Adrenergic Agents. 4. Substituted Phenoxypropanolamine Derivatives as Potential β-Adrenergic Agonists

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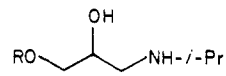
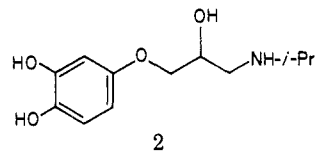
A series of 1-(substituted phenoxy)-3-(*tert*-butylamino)-2-propanols in which the ring substituents were 3,4-dihydroxy (**6f**), 3- and 4-hydroxy (**6g** and **6h**, respectively), 3-hydroxy-4-methylsulfonamido (**6i**), its 3,4-transposed isomer (**6j**), and 4-methylsulfonylmethyl (**6k**) was prepared and examined for β-adrenergic agonist and/or antagonist properties. Two of these compounds, **6f** and **6j**, were potent β-adrenoreceptor agonists in in vitro tests that measure a compound's ability to relax guinea pig tracheal smooth muscle and to increase the rate of contraction of guinea pig right atria. Several compounds had a dose-dependent effect. Although they produced potent β-adrenergic agonist activity at low concentrations, **6g**, **6h**, and **6j** antagonized the effects of a standard β-adrenoreceptor agonist at higher concentrations. The methylsulfonylmethyl derivative **6k** produced β-adrenergic blocking effects as demonstrated by attenuation of isoproterenol-induced increases in the rate of contraction of an isolated rabbit heart preparation. On the basis of these pharmacological results, coupled with NMR spectral data, it appears that the previous suggestion that aryloxypropanolamines interact with β-adrenoreceptors as a consequence of their ability to assume an orientation in which the benzene ring and the ethanolamine moieties can be superimposed on those of corresponding adrenergic phenylethanolamines is invalid. An alternative "bicyclic" rigid conformation involving two intramolecular hydrogen bonds in the protonated form of the aryloxypropanolamines is suggested to account for the similar β-adrenoreceptor activity of these compounds and related phenylethanolamines.

The aryloxypropanolamine structure is generally associated with β-adrenoreceptor antagonist activity. For example, propranolol (**1a**), alprenolol (**1b**), pindolol (**1c**), and related compounds are among the most potent agents of this kind.[1-3] Even the oxypropanolamino analogue **1d**[4] of the selective β_2-adrenergic agonist, the phenylethanolamine 3-[3-α-(*tert*-butylaminomethyl)]-5-hydroxy-*m*-xylene-α,α′-diol,[5] is a potent nonselective β-adrenergic blocking agent. Appropriate substitution on the aryloxy group, however, may result in compounds having marked β-adrenergic agonist activity. Thus, in a series of ring-hydroxylated phenoxypropanolamines several showed marked agonist properties.[6,7] Affinity and intrinsic activity comparable to those of isoproterenol were noted[7] for **2** on guinea pig cardiac β-adrenoreceptors, although others[8] have observed mixed β-adrenergic agonist and antagonist actions for this substance when tested in vitro in rabbit atrial and guinea pig tracheal tissue.



1a, R = 1-naphthyl (propranolol)
b, R = 2-CH_2=$CHCH_2C_6H_4$ (alprenolol)
c, R = 4-indolyl (pindolol)
d, R = 3-HO-5-$HOCH_2C_6H_3$



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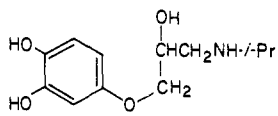

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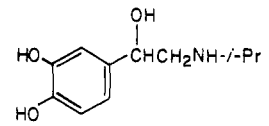

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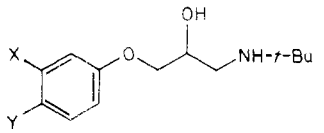
It has been speculated[9] that the β-adrenergic agonist activity of **2** may be related to its ability to assume a conformation **3**. When a model of a phenylethanolamine, e.g., isoproterenol (**4**), is superimposed at the benzene ring on a model of a phenoxypropanolamine, e.g., **3**, side-chain conformations can be assumed so that the ethanolamine moieties are exactly superimposed (compare **3** and **4**). Support for this concept is provided by the very strict steric parameters that dictate the receptor affinity of these compounds. It has been observed frequently that in both phenylethanolamines and phenoxypropanolamines with β-adrenergic agonist or antagonist properties (−) enantiomers with the absolute configuration D are required.[3,9-12]

Reasoning that β-adrenoreceptor activity of phenylethanolamines and aryloxypropanolamines might result from their ability to attain superimposable conformations **3** and **4**, the substituent of a phenoxypropanolamine located para to the ether oxygen should influence biological activity in a fashion similar to that of a meta substituent of a phenylethanolamine. A marked difference in β-adrenergic agonist potency, as measured by their capacity to induce bronchodilation in a histamine-constricted guinea pig lung preparation, has been observed for the meta- and para-hydroxylated derivatives of *N*-*tert*-butyl-β-phenylethanolamine.[13,14] Also, among sulfonanilide[15] and saligenin[16] analogues of catecholamine β-adrenoreceptor agonists, compounds with an *m*-alkylsulfonamido or *m*-hydroxymethyl substituent and a *p*-hydroxyl group are potent adrenergic agonists whereas the isomers in which the ring substituents are transposed are weaker agonists, or sometimes antagonists.[15-17] Thus, comparison of the meta- and para-hydroxylated phenoxypropanolamines with the corresponding phenylethanolamines should provide evidence as to the validity of the concept that these two classes act via conformations **3** and **4** which bear certain similarities. Likewise, phenoxypropanolamines in which the phenoxy group is substituted with *m*-methylsulfonamido and *p*-hydroxyl groups and their isomers in which the substituents are transposed provide a rational basis for testing the relationship suggested[9] to account for their biological similarities. For this reason, a series of such phenoxypropanolamines was prepared and examined for β-adrenergic activity. The *N*-*tert*-butyl analogue (**6f**) of **3** was made for comparative purposes. Additionally, para substitution of a phenylethanolamine with a phenol-simulating substituent, e.g., a methylsulfonamido group,[18] often results in compounds with β-adrenergic antagonist activity. Therefore, a *p*-methylsulfonylmethyl group, our most recently discovered phenolic hydroxyl substitute,[19] was introduced into a phenoxypropanolamine (**6k**).[20] In the present article are reported the synthesis and results

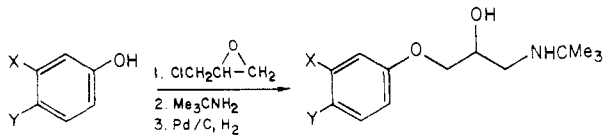
Table I. Benzylated Derivatives of 3-(Substituted phenoxy)-1-(*tert*-butylamino)-2-propanol[a]



No.	X	Y	Mp, °C	Recrystn solvent	Yield, %	Formula[c]
6a[b]	$PhCH_2O$	$PhCH_2O$	158-160	MeCN	61	$C_{29}H_{37}NO_5$
6b	$PhCH_2O$	H	149-152	MeOH-Et_2O	43	$C_{20}H_{28}ClNO_3$
6c	H	$PhCH_2O$	190-192	MeOH-Et_2O	60	$C_{20}H_{28}ClNO_3$
6d	$PhCH_2O$	$MeSO_2(PhCH_2)N$	221-223	MeOH-Et_2O	71	$C_{28}H_{37}ClNO_5S$
6e	$MeSO_2(PhCH_2)N$	$PhCH_2O$	169-171	MeOH-Et_2O	86	$C_{28}H_{37}ClNO_5S$[d,e]

[a] All compounds, except 6a, are HCl salts. [b] Oxalate. [c] Compounds for which the formula is given were analyzed for C, H, and N and analytical values were within ±0.4% of the calculated values. [d] The base had mp 156-159 °C (from MeOH). [e] A cyclohexylsulfamic acid salt melted at 145-147 °C (from EtOH-Et_2O). Anal. ($C_{34}H_{49}N_3O_8S_2$) C, H, N.

Scheme I



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a, X = Y = $PhCH_2O$
b, X = $PhCH_2O$; Y = H
c, X = H; Y = $PhCH_2O$
d, X = $MeSO_2(PhCH_2)N$; Y = $PhCH_2O$
e, X = $PhCH_2O$; Y = $MeSO_2(PhCH_2)N$
f, X = Y = HO
g, X = HO; Y = H
h, X = H; Y = HO
i, X = HO; Y = $MeSO_2NH$
j, X = $MeSO_2NH$; Y = HO
k, X = H; Y = $MeSO_2CH_2$

of preliminary pharmacological studies with this series of ring-substituted phenoxypropanolamine derivatives.

Chemistry. Several routes were used to prepare the phenols **5a–e** which served as precursors to the phenoxypropanolamine derivatives **6**. 3,4-Dibenzyloxyphenol (**5a**),[7,21] as well as 3- and 4-benzyloxyphenols (**5b**[22,23] and **5c**,[24] respectively), were obtained by previously described methods. The methylsulfonamidophenols, **5d** and **5e**, were derived from 4- and 5-acetyl-2-benzyloxymethanesulfonanilides[15] by benzylation and subsequent Baeyer–Villiger oxidation[25] of the resulting *N*-benzylsulfonanilides. Oxidation of the 4-benzyloxyacetophenone precursor to **5d** proceeded readily using peracetic acid,[26] but this method was not effective for oxidation of the isomeric acetophenone precursor of **5e**. In this case, however, oxidation with *m*-chloroperbenzoic acid in chloroform[27] gave **5e** without difficulty. To prepare 4-methylsulfonylmethylphenol (**5k**), 4-benzyloxybenzyl chloride was condensed with magnesium methylsulfinate[28] and the resulting benzyl ether was hydrogenolyzed under catalytic conditions.

As indicated in Scheme I, condensation of phenols **5** with epichlorohydrin in the presence of alkali gave 3-(substituted phenoxy)-1,2-epoxypropane derivatives which underwent ring opening upon treatment with *tert*-butylamine. The predominant products were 1-phenoxy-3-(*tert*-butylamino)-2-propanols **6**. These isomers (Table I) were readily separated from minor amounts of the kinetically less favored 3-phenoxy-2-(*tert*-butylamino)-propanols by fractional recrystallization of their hydrochlorides. Homogeneity of the products **6** was established by TLC. Structural assignments were based on NMR and mass spectral data. Hydrogenolysis of the benzylated derivatives **6a–e** gave the ring-hydroxylated phenoxypropanolamines presented in Table II.

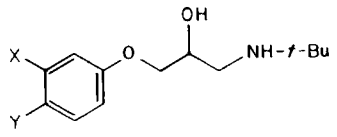
Results and Discussion

That β-adrenoreceptors are of at least two subtypes, i.e., β_1 and β_2, a proposal orginally advanced by Lands and his associates[29-31] and by Furchgott,[32] is thoroughly documented. As a test of potential β_2-adrenergic agonist activity, the 3-(substituted phenoxy)-1-(*tert*-butylamino)-2-propanols **6f–k** (Table II) were examined for their ability to relax spontaneously contracted guinea pig smooth muscle in vitro[33]. Potential β_1-adrenoreceptor stimulant activity was evaluated in a similar in vitro test[33] that measures the increase in the rate of contraction of spontaneously beating guinea pig right atria. The testing results for these compounds and several standard adrenergic agents are tabulated in Table II. The separation ratios provide an index of the specificity of the compounds for β_1 vs. β_2 adrenoreceptors. Where appropriate, data relating to the β-adrenergic blocking properties of some of these compounds are also presented.

In agreement with the earlier observation[7] that 1-(3,4-dihydroxyphenoxy)-3-(2-propylamino)-2-propanol (**2**) has affinity and intrinsic activity for cardiac receptors that are comparable to those of isoproterenol, the *tert*-butyl analogue **6f** was extraordinarily potent in vitro in both the guinea pig right atrial and tracheal tests. In the atrial assay, **6f** was about 310 times more potent than isoproterenol and 650 times more potent than *N*-*tert*-butylnorepinephrine at the ED_{25} level. It was somewhat less potent in the tracheal test; however, even here it was approximately 22 times more potent than isoproterenol, the prototype of β-adrenergic agonists. Thus, **6f** (separation ratio = 0.034) is considerably more selective for cardiac tissue than is isoproterenol (separation ratio = 0.48). The significance of the specificity of this phenoxypropanolamine for cardiac vs. tracheal tissue is even more striking when the separation ratio of **6f** is compared with that of its chemically more closely related counterpart, *N*-*tert*-butylnorepinephrine, which is more potent in the in vitro tracheal test than in the atrial assay, giving a separation ratio of 5.5.

The catecholic phenoxypropanolamine **6f** acted as a full agonist in tracheal tissue; its dose–response curve was parallel to that of isoproterenol and it had an intrinsic activity of 1.0 (Table II). However, the dose–response curve for **6f** in right atrial tissue was significantly flatter than that of isoproterenol, suggesting only partial agonist activity in this tissue even though it had an intrinsic activity of 0.9 (Table II). In contrast, **6f** and isoproterenol were approximately equipotent in increasing heart rate in vivo in anesthetized dogs and here their dose–response curves were parallel (see Experimental Section, pharmacology, method E). The phenoxypropanolamine **6f** was

Table II. 3-(Substituted phenoxy)-1-(*tert*-butylamino)-2-propanol[a]



No.	X	Y	Mp, °C	Recrystn solvent	Yield, %	Formula[b]	Guinea pig tracheal test,[c,d] ED_{50} (molar concn) (95% confidence limits)	Guinea pig atrial rate, [c] ED_{25} (molar concn) (95% confidence limits)	Intrinsic act. (α) in atrial test[e]	Separation ratio[f]
6f	HO	HO	175-177	$EtOH-Et_2O$	65	$C_{13}H_{22}ClNO_4$	3.2×10^{-10} ($1.2\text{-}8.2 \times 10^{-10}$)	1.1×10^{-11} ($0.5\text{-}2.4 \times 10^{-11}$)	0.9	0.034
6g	HO	H	123-125	$Me_2CO-H_2O-Et_2O$	86	$C_{13}H_{22}ClNO_3$	$\sim 2.1 \times 10^{-8}$ [g]	$\sim 5.4 \times 10^{-7}$ [h]	0.3	26
6h	H	HO	196-198	$MeOH-Et_2O$	95	$C_{13}H_{22}ClNO_3$	1.3×10^{-8} ($0.6\text{-}2.6 \times 10^{-8}$)	5.0×10^{-8} [i] ($0.6\text{-}42.0 \times 10^{-8}$)	0.5	3.8
6i	HO	$MeSO_2NH$	208-210	$MeOH-Et_2O$	60	$C_{14}H_{25}ClN_2O_5S$	3.4×10^{-6} [j] ($0.8\text{-}14.0 \times 10^{-6}$)	$\sim 9.0 \times 10^{-5}$, 19%		>27
6j[a]	$MeSO_2NH$	HO	145-146	MeCN	21	$C_{20}H_{37}N_3O_8S_2$	6.6×10^{-9} ($2.8\text{-}15.0 \times 10^{-9}$)	1.2×10^{-6} [k] ($0.5\text{-}3.2 \times 10^{-6}$)	0.4	182
6k	H	$MeSO_2CH_2$	174-175	*i*-PrOH	76	$C_{15}H_{26}ClNO_4S$	4.8×10^{-5}, 0%	4.8×10^{-5}, 0% [l]		
	3,4-$(OH)_2$PhCHOHCH$_2$NH-*i*-Pr (isoproterenol)						7.1×10^{-9} ($5.2\text{-}9.9 \times 10^{-9}$)	3.4×10^{-9} ($2.6\text{-}4.6 \times 10^{-9}$)	1	0.48
	3,4-$(OH)_2$PhCHOHCH$_2$NH-*t*-Bu (*N*-*tert*-butylnorepinephrine)						1.3×10^{-9} ($0.93\text{-}1.8 \times 10^{-9}$)	7.1×10^{-9} ($5.3\text{-}10.0 \times 10^{-9}$)	1	5.5
7	3-HOPhCH(OH)CH$_2$NH-*i*-Pr						$\sim 4.5 \times 10^{-8}$	$\sim 3.7 \times 10^{-8}$	1	0.8
8	4-HOPhCH(OH)CH$_2$NH-*i*-Pr						$\sim 1.1 \times 10^{-7}$	$\sim 7.7 \times 10^{-8}$	0.8	0.7
	3-$MeSO_2$NH-4-HOPhCH(OH)CH$_2$NH-*i*-Pr (soterenol)						2.6×10^{-8} ($0.97\text{-}6.9 \times 10^{-8}$)	7.6×10^{-8} ($1.0\text{-}59.0 \times 10^{-8}$)	0.7	2.9

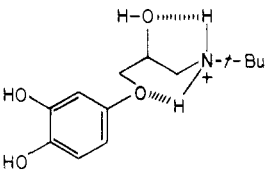
[a] All compounds are HCl salts except 6j which is a cyclohexylsulfamate. [b] See footnote *c*, Table I. [c] See Experimental Section. Where ED's were not determined, results are given as percent response at the indicated concentration. [d] The intrinsic activity, α, i.e., maximum effect of test compound divided by the maximum effect of papaverine, is equal to 1 for all compounds for which ED_{50}'s were obtained, unless indicated otherwise. [e] Determined as defined in footnote *d* but related to maximum isoproterenol-induced response. [f] Guinea pig right atrial test ED_{25} divided by tracheal test ED_{50}. [g] $\alpha = 0.6$. [h] At a concentration of 6.3×10^{-5} M 6g, isoproternol-induced increases in the guinea pig right atrial contraction rate (measured as described in the Experimental Section, pharmacology, general method B) were completely blocked. [i] At a concentration of 8.4×10^{-5} M 6h, isoproterenol-induced increases in the right atrial contraction rate, measured as described in footnote *h*, were completely blocked. [j] $\alpha = 0.8$. [k] At a concentration of 3×10^{-7} M 6j, isoproterenol-induced increases in the right atrial rate (Experimental Section, pharmacology, general method B) were attenuated by 44%. [l] At a concentration of 1×10^{-3} M 6k, isoproterenol-induced increases in the rabbit heart rate, measured as described in the Experimental Section (pharmacology, general method C), were attenuated by 78%. The cardiac rate remained unchanged from that before treatment.

slightly less potent than isoproterenol in decreasing diastolic blood pressure in these anesthetized dog experiments and both the blood pressure and heart rate responses were attenuated by propranolol. To establish that **6f** does not act through the release of endogenous catecholamines, the in vitro guinea pig tracheal and right atrial tests were also carried out with tissues from animals pretreated with reserpine (see Experimental Section, pharmacology, method D). Reserpine pretreatment did not diminish the potency of **6f** in either tracheal or atrial tissue and the slopes of the dose–response curves were the same as obtained in normal tissues. These results indicate that the phenylethanolamines and phenoxypropanolamines probably act via similar mechanisms.

To examine the validity of the speculation that the β-adrenergic activity of catecholic phenoxypropanolamines, such as **6f**, may be associated with the ability of such molecules to assume conformation **3** resembling a conformation **4** of related phenylethanolamines, comparison of the relative potencies of similarly ring-substituted derivatives from the two series was made. Thus, the mono ring-hydroxylated 3-phenoxy-1-(*tert*-butylamino)-2-propanols, **6g** and **6h**, were compared to the corresponding phenylethanolamines, **7** and **8**.

As can be seen from the data in Table II, **6g** and **6h** had comparable potencies in the in vitro test for relaxation of guinea pig tracheal tissue. The *p*-phenol **6h** was perhaps slightly more potent than its meta isomer **6g** and induced maximum relaxation whereas the latter (intrinsic activity, $\alpha = 0.6$) was not a full agonist. Also, in the in vitro guinea pig atrial test the para-hydroxylated derivative **6h** appeared slightly more potent than its meta counterpart **6g** and had somewhat greater intrinsic activity. It may be significant that both isomers at nearly equivalent higher concentrations (**6g**, 6.3×10^{-5} M, and **6h**, 8.4×10^{-5} M) completely blocked isoproterenol-induced increases in right atrial rate. In contrast, the meta-hydroxylated phenylethanolamine isomer **7** was perhaps slightly more potent than its para isomer **8** in both the in vitro guinea pig tracheal and atrial tests and both had full β-adrenergic agonist activity (intrinsic activity, $\alpha = 1$). Thus, the *p*-hydroxyphenoxypropanolamine **6h** resembles more closely the *m*-hydroxyphenylethanolamine **7**. These isomers are more potent than their respective counterparts **6g** and **8** in the two in vitro tests and both produce full agonist activity (intrinsic activity, $\alpha = 1$) in the tracheal preparation. As the potency differences for isomers in both chemical classes are only marginal and as the phenoxypropanolamines, with the exception of **6h** in the tracheal test, behave only as partial agonists, these results do not convincingly contradict or confirm the concept that the similarity of β-adrenergic activity of these two chemical classes may reside in their ability to attain similar conformations, i.e., **3** and **4**.

Considerably more convincing conclusions may be drawn by comparison of the in vitro pharmacological data for the *m*-hydroxy-*p*-methylsulfonamido-substituted phenoxypropanolamine **6i** and its isomer **6j** in which the ring substituents have been transposed with those of the related phenylethanolamines, i.e., soterenol (Table II) and its isomer in which the ring substituents have been interchanged. In the latter compounds introduction of the phenolic-simulating methylsulfonamido group[15,18] in place of the meta catecholic hydroxyl, i.e., soterenol, results in retention of potent β-adrenergic agonist activity whereas the transposed isomer is markedly less potent.[15] A similar result is observed in the phenoxypropanolamine series where the *m*-methylsulfonamido-*p*-hydroxy isomer **6j** is nearly three orders of magnitude more potent than its phenoxy-substituent transposed isomer **6i** in the in vitro guinea pig tracheal test. Also, in the guinea pig atrial test the in vitro potency of **6j** is considerably greater than that of **6i**. It is noteworthy that in this pair of phenoxypropanolamines only the *m*-methylsulfonamido-*p*-hydroxy substituted isomer **6j** was a full agonist, having an intrinsic activity of 1.0 (Table II), in the guinea pig tracheal test. These data argue strongly against the proposition that the adrenergic activity of phenylethanolamines and phenoxypropanolamines results from their ability to achieve the conformations **3** and **4** which permit overlapping of the benzene rings and the ethanolamine side chains. Additional evidence contradicting such a proposal of conformational similarity is provided by NMR spectroscopic studies[34] suggesting that the side chains of the protonated species of aryloxypropanolamines in chloroform solution exist predominantly in the conformation. **9**. This alternative bicyclic "rigid" conformation **9** involving two intramolecular hydrogen bonds in the protonated species may account for the similar adrenergic activity of phenoxypropanolamines and phenylethanolamines assuming they act on the same recepter site and not by an allosteric mechanism.



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The present investigation reaffirms the previous observations[1-4,7] that β-adrenergic activity among phenoxypropanolamines depends greatly on the nature of the aromatic substitution. Thus, **6f** and **6j** have potent agonist activity in the guinea pig tracheal and atrial tests; **6g–i** appear to have dose-dependent partial agonist activity and **6k**,[20] as indicated in Table II, is a β-adrenergic antagonist.

Experimental Section

Melting-points were determined using a Thomas-Hoover capillary melting point apparatus. Boiling points and melting points are uncorrected. Microanalyses were determined by the Analytical and Physical Chemistry Section of Smith Kline & French Laboratories. Where analyses are reported by the symbols of elements, results were within ±0.4% of the calculated value. IR spectra (Nujol mull) were obtained with a Perkin-Elmer 727 spectrophotometer. NMR spectra were recorded with a Perkin-Elmer R-24 60-MHz spectrometer using Me_4Si as the internal reference and the indicated solvent at ambient temperatures. Although IR and NMR spectral data are reported only where considered significant, these spectra were obtained for all reported compounds and were considered consistent with the assigned structures. Mass spectral data were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. All of the final products, **6f–k**, showed expected molecular ion peaks.

Chemistry. General Procedures. A. 3-(Substituted phenoxy)-1,2-epoxypropanes. After a solution of the appropriate phenol (0.01 mol), KOH (0.011 mol), epichlorohydrin (0.03 mol), 5 mL of H_2O, and 30 mL of EtOH was stirred at ambient temperature for 20 h, it was concentrated in vacuo. The residue was suspended in H_2O and the mixture was extracted with Et_2O. After being dried ($MgSO_4$) and treated with decolorizing C, the Et_2O solution was concentrated. Residual 3-(substituted phenoxy)-1,2-epoxypropane precursors to **6a**, **6b**, and **6k** were obtained as nearly colorless liquids which were homogeneous (TLC, GLC) and had the expected spectral (IR, NMR) properties. They were used for further reaction without additional analytical data. Epoxy precursors to **6c**, **6d**, and **6e** were crystalline solids. 3-(4-**Benzyloxyphenoxy**)-1,2-**epoxypropane** was recrystallized

from hexane, mp 63–66 °C (82% yield). **3-[3-Benzyloxy-4-(*N*-benzyl-*N*-methylsulfonamido)phenoxy]-1,2-epoxypropane** was obtained (80% yield) as colorless crystals, mp 141–143 °C (from EtOH). Anal. ($C_{24}H_{25}NO_5S$) C, H, N. **3-[4-Benzyloxy-3-(*N*-benzyl-*N*-methylsulfonamido)phenoxy]-1,2-epoxypropane** was obtained (90% yield) as colorless crystals, mp 100–103 °C (from MeOH). Anal. ($C_{24}H_{25}NO_5S$) C, H, N.

B. Addition of *tert*-Butylamine to 3-(Substituted phenoxy)-1,2-epoxypropanes. A solution of 8 mmol of the requisite 3-(substituted phenoxy)-1,2-epoxypropane, 20 mL of *t*-BuNH$_2$, and 50 mL of MeOH was stirred and refluxed for 6 h; then it was concentrated in vacuo. The residue was stripped twice with PhMe; it was converted into a HCl salt by treatment of a solution in EtOH with HCl and Et$_2$O. Recrystallization from the indicated solvents gave the benzylated derivatives of 3-(substituted phenoxy)-1-(*tert*-butylamino)-2-propanol hydrochlorides, **6a–e** (Table I), and **6k** (Table II). Homogeneity of the products was established by TLC (Analtech silica gel GF 250-μ plates, 70:30:3 $CHCl_3$–MeOH–90% HCOOH). NMR spectra of bases, obtained by neutralization of aqueous solutions of HCl salts with aqueous NH_3, were consistent[34,35] with the isomer assignment. For example, the NMR of **6d** in $CDCl_3$ showed signals at 1.09 [s, 9, $NC(CH_3)_3$], 2.38 (s, 2, CH_2NCH_2Ph), 2.70 (m, 2, CH_2N), 3.76 (s, 2, $ArOCH_2C$), and 3.80 ppm (m, 1, $OCH_2CHOHCH_2$).

C. Hydrogenolysis of Benzylated Derivatives of 3-(Substituted phenoxy)-1-(*tert*-butylamino)-2-propanols. A mixture of 2 mmol of the appropriate benzylated derivative of 3-(substituted phenoxy)-1-(*tert*-butylamino)-2-propanol hydrochloride **6a–d** or cyclohexylsulfamate **6c**, 1.0 g of 10% Pd/C (wetted with H_2O), and 100 mL of MeOH was hydrogenated at ambient temperature and an initial H_2 pressure of 3.5 kg/cm^2. After H_2 uptake was completed (about 10 min was required for benzyloxy derivatives; 1 h for *N*-benzylated sulfonamides), the mixture was filtered. The filtrate was concentrated and the residue was stripped twice with PhMe. Recrystallization of residual solids from the solvent systems indicated in Table II afforded **6f–j**. Homogeneity of the products was based on observation of a single spot on Analtech silica gel GF 250 μ TLC plates upon development with the system indicated in general procedure B or with 90:10:3 $CHCl_3$–MeOH–90% HCOOH.

3-Benzyloxy-4-nitroacetophenone. To a stirred solution of 58.3 g (0.27 mol) of di-*tert*-butyl malonate in 350 mL of ethylene glycol dimethyl ether was added *cautiously*, in small portions, 22.8 g (0.54 mol) of a 57% dispersion of NaH in mineral oil. After H_2 evolution had subsided, the stirred mixture was refluxed for 10 min; then it was cooled to 25 °C and a solution of 75.5 g (0.27 mol) of 3-benzyloxy-4-nitrobenzoyl chloride[15] was added at a rate which enabled maintenance of reflux. The mixture was refluxed and stirred for 1 h and then it was concentrated in vacuo. The residue was suspended in a solution of 10 mL of HOAc in 300 mL of H_2O and the mixture was extracted with $CHCl_3$. After being dried ($MgSO_4$), the $CHCl_3$ extracts were concentrated in vacuo. The residue was dissolved in 250 mL of HOAc, 1 g of *p*-$MePhSO_3H$·H_2O was added, and the solution was stirred and refluxed until gas evolution stopped. After the solution was concentrated in vacuo, the residue was taken into EtOAc. The solution was extracted with 1 N NH_3 and H_2O; then it was concentrated. After the residue was washed with hexane, it was recrystallized from MeOH to give 51 g (70%) of yellow crystals, mp 90–93 °C (lit.[15] mp 96.5–98.5 °C).

4-Acetyl-*N*-benzyl-2-benzyloxymethanesulfonanilide. To a stirred solution of 24.5 g (0.077 mol) of 4-acetyl-2-benzyloxymethanesulfonanilide[15] in 100 mL of DMF was added *cautiously*, in portions, 3.4 g (0.08 mol) of a 57% dispersion of NaH in mineral oil. After H_2 evolution had subsided, the stirred mixture was heated at 70 °C for 15 min; then it was cooled at 25 °C and a solution of 10.1 g (0.08 mol) of $PhCH_2Cl$ in 20 mL of DMF was added dropwise. The mixture was stirred and heated at 85–90 °C for 2 h; then it was cooled at 25 °C, diluted with ice–H_2O and extracted with EtOAc. After being dried ($MgSO_4$), the EtOAc solution was concentrated. Recrystallization of the solid residue from EtOAc–hexane gave 26.8 g (85%) of colorless crystals, mp 116–118 °C. Anal. ($C_{23}H_{23}NO_4S$) C, H, N.

5-Acetyl-*N*-benzyl-2-benzyloxymethanesulfonanilide was prepared (90% yield) from 5-acetyl-2-benzyloxymethanesulfonanilide[15] in the same manner as described above for the 4-acetyl derivative. It was recrystallized from PhH–hexane to give colorless crystals, mp 121–122 °C. Anal. ($C_{23}H_{23}NO_4S$) C, H, N.

4-Acetoxy-*N*-benzyl-2-benzyloxymethanesulfonanilide. A solution of 23.1 g (0.056 mol) of 4-acetyl-*N*-benzyl-2-benzyloxymethanesulfonanilide, 25.0 g (0.145 mol) of *m*-chloroperbenzoic acid, and 150 mL of $CHCl_3$ was allowed to stand in the dark at 25 °C for 12 days. The mixture was filtered to remove precipitated *m*-chlorobenzoic acid; the filtrate was extracted with 1 N $NaHCO_3$ and H_2O and then it was dried and concentrated. Residual solid was recrystallized from EtOAc–hexane to give 14.7 g (61.7%) of colorless crystals, mp 126–129 °C. Anal. ($C_{23}H_{23}NO_5S$) C, H, N.

5-Acetoxy-*N*-benzyl-2-benzyloxymethanesulfonanilide. To a 6–9% solution of peracetic acid in HOAc prepared from 450 g of Ac_2O and 100 g of 30% H_2O_2 according to literature directions[26] was added 26.3 g (0.065 mol) of 5-acetyl-*N*-benzyl-2-benzyloxymethanesulfonanilide. The resulting solution was heated at 40–45 °C for 4 h; it was then stirred at 25 °C for 4 days. The mixture, containing a solid precipitate, was poured into 750 mL of H_2O containing 2.0 g of $Na_2S_2O_5$. Filtration afforded 20.1 g (73% yield) of lustrous flakes, mp 142–144 °C. Anal. ($C_{23}H_{23}NO_5S$) C, H, N.

***N*-Benzyl-2-benzyloxy-4-hydroxymethanesulfonanilide (5d).** To a stirred suspension of 14.1 g (0.033 mol) of 4-acetoxy-*N*-benzyl-2-benzyloxymethanesulfonanilide in 100 mL of MeOH was added a solution of 6.3 g (0.046 mol) of K_2CO_3 in 100 mL of H_2O. The stirred mixture was heated on a steam bath until solution was completed. After being stirred at 25 °C for 20 h, the resulting mixture was concentrated in vacuo; H_2O and 2 N HCl were added to give pH 2. The mixture was extracted with Et$_2$O; the extracts were dried and concentrated. Residual solid was recrystallized from EtOAc–hexane to give 9.2 g (73% yield) of colorless crystals, mp 131–132 °C. Anal. ($C_{21}H_{21}NO_4S$) C, H, N.

***N*-Benzyl-2-benzyloxy-5-hydroxymethanesulfonanilide (5e)** was prepared from 5-acetoxy-*N*-benzyl-2-benzyloxymethanesulfonanilide in the same manner as described for **5d**. Colorless crystals (96% yield), mp 153–155 °C (from EtOAc–hexane), resulted. Anal. ($C_{21}H_{21}NO_4S$) C, H, N.

Pharmacology Methods. A. Guinea Pig Tracheal Chain Test. This test was performed by the same procedure described previously.[33]

B. Guinea Pig Right Atria Test. This test was carried out in the same manner as described previously.[19] The same preparation was also employed to evaluate **6g–j** for their ability to attenuate isoproterenol-induced increases in atrial contraction rate. In these experiments, doses of isoproterenol (2.8×10^{-9}, 2.8×10^{-8} M) were added to the bath in a cumulative manner to establish control increases in the rate of contraction. The bath chamber and tissue were washed with pH 7.3 Kreb's HCO_3^- solution.[36] After the contraction rate had returned to the equilibrated control value, bath concentrations were adjusted to 6.3×10^{-5} M **6g**, 8.4×10^{-5} M **6h**, 3×10^{-7} M **6i**, or 3×10^{-7} M **6j** during a period of 15–30 min. Isoproterenol, in the same concentrations employed previously, was then administered. β-Adrenergic blockade was measured by comparing the latter response to isoproterenol with that determined previously.

C. Rabbit Heart Test. This test was performed as described previously.[19]

D. Tracheal and Right Atrial Tissue from Reserpinized Guinea Pigs. The trachea and right atrium were removed, as in general pharmacology methods A and B, from guinea pigs that had previously been given 5 mg/kg, ip, of reserpine once daily for 2 days to deplete tissue levels of endogenous amines. A predetermined amount of tyramine that produced near maximal responses in these tissues from nonreserpinized animals was injected into the bath. Failure to induce a response demonstrated that the reserpine treatment had depleted the tissues of endogenous catecholamines. Tyramine was washed from the bath of the depleted tissues in the usual manner. After the spontaneously contracted tracheal chain and the spontaneously beating right atria had returned to baseline levels, they were employed for testing as described in the general pharmacology methods A and B.

E. Dog Cardiovascular Tests. Blood pressure was measured via a catheterized femoral artery in two anesthetized dogs. Heart

rate was recorded from a standard lead II electrocardiogram. Doses of isoproterenol and **6f** (calculated as the free base) were injected iv via a femoral vein catheter in a randomized block design in each animal prior to a 2 mg/kg iv infusion of propranolol administered during a 5-min period. After the infusion of propranolol, isoproterenol and **6f** were again injected iv in a sequential fashion. Parallel lines were fitted for average dose–response curves.

References and Notes

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