic acid to yield the hydrogen maleate salt of **5**, mp 170–171 °C. Anal. ($C_{13}H_{20}N_2O_3 \cdot C_4H_4O_4$) C, H, N.

(*S*)-2-[2-(3-*tert*-Butylamino-2-hydroxypropoxy)-3-pyridyl]-4-trifluoromethylimidazole (1b). To $NaOAc \cdot 3H_2O$ (2.8 g, 0.02 mol) in H_2O (20 mL) was added 1,1-dibromo-3,3,3-trifluoroacetone[16] (2.8 g, 0.01 mol) and the resulting mixture heated on a steam bath for 20 min. After cooling, the solution was added to **5** (1.7 g, 0.007 mol) in MeOH (50 mL), CH_2Cl_2 (50 mL), and concentrated NH_4OH (20 mL). The resulting two-phase system was stirred overnight at room temperature, the MeOH and CH_2Cl_2 were removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were extracted with saturated Na_2CO_3 (10 mL), dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The residue was chromatographed on alumina (100 g, E. Merck acid washed) and the product eluted with 1% MeOH–$CHCl_3$. The product was recrystallized from H_3CCN containing maleic acid to give the hydrogen maleate salt of **1b** (1.0 g, 31%), mp 180 °C. Anal. ($C_{16}H_{21}F_3N_4O_2 \cdot C_4H_4O_4$) C, H, N.

(*S*)-2-(3-*tert*-Butylamino-2-hydroxypropoxy)-5-cyanopyridine (7). To (*S*)-2-phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine (9.4 g, 0.04 mol) in DMF (50 mL) was added 57% NaH in mineral oil (1.7 g, 0.04 mol). The mixture was stirred at room temperature for 15 min, heated for 0.5 h on a steam bath, and then allowed to cool to room temperature. A solution of **6**[13] (6.9 g, 0.05 mol) in DMF (30 mL) was added and the mixture stirred at room temperature. After 17 h, the solvent was removed under reduced pressure and the residue treated with H_2O (10 mL) and C_6H_{14} (10 mL). A solid separated and was filtered. Recrystallization from C_6H_{14} yielded 5 g of (*S*)-2-phenyl-3-*tert*-butyl-5-(5-cyano-2-pyridyloxymethyl)oxazolidine which was used without purification in the next step.

A solution of (*S*)-2-phenyl-3-*tert*-butyl-5-(5-cyano-2-pyridyloxymethyl)oxazolidine (3 g, 0.0089 mol) in 1 N HCl (15 mL) was warmed on a steam bath for 5 min and then stirred at room temperature for 0.5 h. The solution was extracted with $CHCl_3$; the aqueous layer was separated and adjusted to pH 10 with 40% NaOH solution. The mixture was extracted with $CHCl_3$; the $CHCl_3$ extract was dried over Na_2SO_4 and concentrated under reduced pressure to an oil which was recrystallized from C_6H_{14} to yield **7** (1.4 g, 63%), mp 105–106 °C. Anal. ($C_{13}H_{19}N_3O_2$) C, H, N.

(*S*)-6-(3-*tert*-Butylamino-2-hydroxypropoxy)nicotinaldehyde (8). A solution of **7** (1.2 g, 0.005 mol) in $C_6H_5CH_3$ (30 mL) was heated to reflux and 5 mL of solvent removed by distillation. The solution was cooled in a dry ice–acetone bath and diisobutylaluminum hydride (25.3% in $C_6H_5CH_3$, 0.0175 mol) was added dropwise with stirring under N_2. After stirring for 1 h, MeOH (5 drops) and H_2O (5 drops) were added. The mixture was allowed to warm to room temperature, H_2O (10 mL) was added, and the resulting mixture was extracted with $CHCl_3$. The organic extract was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was suspended in 10% HCl (10 mL) and warmed on a steam bath for 0.5 h. The solution was adjusted to pH 10 with NaOH solution and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield **8** (0.8 g, 63%) which was used in the next step without further purification.

(*S*)-2-[2-(3-*tert*-Butylamino-2-hydroxypropoxy)-5-pyridyl]-4-trifluoromethylimidazole (1c). To a solution of $NaOAc \cdot 3H_2O$ (2.16 g, 0.016 mol) in H_2O (15 mL) was added 1,1-dibromo-3,3,3-trifluoroacetone[16] (2.16 g, 0.008 mol) and the mixture heated for 0.5 h on a steam bath. After cooling, the solution was added to **8** (1 g, 0.0040 mol) in MeOH (50 mL) and concentrated NH_4OH (15 mL). After standing 20 h at room

temperature, the MeOH was removed under reduced pressure. Saturated Na_2CO_3 solution (10 mL) and EtOAc (50 mL) were added to the residue. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on alumina and the product eluted with $CHCl_3$–MeOH using a gradient elution technique. The fractions containing product were combined and concentrated; the residue was dissolved in EtOAc and the solution washed with saturated Na_2CO_3 solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting residue was recrystallized from C_6H_6–C_6H_{14} to yield **1c** (0.65 g, 43%) as the monohydrate, mp 110–120 °C. Anal. ($C_{16}H_{21}F_3N_4O_2 \cdot H_2O$) C, H, N.

Preparation of 2-[4-(3-*tert*-Butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole (2d). Method A. 2-[4-(3-Chloro-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole (11). To $NaOAc \cdot 3H_2O$ (5.8 g, 0.044 mol) in H_2O (20 mL) was added 1,1-dibromo-3,3,3-trifluoroacetone[16] (5.8 g, 0.022 mol) and the resulting mixture heated on a steam bath for 0.5 h. After cooling, the solution was added to *p*-**10**[17] (4.2 g, 0.02 mol) in MeOH (100 mL) and concentrated NH_4OH (25 mL). After standing at room temperature for 4.5 h, the MeOH was removed under reduced pressure, and the solid which separated was filtered off and recrystallized from H_3CNO_2 to yield **11** (1.65 g, 26%), mp 181–183 °C. Anal. ($C_{13}H_{12}ClF_3N_2O_2$) C, H, N.

2-[4-(2,3-Epoxypropoxy)phenyl]-4-trifluoromethylimidazole (12). To a solution of **11** (1.92 g, 0.006 mol) in MeOH (100 mL) was added crushed KOH (1.5 g, 0.032 mol) and the mixture stirred at room temperature. After 3 h, the reaction was neutralized with AcOH and concentrated under reduced pressure. The residue was triturated with H_2O (25 mL), filtered, and recrystallized from C_6H_6–C_6H_{14} to yield **12** (1.2 g, 68%), mp 152–153.5 °C.

2-[4-(3-*tert*-Butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole (2d). A solution of **12** (2.5 g, 0.0085 mol) in *tert*-butylamine (20 mL) was heated at reflux for 6 h. The excess *tert*-butylamine was removed by distillation at atmospheric pressure. The residue was triturated with H_3CNO_2 (5 mL) and the resulting solid removed by filtration. Recrystallization from H_3CCN yielded **2d** (1.2 g, 38%), mp 185.5–186.5 °C. Anal. ($C_{17}H_{22}F_3N_3O_2$) C, H, N.

The meta isomer **2c** was prepared by essentially the same procedure in 54% yield utilizing 3-(2,3-epoxypropoxy)benzaldehyde.[18] After recrystallization from H_3CNO_2, **2c** melted at 139–141 °C. Anal. ($C_{17}H_{22}F_3N_3O_2$) C, H, N.

Preparation of (*S*)-2-[4-(3-*tert*-Butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole [(*S*)-2d]. Method B. (*S*)-4-(3-*tert*-Butylamino-2-hydroxypropoxy)benzaldehyde (14). To a solution of (*S*)-2-phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine (47 g, 0.2 mol) in C_5H_5N (75 mL) was added portionwise *p*-toluenesulfonyl chloride while maintaining the internal temperature between 25 and 30 °C. After completion of the addition, the mixture was maintained at 25–30 °C. After 2 h, a cold solution of K_2CO_3 (27.6 g, 0.2 mol) in H_2O (150 mL) was added and the mixture extracted with $CHCl_3$ (3 × 100 mL). The organic extracts were dried over Na_2SO_4, filtered, and first concentrated under 20 mm of pressure and then at 1 mm while keeping the temperature below 50 °C. The residual oil was dissolved in DMF (100 mL) and added dropwise to a refluxing solution of the sodium salt of *p*-hydroxybenzaldehyde **9** (24.4 g, 0.2 mol) in DMF (200 mL). After refluxing for 10 h, the reaction mixture was concentrated first at 20 mm and then at 1 mm. The residue was treated with 5% NaOH solution and extracted with $CHCl_3$. The organic extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on alumina (500 g) and the product eluted with $CHCl_3$. The crude oil was distilled at 240 °C (0.3 mm) and the distillate (21 g) treated with 1 N HCl (75 mL). The mixture was heated on a steam bath for 0.5 h, cooled, and extracted with Et_2O (2 × 75 mL). The aqueous layer was made basic by the addition of 20% NaOH solution and extracted with $CHCl_3$. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residue was recrystallized from C_6H_{14} to yield the para isomer of (*S*)-**14** (14.5 g, 29%), mp 60–62 °C.

(*S*)-2-[4-(3-*tert*-Butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole (2d). To $NaOAc \cdot 3H_2O$ (20.2 g, 0.15 mol) in H_2O (100 mL) was added 1,1-dibromo-3,3,3-trifluoroacetone[16] (20.2 g, 0.075 mol) and the resulting mixture heated on a steam bath for 0.75 h. After cooling, the solution was added to the *S* isomer of *p*-**14** (12.5 g, 0.05 mol) in MeOH (200 mL) and concentrated NH_4OH (75 mL). After standing for 5 h at room temperature, the MeOH was removed under reduced pressure. The mixture was made basic with saturated Na_2CO_3 solution and extracted with EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was recrystallized from H_3CCN to yield (*S*)-**2d** (7.6 g, 41%), mp 182–183 °C. Anal. ($C_{17}H_{22}F_3N_3O_2$) C, H, N.

The *R* isomer, (*R*)-**2d**, was prepared by the same procedure in 56% yield, starting with (*R*)-2-phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine prepared from (*R*)-glycolamine.[14] After recrystallization from H_3CCN (*R*)-**2d** melted at 182–183 °C. Anal. ($C_{17}H_{22}F_3N_3O_2$) C, H, N.

Preparation of 2-[4-(3-*tert*-Butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole (2d). Method C. 3-*tert*-Butylamino-1-(4-formylphenoxy)-2-propanol (14). To 4-(2,3-epoxypropoxy)benzaldehyde[18] (20 g, 0.11 mol) was added *tert*-butylamine (50 mL) and the resulting solution was heated 17 h at reflux. The excess *tert*-butylamine was removed at atmospheric pressure to yield a solid residue. To this residue was added 6 N HCl (200 mL) and the reaction mixture heated 5 h at steam bath temperature. The solution was cooled and concentrated to 100 mL under reduced pressure. The concentrated solution was made basic with saturated Na_2CO_3 solution and extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated under reduced pressure to a solid which after recrystallization from H_3CCN yielded 3-*tert*-butylamino-1-(4-formylphenoxy)-2-propanol (**14**) (18 g, 61%), mp 123–125 °C. Anal. ($C_{14}H_{21}NO_3$) C, H, N.

3-*tert*-Butylamino-1-(2-formylphenoxy)-2-propanol was prepared by the same procedure utilizing 2-(2,3-epoxypropoxy)-benzaldehyde.[18] The crude product was chromatographed on silica gel and eluted with 20% MeOH–$CHCl_3$. Recrystallization from H_3CCN yielded the *o*-aldehyde **14** (34%), mp 95–97 °C. Anal. ($C_{14}H_{21}NO_3$) C, H, N.

2-[4-(3-*tert*-Butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole (2d). To $NaOAc \cdot 3H_2O$ (11.8 g, 0.088 mol) in H_2O (40 mL) was added 1,1-dibromo-3,3,3-trifluoroacetone[16] (11.8 g, 0.044 mol). The solution was heated for 0.75 h on a steam bath, cooled, and added to a solution of *p*-**14** (5 g, 0.02 mol) in MeOH (200 mL) and concentrated NH_4OH (25 mL). After standing for 5 h at room temperature, the MeOH was removed under reduced pressure. Saturated Na_2CO_3 solution (25 mL) and $CHCl_3$ (50 mL) were added to the residue and after shaking, a solid separated. The product was filtered, washed with H_2O, and recrystallized from H_3CCN to yield (*RS*)-**2d** (3 g, 41%), mp 189–191 °C. Anal. ($C_{17}H_{22}F_3N_3O_2$) C, H, N.

The ortho isomer **2b** was prepared by essentially the same procedure and purified by recrystallization from H_3CNO_2 in a yield of 44%, mp 105–107 °C. Anal. ($C_{17}H_{22}F_3N_3O_2$) C, H, N.

Pharmacology. Antihypertensive activity was estimated in vivo in SH rats as described by Watson and Ludden.[15] Compounds were administered orally and/or intraperitoneally.

The peripheral vasodilating activity was determined in adult mongrel dogs of either sex (8–13 kg body weight). The test animals were anesthetized with vinbarbital, 50 mg/kg iv. The trachea was cannulated and the vagi were cut. Systemic arterial pressure was recorded from the right carotid artery. The right iliac artery was exposed through a midline incision and a Micron blood flow transducer (3.0 mm) was secured around the artery. The left femoral artery was cannulated with PE 90 tubing and the tip of the catheter was advanced until it was positioned at the iliac bifurcation. Drug injections were made intraarterially through the catheter and the changes in blood flow were recorded. In each experiment, isoproterenol, 0.4 μg ia, was injected before and after timolol to assess the extent of β-adrenergic blockade. In all experiments, timolol whether administered at 320, 800, or 2000 μg/kg iv completely blocked the vasodilator response to isoproterenol, 0.4 μg ia.

To determine β-adrenergic blocking activity, mongrel dogs of either sex weighing between 8 and 13 kg were anesthetized with vinbarbital, 50 mg/kg iv; the vagi were cut and blood pressure was recorded through a femoral artery catheter. Drug injections were made through the femoral venous catheter. The trachea was cannulated but artificial respiration was used only if required.

Heart rate was recorded electronically from the blood pressure pulse. Isoproterenol was injected at 0.5 μg/kg iv and the resultant hypotension and tachycardia were computed. Test compounds were administered cumulatively until nearly complete inhibition of isoproterenol effects was achieved.

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Adrenergic Agents. 6.[1] Synthesis and Potential β-Adrenergic Agonist Activity of Some Meta-Substituted *p*-Hydroxyphenylethanolamines Related to Salbutamol

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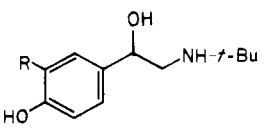
Salbutamol, an adrenergic receptor agonist with selectivity for tracheobronchial vs. cardiac muscle, differs from the catecholamine *N*-*tert*-butylnorepinephrine in that it bears a hydroxymethyl, rather than a phenolic, group in the meta position. In a search for new bronchodilating agents with minimal cardiovascular side effects, a series of derivatives, in which this *m*-hydroxymethyl group is modified, was prepared. These compounds were examined for potential bronchodilator activity in an in vitro test that measures relaxation of guinea pig tracheal smooth muscle. Potential cardiac stimulant activity was evaluated in vitro by monitoring changes in the rate of contraction of spontaneously beating guinea pig right atria. Although many of these compounds retained a high degree of potency, all were less effective than salbutamol in the tracheal test. Several of the derivatives, notably ones bearing 1-hydroxyethyl (**1d**), 1,2-dihydroxyethyl (**1f**), 1-hydroxy-2-methoxyethyl (**1g**), and 2-hydroxy-1-methoxyethyl (**1h**) substituents in place of the parent's *m*-hydroxymethyl group, however, were considerably more selective for tracheobronchial vs. cardiac muscle in the in vitro tests utilizing guinea pig tracheal and right atrial muscle.

Structural modifications of the meta substituent in *p*-hydroxyphenylethanolamines have produced many potent and selective β-adrenoreceptor agonists, some of which are therapeutically effective bronchodilators. In previous publications, we described the synthesis and β-adrenoreceptor agonist activity of carbuterol (**1a**)[2] and sulfonterol (**1b**)[3] which, among others, belong to this class of chemical compounds. Salbutamol (**1c**),[4] an orally effective bronchodilator in the clinic,[5] was one of the first



1a, R = H_2NCONH
b, R = $MeSO_2CH_2$
c, R = $HOCH_2$
d, R = $MeCH(OH)$
e, R = $Me_2C(OH)$
1f, R = $HOCH_2CH(OH)$
g, R = $MeOCH_2CH(OH)$
h, R = $HOCH_2CH(OMe)$
i, R = $MeSO_2CH_2CH(OH)$
j, R = t-$BuNHCH_2CH(OH)$

compounds to demonstrate that replacing the *m*-hydroxyl group of catecholamines with a hydroxymethyl group can improve the selectivity for tracheobronchial vs. cardiac muscle. In vitro studies in guinea pig tracheal and right atrial preparations show that sulfonterol has a much larger separation ratio[6] than salbutamol.[3] It seems plausible that modification of the *m*-hydroxymethyl group of salbutamol might further improve the selectivity. In the present article are described the synthesis and results of preliminary pharmacological examination for β-adrenoreceptor agonist activity of several compounds **1d–j** of this type.

Chemistry. Synthesis of the 1-hydroxyethyl derivative **1d** is outlined in Scheme I. Acylation of methyl salicylate with AcCl–$AlCl_3$ followed by benzylation afforded **2** in a more direct method than that previously reported.[4] The ketal derived from **2** was reduced with $LiAlH_4$ to give the hydroxyketal **3** which was oxidized to the aldehyde **4** with MnO_2. Treatment of **4** with MeMgI followed by hydrolysis of the ketal group during the work-up led to the secondary alcohol **5**. Formation of the ethanolamine side chain was