drug (ip) and immediately placed in a motor activity cage which rests on the Animex apparatus. The activity meter was pretuned and the sensitivity set at 40 μA before each test session. The activity cage was a blackened box which contained a light and a ventilation fan which produced constant low-level noise. Thus, extraneous audible and visual distractions were minimized. The activity of each animal was measured separately, and the animals were used once. Results are expressed as cumulative activity counts for the 1-h session.

Atrial Studies. Adult male Sprague–Dawley rats (180–250 g) were used in all experiments. When employed, reserpine pretreatment consisted of a single ip injection (2 mg/kg) 18 h before the animals were killed. For atrial release studies, a Tris buffer (pH 7.4) of the following composition (millimolar concentrations) was employed: NaCl, 140; KCl, 5; $CaCl_2$, 1.5; $MgSO_4$, 1.2; Tris, 10; and *d*-glucose, 10.[25] The medium was equilibrated with 100% O_2, and all incubations and manipulations were performed at 37 °C.

For atrial rate studies, a Krebs–Henseleit buffer[26] was employed (pH 7.4). The medium was equilibrated with 95% O_2–5% CO_2. All media contained disodium edetate (3×10^{-5} M) and ascorbic acid (10^{-4} M) to prevent chemical oxidation of NE and β-thujoplicin (10^{-4} M) as an inhibitor of catechol *O*-methyltransferase.[27]

In isolated atrial rate experiments, the heart was quickly removed and placed in a dish of fresh Krebs–Henseleit medium.[26] A strand of 2-0 surgical silk was affixed to each atrial apex, and then the ventricles were removed. The atria were then mounted in a 20-mL jacketed (37 °C) tissue bath and attached to a Grass strain gauge (250–500 mg resting tension). Responses were recorded using a Grass Model 7 physiograph. The incubation medium was continuously equilibrated with 95% O_2–5% CO_2. After a constant basal rate was established, the atria were treated with the appropriate drug in a volume of 20 μL. After a constant response was obtained, usually after 2 min, the next higher concentration of drug was added. This process was repeated until a cumulative concentration–effect curve was obtained.

In experiments where monoamine oxidase inhibition was desired, the atria were incubated in the presence of pargyline (10^{-4} M) for 10 min, followed by washing, before test drugs were added. Results are expressed as mean atrial rate at peak response (2 min) after addition of the test drug.

When drug-induced efflux of [^{3}H]NE from reserpine- and pargyline-treated atrial tissue was measured, the method described by Paton[25] was used. Briefly, reserpine-pretreated (2 mg/kg ip 18 h prior to experiment) animals were killed by decapitation, and the hearts were quickly removed. The atria were dissected; fat and connective tissue were removed. Each pair of atria was cut into six pieces of tissue. The tissue pieces were incubated in medium containing pargyline (10^{-4} M) for 30 min, washed, and then incubated with 10^{-7} M [^{3}H]NE for 1 h. After each piece of tissue was suspended on a fine hook, the tissue samples were transferred every 5 min to a series of tubes containing fresh medium. Test drugs were present in the tubes from 60 to 100 min of efflux. At the end of the efflux period, each piece of tissue was homogenized in 3 mL of absolute ethanol. The amount of radioactivity in aliquots of the tissue and media samples was determined by liquid scintillation spectrometry. Samples were corrected for quenching by conversion of counts per minute to disintegrations per minute. The efflux of NE was expressed as an efflux coefficient *f*:

$$f\ (\text{min}^{-1}) = \frac{\Delta A}{\Delta t \cdot A_t}$$

where ΔA is the disintegrations per minute lost from the tissue during the time interval Δt and A_t is the ^{3}H-labeled amine content of the tissue midway through the interval Δt. The ^{3}H-labeled amine content of the tissue at each point in the experiment was obtained by adding in reverse order the amount of ^{3}H-labeled amine lost during each efflux period to the amount remaining in the tissue at the end of the experiment.

When concentration–effect curves were obtained, the atrial tissue accumulated [^{3}H]NE as described above. After incubation with the tracer, each piece of tissue was placed into a small, porous basket constructed as a loosely wound coil (4-mm diameter × 7-nm length) at the end of a 4-in. length of 26-gauge nichrome wire. The tissue holders were suspended in a beaker containing 50 mL of fresh medium. The samples were incubated for 10 min, during which time the medium was vigorously stirred (mechanical stirrer) and equilibrated with oxygen. The tissue samples were transferred every 10 min to a beaker of fresh medium until 1 h of washing had been achieved. Each sample was then placed in a tube containing 2 mL of fresh medium and the drug to be tested. The tubes were stoppered and agitated vigorously for 15 min. The tissue samples were removed and homogenized in 3 mL of absolute ethanol. The ^{3}H-labeled amine content of the tissue and medium fractions was determined by liquid scintillation spectrometry.[28] The results were expressed as percent release, where:

$$\%\ \text{release} = \frac{\text{dpm of media}}{\text{dpm of media} + \text{dpm of tissue}} \times 100$$

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Synthesis and β-Adrenergic Blocking Activity of New Aliphatic Oxime Ethers

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New β-adrenergic blocking agents, most of which do not contain an aromatic nucleus, were synthesized. They were derived either from alkylamino-aliphatic oxime ethers or alkylamino-aliphatic ethers. Most active among these are *O*-[3-(*tert*-butylamino)-2-hydroxypropyl]acetoxime (**8**; trachea $pA_2 = 7.65$) and 1-isobutoxy-3-(*tert*-butylamino)-2-propanol (**15**; trachea $pA_2 = 7.49$), both of which displayed bronchoselectivity (β_2/β_1 ratio ~15). The role and importance of the aromatic nucleus in this class of compounds are discussed.

Recently we reported the synthesis of a new series of acetophenone oxime derivatives having marked β-adrenoceptor blocking activity.[2a] Our results showed that the intercalation of a >C=N– bond in the side chain of the

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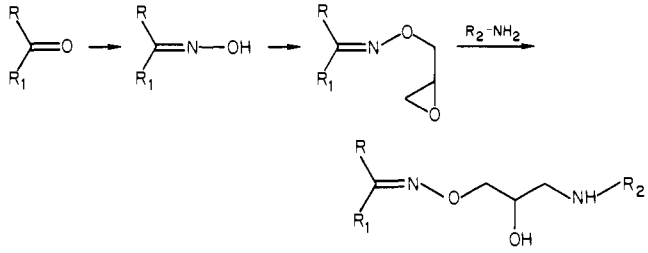
Table I. Physical Properties and β-Blocking Activities of Aliphatic Oxime Ethers

R=NOCH$_2$CHOHCH$_2$NH—R^1

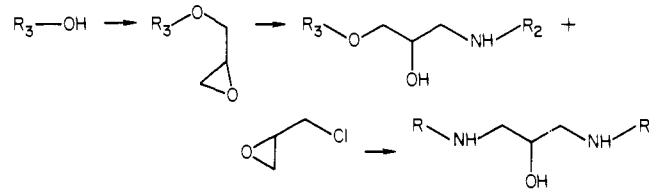
no.	R[a]	R^1	% yield[b]	mp, °C	crystn solvent[c]	emp formula	apparent pA_2[d] atrium[e] (A)	apparent pA_2[d] trachea (T)	broncho-selectivity:[f] T/A
1	$C_6H_5CH_2CH_2C(CH_3)=$	*i*-Pr	30	66	A	$C_{16}H_{26}N_2O_2\cdot$ oxalate	6.82 ± 0.09 (17)	7.68 ± 0.25 (16)	7.4
2	$C_6H_5CH_2CH_2C(CH_3)=$	*t*-Bu	27	77	B	$C_{17}H_{28}N_2O_2\cdot$ oxalate	8.26 ± 0.23 (20)	7.52 ± 0.23 (16)	0.2
3	$CH_3CH_2CH_2C(CH_3)=$	*i*-Pr	22	138	C	$C_{11}H_{24}N_2O_2\cdot$ oxalate	6.41 ± 0.10 (6)	6.00 ± 0.28 (8)	0.4
4	$CH_3CH_2CH_2C(CH_3)=$	*t*-Bu	20	126	A	$C_{12}H_{26}N_2O_2\cdot$ maleate	6.92 ± 0.14 (6)	6.53 ± 0.43 (11)	0.4
5	$CH_3CH_2C(CH_3)=$	*i*-Pr	21	137	C	$C_{10}H_{22}N_2O_2\cdot$ oxalate	6.14 ± 0.30 (6)	6.05 ± 0.20 (7)	0.8
6	$CH_3CH_2C(CH_3)=$	*t*-Bu	16	152	C	$C_{11}H_{24}N_2O_2\cdot$ maleate	6.71 ± 0.20 (8)	6.30 ± 0.17 (7)	0.4
7	$(CH_3)_2C=$	*i*-Pr	6	119	E	$C_9H_{20}N_2O_2\cdot$ fumarate	6.24 ± 0.19 (6)	6.71 ± 0.16 (14)	3
8	$(CH_3)_2C=$	*t*-Bu	16	131	D	$C_{10}H_{22}N_2O_2\cdot$ HCl	6.51 ± 0.05 (7)	7.65 ± 0.32 (12)	14
9	c-C_6H_{10}	*i*-Pr	12	130	F	$C_{12}H_{24}N_2O_2\cdot$ oxalate	5.74 ± 0.10 (10)	6.48 ± 0.32	5.5
10	c-C_6H_{10}	*t*-Bu	19	135	B	$C_{13}H_{26}N_2O_2\cdot$ maleate	6.55 ± 0.15 (6)	7.09 ± 0.18 (6)	3.5
11		*i*-Pr	24	164	F	$C_{16}H_{30}N_2O_2\cdot$ HCl	5.90 ± 0.33 (5)	6.38 ± 0.17 (10)	3
12		*t*-Bu	34	110	F	$C_{17}H_{32}N_2O_2\cdot$ maleate	5.42 ± 0.16 (6)	6.73 ± 0.11 (8)	20.5

[a] All compounds were prepared by sequence A + C, except compounds **9** and **10** for which B + C was used. [b] Yield expressed from the oxime. [c] A, EtOAc; B, EtOAc/*i*-Pr$_2$O; C, MeCN; D, EtOAc/Et$_2$O; E, *i*-PrOH/EtOAc/MeCN (1:2:4); F, EtOAc/MeOH. [d] pA_2 values ± SD, with the number of experiments in parentheses. [e] Antagonism of the isoprenaline-induced positive chronotropic effect. [f] Antilog of the difference between the tracheal and atrial pA_2 values for each antagonist.

Scheme I



Scheme II



β blockers not only did not abolish the β-adrenoceptor action but led in some cases to potent selective β_2 antagonists.[2b] It seemed, therefore, that the distance between the aromatic nucleus and the N atom could be modified, and this point led us to reconsider the role and the importance of the aromatic nucleus itself. To the best of our knowledge, such an examination had not yet been undertaken.

This paper reports the synthesis and pharmacology of new β blockers, most of which do not contain an aromatic nucleus.

Chemistry. Scheme I shows the classical synthetic route starting with the appropriate ketone oximes used for the preparation of compounds **1**–**12** (Table I). Compounds **13**–**18** (Table II) were similarly prepared from the sodium salt of the corresponding alcohol (Scheme II). $NaBH_3CN$ reduction of the oxime ether **8** gave **13**. The 1,3-bis(alkylamino)propan-2-ol derivatives **21** and **22** were obtained by reaction of epichlorohydrin with isopropyl- or *tert*-butylamine.

Discussion and Structure–Activity Relationships

The classic work of Belleau[3] and of Bloom and Goldman[4] attributed an important role to the aromatic portion of the β blockers. Similar conclusions could be drawn from the review of Biel and Lum on β-adrenoceptor blocking agents[5] or from that of Brittain, Jack, and Ritchie[6] or that of C. Kaiser[7] on β-adrenoceptor stimulants. Even a recent publication by Petrongolo et al.[8] based on CNDO-2 cal-

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Table II. Physical Properties and β-Blocking Activities of Miscellaneous Compounds

R—CH_2CHOHCH_2NH—R^1

no.[a]	R	R^1	% yield	mp, °C	crystn[b] solvent	emp formula	apparent pA_2[c] atrium[d] (A)	trachea (T)	broncho-selectivity:[e] T/A
13	*i*-PrNHO	*t*-Bu	48	181	G	$C_{10}H_{24}N_2O_2 \cdot 2HCl$	4.77 ± 0.10 (3)	5.50 ± 0.32 (10)	5.4
14	*i*-PrOCH$_2$O	*i*-Pr	13	96	A	$C_{10}H_{23}NO_2 \cdot$ oxalate	6.01 ± 0.20 (5)	5.45 ± 0.16 (9)	0.3
15	*i*-PrOCH$_2$O	*t*-Bu	45	145	A	$C_{11}H_{25}NO_2 \cdot$ maleate	6.31 ± 0.08 (6)	7.49 ± 0.36 (12)	15
16	*i*-PrO	*i*-Pr	13	111	H	$C_9H_{21}NO_2 \cdot$ oxalate	5.35 ± 0.17 (5)	6.01 ± 0.30 (6)	4.6
17	*i*-PrO	*t*-Bu	70	146	A	$C_{10}H_{23}NO_2 \cdot$ maleate	4.87 ± 0.08 (5)	6.37 ± 0.22 (8)	31.5
18	MeO	*t*-Bu	22	132	I	$C_8H_{19}NO_2 \cdot$ HCl	4.70 ± 0.71[f] (2)	4.13 ± 0.19[f] (4)	0.3
19	HO	*i*-Pr	29	122	G	$C_6H_{15}NO_2 \cdot$ oxalate	4.04 ± 0.18[f] (2)	4.48 ± 0.28[f] (2)	2.7
20	HO	*t*-Bu	54	140	G	$C_7H_{17}NO_2 \cdot$ oxalate	[g]	4.11 ± 0.32[f] (4)	
21	*i*-PrNH	*i*-Pr	28	~250	F	$C_9H_{22}N_2O \cdot 2HCl$	3.7 at 3.10^{-4} (1)	[h]	
22	*t*-BuNH	*t*-Bu	35	>260	F	$C_{11}H_{26}N_2O \cdot 2HCl$	<3.5	4.20 ± 0.07[f] (3)	
23	$C_6H_5CH=CHC(CH_3)=NO$	*i*-Pr	6	160	J	$C_{16}H_{24}N_2O_2 \cdot HCl$	6.06 ± 0.09 (7)	6.12 ± 0.32 (6)	1.2
24	$C_6H_5CH=CHC(CH_3)=NO$	*t*-Bu	11	128	J	$C_{17}H_{26}N_2O_2 \cdot$ maleate	6.55 ± 0.27 (9)	8.02 ± 0.24 (12)	30
propranolol							8.62 ± 0.17 (13)	8.47 ± 0.23 (9)	0.7

[a] For the preparation of 13, see Experimental Section. Compounds 14–18 were prepared by general method D, 19 and 20 by method E, 21 and 22 by method F, and 23 and 24 by the sequence A + C. [b] A, EtOAc; F, EtOAc/MeOH; G, *i*-PrOH; H, *i*-PrOH/Et_2O; I, *i*-PrOH/MeOH; J, *i*-PrOH/EtOAc. [c] pA_2 value ± SD, with the number of experiments in parentheses. [d] Antagonism of the isoprenaline-induced positive chronotropic effect. [e] Antilog of the difference between the tracheal and atrial pA_2 values for each antagonist. [f] Graphical estimation. [g] Inactive at 10^{-4} mol/L. [h] Inactive at 3.10^{-4}.

culations suggested that "the aromatic moiety influences not only the anchoring of the molecule to the receptor but also the drug intrinsic activity". Thus, insofar as β-adrenergic receptor interacting molecules are concerned, a structural resemblance between all the molecules is evident.[9] Necessary structural features for compounds eliciting potent β-adrenergic blocking activity closely parallel those required for β-adrenergic receptor stimulation: a substituted aromatic nucleus, an hydroxyethylamino or hydroxypropyloxyamino side chain, and a secondary amino group. It was also established that the ability to antagonize the effects of isoproterenol resides mainly in the (*R*)-(−)-ethanolamine and (*S*)-(−)-(aryloxy)propanolamine derivatives, stereochemically related to (*R*)-(−)-epinephrine. It is the nature and the position of the substituent on the aromatic ring which confer the agonist or the antagonist properties. The findings reported herein (Tables I and II) based on structures lacking aromatic rings allow certain conclusions to be made regarding the effect of an aromatic ring on β-adrenergic activity.

Table I shows biological results obtained with compounds derived from aliphatic oxime ethers. One of the most interesting compounds is **8**, with a pA_2 of 7.65 measured on isolated guinea pig trachea and a bronchoselectivity of ca. 14. Increasing the size and consequently the lipophilic character of the alkyl group of the oxime did not improve either the pA_2 values or the selectivity of the compounds. It is noteworthy that changing the amino substituent from an isopropyl to a *tert*-butyl group increases the potency. However, the influence on the β_2 selectivity is less clear. Thus, if pairs **7**, **8** and **11**, **12** show an increase in β_2 selectivity in agreement with our previous work,[2a] pairs **3**, **4**; **5**, **6**; and **9**, **10** are poorly selective or nonselective. An even more puzzling result was observed with the *tert*-butyl derivative **2**, which was about 50 times more potent on the atrium than its corresponding isopropyl derivative. Compound **2** which still contains an aromatic ring in the β position with respect to the imino bond has the highest pA_2 value of the compounds listed in Table I and appears to be five times more active on the atrium than on the trachea.

When the β aromatic ring is vinylogously conjugated with the >C=N– bond as in compound **24** (Table II), this gives a very potent derivative which has a β_2 selectivity of 30. It is unlikely that the differences in activities between **23** and **24** or between **1** and **2** are partly the result of mixtures of *syn*- and *anti*-oximes, rather than differences in isopropyl and *tert*-butyl groups, since their NMR spectra are superimposable except for the *N*-alkyl peaks. This table also contains results obtained with the alkylamino aliphatic ethers **14**–**18** and a few related compounds, **13** and **19**–**22**. To rule out the possibility that the >C=N– bond acts as a π area which mimics the aromatic ring, we have reduced the imino bond of **8** with $NaBH_3CN$ to get the hydroxylamine derivative **13** which is still active.

The fact that the ether derivative **15** is equipotent with several compounds of Table I shows that the N atom of the oxime is not crucial for the β activity. Noteworthy is the fact that **15** retains β_2 selectivity. Reducing the size of the alcohol moiety (**16**–**18**) strongly depresses the β-adrenoceptor activity and, hence, indicates that the receptor maintains some steric requirements in this area which are best satisfied in **15**. Analogue **18** is barely active and not selective, while the simplest derivative (**19**) is the least potent of all.

Compounds **21** and **22**, in which the ethereal oxygen of **16** and **17** has been replaced by a nitrogen, were practically inactive, thus showing the importance of the ethereal ox-

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ygen for β-adrenergic activity. A possible explanation for the lack of activity of compounds **19–22** could be due to their low lipophilicity. However, lipophilicity is not considered to be of major importance for in vitro experiments such as those reported here.

In conclusion, this study shows that it is possible to remove the aromatic ring, to move it further away from the oxypropanolamine residue, or to replace it by an appropriate lipophilic alkyl moiety without affecting either potency or the affinity of some β-adrenoceptor blocking substances. Thus, the presence of an aromatic nucleus which is supposed to interact with the receptor by Van der Waals or hydrophobic forces does not seem to be essential, contrary to the generally held view. However, the presence of an ethereal oxygen for β-adrenoceptor activity seems to be crucial, since its omission led to inactive compounds, although the increased hydrophilicity of the compounds may also play a role.

Experimental Section

Melting points were obtained on a calibrated Kofler hot stage apparatus and are uncorrected. Infrared spectra were measured in $CHCl_3$ with a Beckman IR 33 spectrophotometer. NMR spectra were recorded on a Perkin-Elmer R 12 A spectrometer using Me_4Si in a capillary as an external reference. The spectral data were consistent with the assigned structures. All compounds were analyzed for C, H, and N and gave results within ±0.4% of the theoretical values.

Except for benzalacetone oxime, in which *E* and *Z* isomers are present, the oximes moved as a single spot on TLC [$CHCl_3$–EtOAc–$NHEt_2$ (50:45:5) or hexane–EtOAc–$NHEt_2$ (75:20:5)], and in all cases the final product moved as a single spot, even the (±)-camphor-derived compounds **11** and **12** which must be mixtures of diastereomers. The initial ketones are commercially available.

Pharmacological Tests of β-Adrenergic Blocking Activity. β_1-Adrenergic and β_2-adrenergic blocking activities were determined on the atria and trachea of guinea pigs. The antagonism of isoprenaline-induced positive chronotropism was measured on isolated, spontaneously beating right atria according to Horii.[10] The preparations were suspended in a Krebs–Henseleit solution at 32 °C and aerated with a mixture of 95% O_2 and 5% CO_2. Contractions were recorded isometrically. The resting tension was set at 0.5 g. The preincubation time of the antagonists was 30 min before the next cumulative dose–response curve with isoprenaline was performed. The perfusion fluid contained ascorbic acid (10^{-4} g/mL).

β_2-Adrenergic blocking activity was estimated by a slightly modified method of Levy and Wilkenfield.[11] Two equal segments of the trachea were placed in a Krebs–Henseleit solution at 37 °C, gassed with 5% CO_2 in O_2. Contractions were recorded isotonically with a preload of 2.5 g. The bath fluid contained ascorbic acid (10^{-4} g/mL) and phentolamine (10^{-7} g/mL). Fifteen minutes before the cumulative additions of isoprenaline, 10^{-7} g/mL of carbachol was given in order to increase muscle tone. The preincubation time of the antagonists was 60 min.

β-Adrenergic blocking activity was expressed in terms of pA_2 values (logarithm of the reciprocal molar concentration of antagonist which necessitates doubling the concentration of agonist in order to keep the effect constant), as determined according to Arunlakshana.[12] A plot of $\log (x - 1) = f(\log A)$ gives straight lines of slope = 1 for competitive antagonists.

We have checked by Student's *t* test that the slopes were not significantly different from 1.[13] When this was not true, the antagonism was expressed using pD_2'. β_2-Selectivity (T/A ratio) is expressed as the antilog of the difference of the pA_2 between isolated trachea and isolated atria.

Preparation of the Oximes. Procedure A. A solution of the appropriate ketone (1 equiv) and hydroxylamine hydrochloride (2 equiv) in dry pyridine (500 mL) was refluxed under stirring for 12 h. The mixture was then poured into excess water. Usually, the oxime precipitated. It was collected by filtration and recrystallized. When the oximes were oily, they were extracted with EtOAc, washed several times with dilute HCl and finally with water, dried over $MgSO_4$, and evaporated to dryness.

Procedure B. This procedure was used for the synthesis of **9** and **10**. Cyclohexanone oxime was prepared according to ref 14. The oximes (procedure A or B) were then converted to the oxime ethers derivatives according to procedure C.

General Preparation of the Oxime Ether Derivatives. Procedure C. This procedure is illustrated by the synthesis of *O*-[2-hydroxy-3-(isopropylamino)propyl]benzylacetone oxime (**1**). A solution of sodium methoxide was prepared from 1.18 g (50 mg-atoms) of sodium and 150 mL of methanol. Benzylacetone oxime (8.2 g, 51 mmol) was added to this solution over a period of 5 min. The mixture was refluxed for 1 h. The methanol was then thoroughly removed in vacuo, and the dry residue was taken up in 80 mL of anhydrous DMF. This solution was then added dropwise to a solution of 4.75 g (50 mmol) of epichlorohydrin in 20 mL of anhydrous DMF and stirred for 1 h, during which a precipitation of NaCl occurred. The mixture was poured into 500 mL of water and extracted three times with 100 mL of $CHCl_3$. The $CHCl_3$ phase was washed twice with water to remove most of the DMF and dried over $MgSO_4$, and the solvent was evaporated.

The above crude epoxide was dissolved in 20 mL of ethanol containing 14 g of isopropylamine and refluxed for 12 h. After the solution cooled, the solvents were removed at a reduced pressure and the oily residue was dissolved in dilute HCl (10%). Neutral and acidic materials were extracted twice with ethyl ether. The aqueous phase was made alkaline with K_2CO_3 and extracted again with ether. The organic phase was dried over $MgSO_4$ and the solvent evaporated. Finally, **1** was purified by column chromatography. A 4 × 50 cm column was slowly packed with 200 g of silica gel in $CHCl_3$. The sample of crude **1** was applied in $CHCl_3$ and eluted first with 20% EtOAc in $CHCl_3$ to remove impurities (fractions of 100 mL were collected) and then with a mixture of $CHCl_3$–EtOAc–$NHEt_2$ (40:45:5). On the basis of TLC homogeneity (same eluent) fractions 10–30 were combined to give 6.9 g of **1** (46%): ^1H NMR ($CDCl_3$) δ 7.25 (s, 5 H), 3.75–4.20 (m, 3 H), 2.2–3.05 (m, 7 H), 1.85 (s, 3 H), 1.05 (d, J = 6 Hz, 6 H). **1** (5.5 g, 0.02 mol) was dissolved in anhydrous ethyl ether and mixed with 2.5 g of oxalic acid in a minimum of acetone. Ether was added, and the oily residue was induced to crystallize by scratching. Two recrystallizations from EtOAc gave 4.8 g of **1** (66%), mp 66 °C. Anal. ($C_{18}H_{28}N_2O_2$) C, H, N.

Preparation of the Ether Derivatives 14–18. Procedure D. The following method applied for **15** is typical. A solution of sodium isobutoxide was prepared from 1.72 g (75 mg-atoms) of sodium and 100 mL of isobutyl alcohol. After the solution was cooled, 5.9 mL (75 mmol) of epichlorohydrin in 30 mL of isobutyl alcohol was added dropwise. The solution was stirred for 2 h and the NaCl formed was filtered off. Isopropylamine (13.4 g, 0.226 mol) was added and the solution stirred magnetically for 20 h at room temperature. The solvents were removed at reduced pressure and the oily residue, dissolved in 100 mL of ethyl ether, was treated with 8.7 g (75 mmol) of maleic acid in 20 mL of acetone. The maleate of **15** (3.1 g), mp 145 °C, was obtained, which was recrystallized from 2-PrOH–MeOH (7:3). Anal. ($C_{14}H_{27}NO_6$) C, H, N.

Preparation of Compounds 19 and 20. Procedure E. A solution of 14.8 g (0.2 mol) of glycidol and 35.5 g (0.6 mol) of isopropylamine in 100 mL of EtOH was stirred at room temperature for 3 h. The solvents were evaporated, and the white residue was dissolved in 100 mL of 3 N HCl. The aqueous phase was washed with ethyl ether, made alkaline using K_2CO_3, and

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extracted with EtOAc (3 × 70 mL). The organic phase was dried ($MgSO_4$) and evaporated to give 10.7 g of a viscous oil, which was purified through its oxalate to yield 13 g of **21** recrystallized from 2-PrOH, mp 122 °C. Anal. ($C_8H_{17}NO_6$) C, H, N. **22** was prepared similarly using t-$BuNH_2$.

Preparation of Compounds 21 and 22. Procedure F. Compounds **21** and **22** were prepared by heating under reflux for 12 h a solution of epichlorohydrin (0.1 mol) with an excess of i-$PrNH_2$ or t-$BuNH_2$ in 100 mL of EtOH. The solvents were evaporated and the crystalline residue dissolved in 10% aqueous NaOH. Excess K_2CO_3 was added and the mixture was extracted with EtOAc (3 × 70 mL), dried over $MgSO_4$, and filtered. HCl gas was then bubbled through the EtOAc solution to afford the hydrochlorides **21** and **22**.

Preparation of Compound 13. Procedure G. To a solution of 3.81 g (12 mmol) of the maleate of **8** in 50 mL of MeOH was added 2.4 g of $NaBH_3CN$ in small portions. The pH was adjusted to 3–4 by 2 N HCl after each addition. The solution was stirred for 1 h and the MeOH was evaporated under reduced pressure (~30 °C). Excess K_2CO_3 was added and the mixture was extracted three times with EtOAc. The organic phase was dried and evaporated, and the residue was taken up in anhydrous ethyl ether. After filtration of excess $NaBH_3CN$, **13** (2 g) was obtained: IR 3400 (very broad, OH, NH), absence of imine bond near 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (m, 3 H), 3.20 (m, 1 H), 2.65 (m, ~4 H, 2-NH and N-CH_2), 1.1 (s, 9 H), 1.0 (d, $J \approx 6$ Hz, 6 H). The hydrochloride (2.1 g) was recrystallized from 2-PrOH: yield 1.6 g (46%); mp 181 °C. Anal. ($C_{10}H_{26}Cl_2N_2O_2$) C, H, N.

Adrenergic Receptor Agonists. Benzofuranylethanolamines

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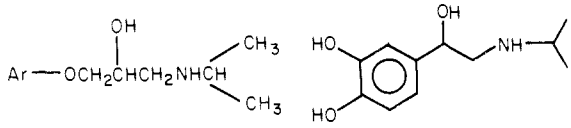
Two hydroxy-substituted benzofuranylethanolamines (**9** and **10**), analogues of adrenoceptor-active aryloxypropanolamines, were prepared and their β-adrenoceptor activity was examined. Compound **9** was found to be a β_1-selective adrenergic agonist with high intrinsic activity. Due to the rigidity of the benzofuranyl moiety of **9**, its functional groups cannot be brought into the same spatial positions as those of a phenylethanolamine-type agonist like isoprenaline. This could indicate that adrenergic agonists of the aryloxypropanolamine type and of the phenylethanolamine type are differently bound to the receptor when eliciting the effect.

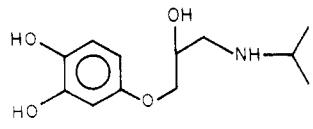
β-Adrenergic blocking agents in clinical use today are mostly aryloxypropanolamines of type **1**. Their β-blocking property is often combined with a β-agonistic activity,[1] and this receptor-stimulating effect is sometimes dominating, e.g., for compounds **2**[2] and **3**[3]. Recently, (*S*)-(−)-1-(4-hydroxyphenoxy)-3-(isopropylamino)-2-propanol (prenalterol; **4**) was described as a β_1-selective adrenoceptor agonist with an intrinsic activity slightly below that of isoprenaline.[4]



1

5

2, Ar = 3,4-$(OH)_2$-C_6H_4-
3, Ar = 2-thiazolyl
4, Ar = 4-OH-C_6H_5-



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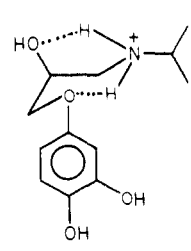

7

It is often suggested that adrenergic agonists like isoprenaline (**5**) are bound to the receptor via the phenolic OH groups, the OH group of the side chain, and the amino group. The aromatic nucleus and the isopropyl group may also participate in this respect.[5] The receptor is then triggered as a consequence of this multifunctional binding.

Adrenergic receptor agonists of the aryloxypropanolamine type like prenalterol (**4**) are assumed to bind to the same functional groups of the receptor as the phenylethanolamines, e.g., isoprenaline (**5**).[6] However, in the aryloxypropanolamines, the aromatic nucleus and the ethanolamine chain are separated by the $-OCH_2-$ moiety. Therefore, it is not obvious how the functional groups of the phenylethanolamines and the aryloxypropanolamines can occupy the same sites of the receptor.

To overcome this difficulty, folded conformations have been proposed in the literature. Comer[7] suggested that the β-adrenergic agonist activity of aryloxypropanolamines may be related to their ability to assume the folded conformation (**6**) which could be superimposed on the extended phenylethanolamine structure. Based on pharmacological results and NMR spectral data, Kaiser et al.[6,8] instead proposed a bicyclic conformation (**7**) that would

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