a hydrogen flame ionization detector and a 1.5 m × 3 mm i.d. glass column containing 1% XE-60 on 60–80 mesh Chromosorb W at 210 °C.

p-Nitrophenyl phosphate (Sigma Chemical Co.), used as the reference compound for enzymatic hydrolysis, was incubated by the same procedure as Δ^8-THC phosphate. The liberated *p*-nitrophenol was assayed as follows. The incubation mixture was centrifuged for 10 min at 2000 rpm after the addition of 5 mL of water. To 2.0 mL of the supernatant, 1 mL of 2 N KOH was added and the final volume was adjusted to 10 mL with water. *p*-Nitrophenol in this solution was then determined spectrophotometrically at 400 nm.

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2-Methoxyphenylethanolamines, Potential β-Adrenergic Blocking Agents

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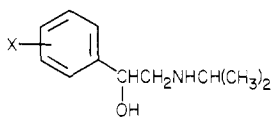
The effect of the introduction of a 2-methoxy substituent on the β-adrenergic antagonistic properties of a series of 3- and 4-substituted phenylethanolamines (1) was studied. Both the series of bromo- and methyl-substituted compounds behaved similarly, indicating that electronic forces are not significant in determining β-adrenergic antagonist activity. When compared with the corresponding phenylethanolamines without a 2-methoxy substituent, the 2-methoxy-4-substituted derivatives (**3a** and **3d**) had enhanced potency and selectivity but the 2,3- (**3b** and **3e**) and the 2,5-disubstitution patterns (**3c** and **3f**) showed a loss of activity. The inconsistent changes in activity prevented any firm conclusions being made about the effect of the ether oxygen and the β-adrenoceptor antagonistic activity of phenoxypropanolamines.

Two distinct chemical classes may exert action as antagonists of β-adrenoceptors. The 1-phenylethanolamines **1** resemble closely the structure of the natural biogenic catecholamines,[1] while the 1-alkylamino-3-aryloxy-2-propanols **2** (aryloxypropanolamines) contain an oxy-



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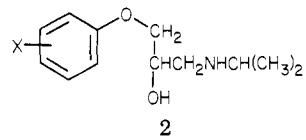

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a, X = 2-OMe
b, X = 4-Br
c, X = 3-Br
d, X = 5-Br
e, X = 4-CH_3
f, X = 3-CH_3
g, X = 5-CH_3

methylene group inserted between the aryl ring and the ethanolamine side chain.[2]

The similarity of β-adrenoceptor antagonistic action may be due to the ability of the phenoxypropanolamines to assume a conformation about the oxymethylene bonds (**2**) so that when the benzene rings of models of phenethanolamines **1** and phenoxypropanolamines **2** are aligned the ethanolamine side chains may assume conformations which are superimposable.[3]

Recently an alternative bicyclic rigid conformation involving intramolecular hydrogen bonding between the protonated nitrogen substituent and the ether and alcoholic oxygens has been proposed to account for the similar activity of the two classes.[4]

Although either suggestion may help to account for the similarity of action of the two classes of β-adrenergic blocking agents, they do not explain the general observation that the phenoxypropanolamines are often more potent and selective for the β_1-adrenoceptors than the phenylethanolamines. We considered that the phenoxypropanolamines had the possibility of additional bonding between the extra ether oxygen and the β-adrenoceptor site, and this may in some way contribute to the extra activity and selectivity. To test this we have prepared for comparison of their β-adrenergic blocking properties a series of phenylethanolamines with and without a 2-methoxy group.

These 2-methoxyphenylethanolamines have the possibility of extra interaction with the β-adrenoceptor site and have potential as potent and β_1-selective blocking agents, as they appear to be able to adopt a conformation where all the essential features of the phenoxypropanolamines are available for interaction with the receptor sites.

In the present article are reported the synthesis and results of preliminary pharmacological studies of a series of 2-methoxyphenylethanolamine derivatives.

Chemistry. Both the 2-methoxy-5-substituted and the 2-methoxy-4-substituted phenethylamines **3** were prepared from the appropriate acetophenones **4** which were obtained by Fries rearrangement of the acetates[5-7] (see Scheme I).

The acetophenones were converted into the epoxides **5** by bromination of the side chain, reduction of the ketone, and reaction of the bromohydrin with base.

The 2-methoxy-3-substituted phenethylamines were prepared from the corresponding aldehydes **6** as our Fries rearrangement of *o*-bromo acetate gave rise to multiple products.[8] Our o-hydroxyaldehydes were prepared conveniently but in low yields by the Duff reaction.[9]

The appropriate 2-methoxy-3-substituted benzaldehydes (**5**, Z = Br, CH_3) were obtained by methylation of the

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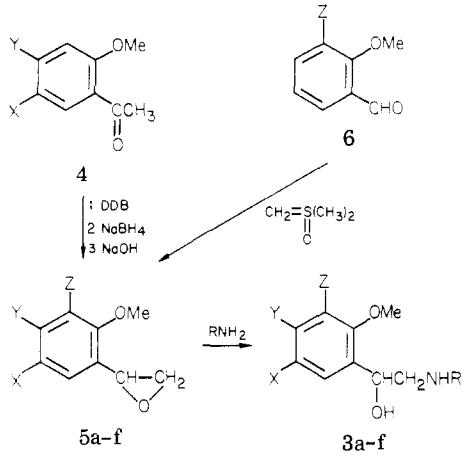
Scheme I



a, Y = Br; Z = X = H
b, Z = Br; X = Y = H
c, X = Br; Z = Y = H
d, Y = CH_3; Z = X = H
e, Z = CH_3; X = Y = H
f, X = CH_3; Y = Z = H

Table I. 2-Methoxyphenylethanolamines 3 as Their HCl Salts

compd	mp, °C	formula	analyses
3a·HCl	193–196	$C_{12}H_{19}BrClNO_2$	C, H, Br, Cl, N
3b·HCl	187–189	$C_{12}H_{19}BrClNO_2$	C, H, Br, Cl, N
3c·HCl	210–211	$C_{12}H_{19}BrClNO_2$	C, H, Br, Cl, N
3d·HCl	158–159	$C_{13}H_{22}ClNO_2$	C, H, Cl, N
3e·HCl	162–164	$C_{13}H_{22}ClNO_2$	C, H, Cl, N
3f·HCl	142–143	$C_{13}H_{22}ClNO_2$	C, H, Cl, N

phenolic group using methyl iodide in ethanolic potassium hydroxide. Reaction of the aldehydes with dimethylsulfoxonium methylide[10] gave the epoxides in good yield (**5**, X = Y = H; Z = Br, CH_3).

To minimize the formation of abnormal products[11,12] the reactions of the epoxides **5** with isopropylamine were performed betweeen 40 and 60 °C and took several days to reach completion. The crude phenethylamines were conveniently purified by conversion to the hydrochloride salts (Table I).

For the 2-methoxyphenylethanolamines the methine proton was found at lower field than the methylene protons and appeared as a quartet, indicating that the methylene protons were not magnetically equivalent.[13]

Conformational analysis of some aryloxypropanolamines **2** revealed a relatively large base to salt shift [$\Delta = \delta$ (salt) - δ (base)] of 0.7 ppm for the methine proton attached to the hydroxylated 2-carbon atom.[14] To explain the large shift, it was proposed that the salts may exist in a nonpolar solvent in a stable rigid conformation involving two intramolecular hydrogen bonds to form a 6–5 bicyclic chelated structure.

The 2-methoxyphenylethanolamines **3** may also offer the possibility of intramolecular hydrogen bonding between the ammonium group and the 2-hydroxyl group and ether oxygen atom to form a 7–5 bicyclic chelated structure (**7**).

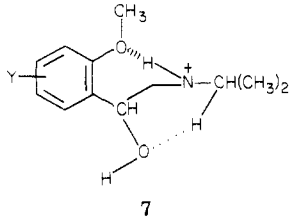


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Table II. Salt to Base Shifts for the Methine Protons

compd	(methine HCl, δ, ppm)	-	(methine free base)	=	Δ
3a	5.49	-	4.84	=	0.65
3b	5.81	-	5.50	=	0.31
3c	5.55	-	5.25	=	0.30
3f	5.55	-	4.90	=	0.65

In deuteriochloroform the base to salt shift of the methine proton was found to vary between 0.30 and 0.65 ppm (see Table II) and the position of the methoxyl protons was essentially unchanged, thus giving no conclusive evidence for intramolecular hydrogen bonding.

Experimental Section

The synthetic methods employed are illustrated by the following examples.

A. Procedure for Preparation of 2-Methoxy-4- and 5-substituted Styrene Oxides from Phenacyl Bromides. 2-Methoxy-5-bromostyrene Oxide (5c). A solution of sodium borohydride (0.03 mol) in water (30 mL) was added dropwise to a stirred solution of 2,5′-dibromo-2′-methoxyacetophenone (9.2 g, 0.03 mol) in dioxane (100 mL). After the reaction mixture had been stirred at 0–10 °C for 1 h the excess borohydride was decomposed with acid, and the solution was poured into water and extracted with ether. The ether was concentrated to give the bromohydrin which was added immediately to a solution of sodium hydroxide (2 N) which was stirred at 60 °C for 15 min and then stirred at room temperature for a further 30 min. The reaction mixture was then extracted with ether to give the epoxide as a colorless oil (6.5 g, 94%) with bp 116–118 °C (1 mmHg). Anal. ($C_9H_9BrO_2$) C, H, Br.

B. Procedure for Preparation of 2-Methoxy-3-substituted Styrene Oxides from 2-Methoxybenzaldehydes 6. 2-Methoxy-3-methylstyrene Oxide (5e). 2-Methoxy-3-methylbenzaldehyde (30.0 g, 0.2 mol) in dimethyl sulfoxide was added to a solution of dimethyloxosulfonium methylide (0.2 mol) in dimethyl sulfoxide (30 mL), and the reaction mixture was heated to 55 °C for 30 min. The mixture was then poured into water and extracted with ether which was dried ($MgSO_4$) and evaporated to give the epoxide **5e** as a colorless oil (19.7 g, 60%) with bp 62–63 °C (0.25 mmHg). Anal. ($C_{10}H_{12}O_2$) C, H.

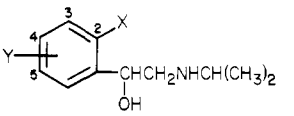
Due to thermal decomposition some epoxides were not purified by distillation but were reacted directly with the amines after NMR and mass spectral analysis had confirmed that the epoxide was the major material.

C. Procedure for Preparation of 1-(2′-Methoxy-3′-, 4′-, or 5′-substituted phenyl)-2-isopropylaminoethanols 3 and Their Hydrochloride Salts. 1-(2′-Methoxy-4′-bromophenyl)-2-isopropylaminoethanol (3a). Isopropylamine (0.04 mol) was added all at once to 2-methoxy-4-bromostyrene oxide (**5a**) (2.3 g, 0.01 mol) dissolved in dry benzene (10 mL) and ethanol (5 mL), and the mixture was stirred at 50 °C until TLC analysis revealed that all the epoxide had reacted (6 days). The excess amine and solvent were then removed under reduced pressure to give the phenylethanolamine **3a** which crystallized from benzene–petroleum ether (1.9 g, 66%): mp 101–103 °C; NMR ($CDCl_3$) δ 1.03 [d, 6 H, $C(CH_3)_2$], 2.32–3.05 [m, 5 H, OH, NCH_2, $NH(R)_2$, $CH(R)_2$], 3.75 (s, 3 H, $ArOCH_3$), 4.84 (q, 1 H, ArCH), 6.85–7.32 (m, 3 H, aromatic protons); mass spectrum [m/e, I (%)] M^+ 289, 287 (<1), 72 (100). Anal. ($C_{12}H_{18}BrNO_2$) C, H, Br, N.

Treatment of **3a** with ethereal HCl gave **1-(2′-methoxy-4′-bromophenyl)-2-isopropylaminoethanol hydrochloride** as a colorless powder: mp 193–196 °C; NMR ($CDCl_3$) δ 1.49 [d, 6 H, $C(CH_3)_2$], 2.90–3.55 [m, 3 H, NCH_2, $CH(R)_2$], 7.73 (s, 3 H, $ArOCH_3$), 5.49 (q, 1 H, ArCH), 6.92–7.50 (m, 3 H, aromatic protons); $\Delta = \delta$ ppm (methine HCl salt) (5.49) - δ (methine free base) (4.84) = 0.65; mass spectrum [m/e, I (%)] M^+ 289, 287 (<1), 72 (100), 36 (7). Anal. ($C_{12}H_{19}BrClNO_2$) C, H, Br, Cl, N.

Pharmacological Methods. Compounds were screened for β_1 (cardiac) and β_2 (tracheal) adrenoceptor activity using guinea pig isolated tissues. The guinea pig isolated trachea and isolated paired atria were set up by the procedures described previously.[15] Antagonist action was measured[16] by first obtaining a dose-

Table III. Effect of 2-Methoxy Substituent on β-Adrenergic Antagonist Activity of *N*-Isopropylmonobromo- and -monomethylphenethanolamines



			antagonist act. on isolated guinea pig tissues							
			β_1, atria				β_2, trachea			
compd	X	Y	pA_2 (mean)	SEM[a]	n[b]	i.a.[c]	pA_2 (mean)	SEM	n	i.a.
1a	OCH_3		6.21	0.07	5	0.5	6.92	0.09	4	0.5
1b	H	4-Br	6.8		3	<0.1	6.7		3	<0.1
3a	OCH_3	4-Br	8.24	0.12	5	0.2	7.87	0.13	5	0.2
1c	H	3-Br	6.2	0.09	4	0.3	5.9	0.11	4	0.3
3b	OCH_3	3-Br	v low		2	low	v low		2	low
3c	OCH_3	5-Br	5.83	0.03	3	0.3	6.03	0.05	3	low
1e	H	4-CH_3	6.9	0.07	3	0.5	6.5		3	0.8
3d	OCH_3	4-CH_3	8.0	0.11	4	0.25	6.4	0.04	4	0.3
1f	H	3-CH_3	6.1	0.17	3	0.7	5.7	0.02	3	0.4
3e	OCH_3	3-CH_3	v low		2	0.5	v low		2	0.1
3f	OCH_3	5-CH_3	5.6	0.12	4	0.3	5.6	0.24	4	0.3
propranolol[d]			8.70	0.11	5	0	8.86	0.04	5	0
atenolol[d]			7.36	0.08	5	0	5.90	0.11	5	0
practolol[d]			6.67		3	0	5.20		3	0.2

[a] SEM = standard error of mean. [b] n = number of experiments. [c] i.a. = intrinsic activity. [d] Standard.

response curve for the standard agonist isoproterenol, by cumulative addition of isoproterenol to the preparation, expressing the response as a percentage of the maximum obtained. At least 30 min after washing the agonist from the bath, to allow the tissue to stabilize, the antagonist was added and left to equilibrate for 20 min before repeating the dose–response measurements with isoproterenol. This was done for three concentration levels of antagonist. From the shift of the dose–response curve, the dose ratio of the agonist in the presence and absence of an antagonist was measured. The process was repeated on further tissue preparations until at least three values for dose ratio were obtained for each antagonist concentration, and the log (dose ratio − 1) was plotted against (−log antagonist concentration) to give pA_2 values and the slope of the line.[16] If partial agonist activity was present in the compound tested, it was measured as a proportion of the maximal agonist effect of isoproterenol on that tissue. Propranolol was used as a standard antagonist and atenolol as a standard β_1-selective antagonist. Standard errors of the mean pA_2 values were calculated.

Results and Discussion

The preparation and pharmacology of the monobromo- and monomethylphenylethanolamines have been reported by us previously.[15] The pharmacological activity of 2-methoxy-*N*-isopropylphenylethanolamine (1a), which was briefly reported elsewhere,[17] was assessed to provide a comparison with results for activity of the methoxybromo- and methyl-disubstituted compounds. Compound 1a was found to have dual action, having partial agonist as well as antagonist activity on the atrial β_1 and the tracheal β_2 preparations. This partial agonist action was measured by pD_2 values (−log EC_{50}), which were 6.3 on the atrial and 6.8 on the tracheal preparation, and by intrinsic activity, which was 0.5 on each preparation compared with isoproterenol. That is, the maximum agonist effect of compound 1a was 50% of the maximum obtained with isoproterenol and 20 times less potent than isoproterenol. Most of the compounds in Table III were weak partial agonists. The intrinsic activities, compared with isoproterenol as 1.0, of compounds **3a** and **3d** were between 0.2 and 0.3.

Table III illustrates the pharmacological activity of *N*-isopropylphenylethanolamines with bromo substitution in the 3 and 4 positions of the phenyl ring, the influence on this activity of the introduction of a 2-methoxy group into the ring, and the corresponding effects with methyl substitution. Of the two monobromo derivatives the para isomer **1b** was more active on both tissue preparations and both compounds were essentially nonselective. The introduction of a 2-methoxy substituent into the 4-bromo isomer led to a marked increase in antagonist action (**1b** to **3a**). The β_1-andrenoreceptor antagonist action of **3a** is approximately 28 times greater than that for the monobromo derivative **1b** and is nearly as high as propranolol. The selectivity of **3a** for β_1-adrenoceptors is twofold and not significant.

Of the two possible positions for the introduction of a 2-methoxy substituent into the meta-substituted bromophenethanolamine (**1c**), one example is compound **3c**, containing the 2-methoxyl substituent para to the bromo group. This behaved as a weak antagonist with activity similar to the monobromo derivative **1c** and less than that of the 2-methoxy derivative 1a. The second example is compound **3b**, where the 2-methoxy substituent had been inserted adjacent to the *m*-bromo substituent, and this compound (**3b**) possessed no measurable activity. In this case the bromo substituent may, through steric hindrance, cause the methoxy substituent to assume conformations which then interfere with the interaction of the 2-hydroxyl group with the receptor.

A parallel pattern of activity was found for the methyl-substituted compounds (see Table III), indicating that methyl and bromo substituents influence the β-adrenoceptor similarly. The 4-methyl compound **1e** was similar in action but a more potent antagonist than the 3-methyl compound **1f**. The change in activity of the 3-substituted methyl compound **1f**, as a 2-methoxy substituent was inserted into each of the two possible positions, was similar to that found with the bromo derivatives, and the 2,3-disubstituted compound **3e** was almost inactive.

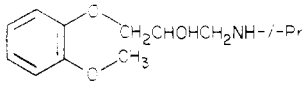
Introduction of a 2-methoxy substituent into the 4-methyl derivative **1e** led to compound **3d** with an enhancement of the degree of β_1-antagonist action and β_1-selectivity. Compound **3d** is a potent β_1-selective adrenoceptor antagonist, with both potency and selectivity, measured by guinea pig isolated tissues, greater than practolol and atenolol. The difference between the pA_2 values from β_1 and β_2 preparations indicates a β_1-selectivity ratio for compound **3d** of 40, compared with selectivity values obtained in this laboratory for both atenolol and

practolol of 30. From the determination of the pA_2 values for the two active compounds (**3a** and **3d**), the slope of the Schild plot[16] was not significantly different from one. This indicates that compounds **3a** and **3d** are competitive antagonists.

In summary, the methyl- and bromo-substituted compounds behave similarly, indicating that steric factors are more significant to the activity than electronic forces. The inactivity of the 2,3-disubstituted derivatives **3b** and **3c** may be explained by the steric interaction between the 3-substituent and the 2-methoxyl which may force the methoxyl group to interfere with the interaction of the β-hydroxyl group and the receptor.

It is of interest that some 2-methoxyphenylethanolamines (**3a,d**) have potencies as high as those of the standard phenoxypropanolamines (see Table III). However, after an enhancement of antagonist activity with the 2,4 pattern, the loss of activity for the 2,5-disubstitution pattern is noteworthy. Unfortunately, these inconsistent changes in activity brought about by the introduction of a 2-methoxyl group into phenylethanolamaines prevent any firm conclusion being made about the extra ether oxygen and receptor binding.

Other workers have also prepared analogues of β-adrenergic blocking agents which contained features of both the phenylethanolamine and the phenoxypropanolamine skeleton.[18] An unexpected increase in potency was found when the 2-methoxy derivative 8 was changed to the benzodioxan structure **9**. The more rigid molecule (**9**) has



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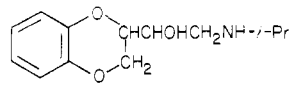

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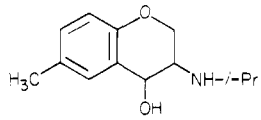

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an alkyl substituent in the side chain which would normally have been expected to decrease potency.

We have also prepared *cis*- and *trans*-3-aminochroman-4-ols **10** which may be regarded as cyclized forms of our 2-methoxyphenylethanolamines **3**.[19,20] This modification imposes steric constraint but leaves the hydroxyl and the secondary amino groups, both of which, together with an appropriate aryl substituent, are necessary for β-adrenergic blocking activity. However, in this case cyclization led to a severe loss of activity as preliminary tests revealed that although the cis derivative was more active than the trans derivative, both were essentially inactive as β-adrenergic blocking agents.

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New Synthetic Routes to Tilorone Dihydrochloride and Some of Its Analogues[1]

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New synthetic routes to the orally active, interferon-inducing antiviral agent tilorone dihydrochloride, 2,7-bis-[(diethylamino)ethoxy]fluoren-9-one dihydrochloride (**1a**), were developed. The routes involved the preparation and solvolysis of tetrazonium fluoroborate salts of 2,7-diaminofluoren-9-one. Nonplanar (**1b**), 9-sulfone (**1c**), and fluorene (**1d**) analogues of tilorone dihydrochloride were also prepared. Compounds **1b** and **1c** were evaluated for interferon induction.

Tilorone dihydrochloride (**1a**), 2,7-bis[2-(diethylamino)ethoxy]fluoren-9-one dihydrochloride, was first reported as an orally active, interferon-inducing, antiviral agent in 1970.[2]

More than 100 articles have since confirmed the usefulness of **1a** as an antiviral,[2,3] antitumor,[4] and antiinflammatory agent.[5] To arrive at a better understanding of the interferon-inducing activity of **1a**, we synthesized

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