the presence or absence of agents in the aqueous phase, were recorded on a differential scanning calorimetric (Model DSC-2, Perkin Elmer) at a heating rate of 2.5 °C/min. A 10-μL sample (1 mg of phospholipid) was appled and encapsulated in an aluminum sample pan. Both abscissa (temperature) and ordinate (transition energy) were calibrated with indium and lead as standards. The calorimetric enthalpy changes (ΔH_{cal}) were measured from the area under the peak. The standard van't Hoff enthalpy changes (ΔH_{vH}) were calculated by eq 7 where T_m is the

$$H_{vH} = 6.9 \frac{T_m^2}{\Delta T_{1/2}} \quad (7)$$

phase transition of the phospholipid and $\Delta T_{1/2}$ is the half-width of the transition peak, and the cooperativity of the transition process of the phospholipid liposome was followed by the definition of Hinz and Sturtevant (eq 8).[31]

$$n = \frac{\Delta H_{vH}}{\Delta H_{cal}} \quad (8)$$

Circular Dichroism Measurements. A Jasco Model ORD/CD5 with Sproul Scientific SS 10 modification was used for circular dichroism (CD) measurments. To minimize the scattering effect, the cell was positioned as close as possible to the photomultiplier.

Acknowledgment. We thank Dr. T. R. Beattie and Ms. C. S. Tripp for initiating this DSC work, to Dr. W. Stoeckenius for providing purple membrane and laboratory facilities to carry out some experiments in this study, and to Drs. J. M. Sturtevant, P. Kroon, J. C. Robbins, and T. W. Doebber for helpful discussions.

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β-Adrenergic Blocking Agents. α- and γ-Methyl(aryloxy)propanolamines

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Received April 3, 1981

A series of γ-methyl- (**5**) and α-methyl(aryloxy)propanolamines (**6**) were synthesized and evaluated for β-adrenergic blocking action. The binding constant (K_D) was determined for compounds **5a–j** on cultured C6-2B astrocytoma cells. Compounds **5a–j** and **6a–e** were evaluated for β_1-antagonist action on guinea pig atria and β_2-antagonist action on guinea pig tracheal strips. Several γ-methyl(aryloxy)propanolamines showed affinity for β receptors and a possible preference for β_2 receptors.

The realization that β-adrenoceptors are not homogeneous but instead can be subdivided into at least two subclasses (β_1 and β_2) has resulted in the publication of numerous articles dealing with β_1- and β_2-adrenoceptor agonists and antagonists. Several years ago we were asked to prepare a series of α-methyl(aryloxy)propanolamines which were under active consideration as β_2 selective antagonists.[1] Since then, studies have shown that introduction of a methyl group into the α position of the nonselective β-adrenoceptor antagonist propranolol does enhance the selectivity of propranolol toward the β_2-adrenoceptors.[2,3] While investigating a general synthetic method for synthesis of the α-methyl(aryloxy)propanolamines, we discovered a novel method for preparing γ-methyl(aryloxy)propanolamines.[4] The only γ-methyl(aryloxy)propanolamine that had been reported previous to this was the erythro/threo mixture of propranolol (**5i**) reported by Howe.[5] While Howe's study suggested that introduction of the methyl group into the side chain gave compounds which are less potent antagonists, the study only considered the effects of the compounds on the heart and, thus, β_1 adrenoceptors. Subsequent studies by Howe and co-workers[6,7] have shown that semirigid γ-alkyl(aryloxy)propanolamines (**1** and **2**) are very potent β_1-adrenoceptor antagonists. We now report our studies directed toward elucidating the structural relationship of

Scheme I

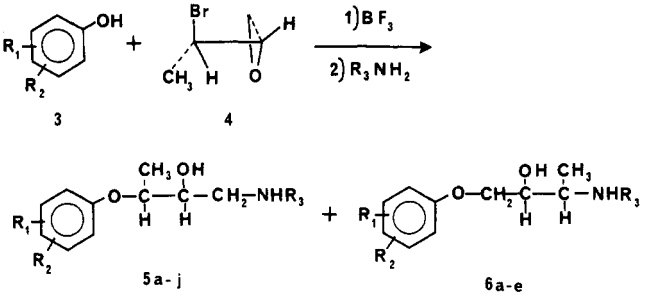

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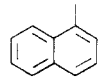
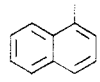
Table I. γ-Methyl- (5) and α-Methyl(aryloxy)propanolamines (6)

no.	R_1	R_2	R_3	mp, °C	yield,[h] %	formula
5a	H	H	$C(CH_3)_3$	132-135[a,b]	41	
5b	3-CH_3	4-CH_3	$CH(CH_3)_2$	122.5-123.4[a,f]	20.6	$C_{15}H_{25}NO_2 \cdot HCl$
5c	3-CH_3	4-CH_3	$C(CH_3)_3$	154-157[a,b]	14.4	
5d	H	4-C_2H_5	$CH(CH_3)_2$	177-180[d,c]	14.2	$C_{15}H_{25}NO_2 \cdot C_6H_3N_3O_7$[i]
5e	H	4-C_2H_5	$C(CH_3)_3$	150-152[a,c]	21.0	
5f	3-Cl	4-Cl	$CH(CH_3)_2$	134.5-136[a,b]	81	$C_{13}H_{19}Cl_2NO_2 \cdot HCl$
5g	2-$CH_2CH{=}CH_2$	H	$CH(CH_3)_2$	134-135[d,e]	28.5	$C_{16}H_{25}NO_2 \cdot C_6H_3N_3O_7$[j]
5h	2-$CH_2CH{=}CH_2$	H	$C(CH_3)_3$	122-125[a,g]	27	$C_{17}H_{27}NO_2 \cdot HCl$
5i			$CH(CH_3)_2$	163-164[a,b]	15.2	$C_{17}H_{23}NO_2 \cdot HCl$
5j			$C(CH_3)_3$	157-158[a,c]		$C_{18}H_{25}NO_2 \cdot HCl$
6a	H	H	$C(CH_3)_3$	135-139[a,b]	7.0	
6b	3-CH_3	4-CH_3	$CH(CH_3)_2$	134-135[a,b]	9.2	$C_{15}H_{25}NO_2 \cdot HCl$
6c	3-CH_3	4-CH_3	$C(CH_3)_3$	159-161[a,b]	8.1	
6d	H	4-C_2H_5	$CH(CH_3)_2$	118-119.5[d,e]	7.0	$C_{15}H_{25}NO_2 \cdot C_6H_3N_3O_7$
6e	H	4-C_2H_5	$C(CH_3)_3$	174-176[a,b]	8.4	

[a] Hydrochloride salt. [b] From EtOAc. [c] From EtOAc-c-C_6H_{12}. [d] Picrate salt. [e] From c-C_6H_6. [f] From EtOAc-hexanes. [g] From c-C_6H_6-c-C_6H_{12}. [h] Yield was based on crude free base. [i] N: calcd, 11.66; found, 11.20. [j] C: calcd, 53.65; found, 54.16.

the γ-methyl substituent and β_1- and β_2-adrenoceptor blockade.

Chemistry. Synthesis of the γ-methyl(aryloxy)-propanolamines (5) was accomplished, as previously reported,[4] by addition of substituted phenols (3) to *threo*-3-bromo-1,2-epoxybutane (4) using catalytic amounts of boron trifluoride etherate (Scheme I). When phenol, 3,4-dimethylphenol, or 4-ethylphenol was used, **5a–e** were accompanied by the α-methyl(aryloxy)propanolamines (**6a–e**), which were separated by column chromatography. When 2-allylphenol, 3,4-dichlorophenol, or 1-naphthol was used, only the rearrangement product **5f–j** was obtained (Table I). With the introduction of the methyl group at C-3 or C-1 of the propanolamine side chain, erythro and threo forms of the compound are possible. There is no indication that **5** or **6** are mixtures, but rather it appears that they each consists of a single compound. With the previous benzodioxan and chroman analogues reported by Howe and co-workers[5,6] (**1** and **2**), where diasteriomers were separated, a distinct difference in the chemical shift and coupling pattern was noted for the γ proton of the erythro and threo isomers. A chemical-shift difference of δ 0.1–0.6 was found. This would suggest that if compound **5** is a mixture of isomers, one should find a complex and varied chemical shift for the γ proton. To the contrary, we have found that **5a–e,g,h** all show a five peak pattern (ABX_3) for the γ proton in the region of δ 4.0–4.57 with a $w_{1/2}$ of 14–16 Hz. Compounds **5i** and **5j** both have the γ proton appearing as a five-peak pattern at δ 4.23–4.73 with a $w_{1/2}$ of 16 Hz. In **5f** the γ proton overlapped the β proton and could not be distinguished. At the present time, the NMR suggests a single compound but does not distinguish the configuration of this compound.

Results and Discussion

Two in vitro assays were used to assess the β-adrenoceptor antagonistic activity of compounds **5** and **6**. Compounds **5a–j** were tested on cultured C6-2B astrocytoma cells by studying their ability to prevent the radioiodinated β-adrenergic receptor probe [^{125}I]iodohydroxybenzylpindolol ([^{125}I]HYP) from binding to the cellular receptor sites. The results are reported in Table II as the concentration of test compound needed to displace 50% of the bound antagonist, [^{125}I]HYP, and is reported as the apparent K_D. The compounds **5a–j** and **6a–e** were also evaluated on the spontaneously beating guinea pig atrial preparations as an indication of β_1-receptor blocking activity and on guinea pig tracheal strips used to evaluate β_2-receptor blocking activity (Table III).[9,10]

Table II. Displacement Constants for γ-Methyl(aryloxy)propanolamines (5) on [^{125}I]Iodohydroxybenzylpindolol Binding Sites

compd	K_D, mol
5a	3×10^{-7}
5b	2×10^{-7}
5c	2×10^{-7}
5d	2×10^{-6}
5e	2×10^{-6}
5f	5×10^{-7}
5g	5×10^{-8}
5h	1.5×10^{-8}
5i	4×10^{-8}
5j	5×10^{-9}
(−)-propranolol	7×10^{-10}

The binding studies on the γ-methyl(aryloxy)-propanolamines, **5**, give results which parallel previous structure–activity relationships (SAR).[11] Hydrogen or alkyl substitution at the 3 and/or 4 position of the aromatic ring has not previously been reported to elicit strong β-antagonist activity. Therefore, it is not surprising that compounds **5a–e** have low-binding affinity. Substitution of the 3,4 position of the aromatic ring with chloro, **5f** (as in the phenylethanolamine antagonist), or 2-allyl, **5g–h**, or replacement of the phenyl with 1-naphthyl, **5i–j**, did result in agents with good affinity for the β receptor. It is especially encouraging since the K_D for γ-methylalprenolol (**5g**), which is a racemate, is within one-tenth of the K_D reported for isomerically pure (−)-alprenolol (3.4×10^{-9}).[11] Increasing the size of alkyl or aralkyl substitution on the amine nitrogen would be expected to increase the

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Table III. Effects of Methyl(aryloxy)propanolamines on Guinea Pig Atria and Tracheal Strips

	atria (β_1)			trachea (β_2)		
compd	EC_{50}[a,b]	±1 SEM[c]	test EC_{50}/ control EC_{50}	EC_{50}[a,b]	±1 SEM[c]	test EC_{50}/ control EC_{50}
control	158.6 (65)	142.0-177.2	1.00	2 191 (60)	2 009-2 389	1.00
propranolol	1911.6 (6)	1427.7-2559.3	12.05	10 229 (4)	6 453-16 214	4.67
5a	798.8 (3)	695.2-917.8	5.04	13 023 (3)	10 649-15 924	5.94
5b	676.0 (3)	575.5-794.1	4.26	4 064 (3)	2 675-6 174	1.85
5c	490.1 (4)	261.0-920.1	3.09	10 689 (3)	8 762-13 038	4.88
5d	504.8 (4)	306.5-831.2	3.18	1 964 (6)	1 715-2 250	0.90
5e	198.9 (3)	150.3-263.4	1.25	1 918 (3)	1 189-3 095	0.88
5f	259.3 (4)	210.5-319.3	1.63	4 123 (3)	3 859-4 405	1.88
5g	736.6 (4)	627.1-893.0	4.64	6 176 (3)	4 522-8 433	2.82
5h	615.9 (3)	477.6-794.3	3.88	4 383 (3)	1 583-12 134	2.00
5i	2278.9 (7)	1725.4-3036.1	14.37	15 057 (6)	12 698-17 853	6.87
5j	1815.8 (3)	1528.5-2157.0	11.45	25 857 (3)	18 383-36 365	11.80
6a	522.8 (4)	479.4-570.1	3.30	4 406 (3)	2 717-7 145	2.01
6b	996.8 (3)	662.3-1500.2	6.28	2 962 (6)	2 137-4 104	1.35
6c	206.4 (3)	90.3-471.5	1.30	1 774 (3)	1 419-2 216	0.81
6d	402.6 (4)	161.7-1002.2	2.54	4 420 (6)	3 800-5 140	2.02
6e	206.9 (5)	132.3-323.6	1.30	2 127 (3)	797-5 681	0.97

[a] Number in parentheses indicates number of replications, with each replication being done on a fresh preparation. [b] EC_{50} values represent micrograms of isoproterenol in a 40-mL bath required to elicit 50% of the maximal increase in atrial rate or 50% maximal tracheal relaxation in the presence of 1 μg of propranolol or 10 μg of test compounds. [c] Range of EC_{50} values encompassed by ±1 times standard error of the mean.

antagonism at the β-adrenergic receptor.[12] This was found to occur with **5h** and **5j**. In general, it would appear that the presence of the γ-methyl substituent caused a decrease in binding on the order of one-tenth compared with compounds of similar structure.

Results from the isolated atrial and tracheal strip preparations are not as easily interpreted. If one applies the term "active" to those compounds which at 10 μg had an effect approximately equal to or exceeding that obtained with 1 μg of propranolol, it is clear that none of the α-methyl compounds, **6a–e**, had significant activity. The unsubstituted phenyl, **5a**, and the 3,4-dimethylphenyl, **5c**, derivatives were markedly weaker than propranolol in the atrial system but were somewhat more effective than 1 μg of propranolol in the tracheal system. γ-Methylpropranolol (**5i**) had substantial β-receptor blocking activity but was no more selective than propranolol itself. The *tert*-butyl derivative, **5j**, which had substantial activity in both test systems, showed a distinctly stronger relative effect in the tracheal preparation. One might conclude that the addition of a γ-methyl group to the side chain of (aryloxy)propanolamines decreases activity of these β blockers but at the same time may confer a shift toward β_2-adrenoceptor antagonism and away from β_1-adrenoceptor action.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Satisfactory IR and ^1H NMR spectra were obtained for all compounds reported. ^1H NMR spectra were recorded on a Varian EM-360 spectrometer using Me_4Si as an internal standard.

1-(*tert*-Butylamino)-3-(2-allylphenoxy)butan-2-ol (5h). To a stirred solution of 2-allylphenol (32.2 g, 0.24 mol) and freshly distilled BF_3–Et_2O (0.7 g) in dry C_6H_6 (220 mL) maintained at 0–5 °C was added 4[4] (9.2 g, 0.06 mol) in benzene (30 mL). The addition took 0.75 h and was followed by 1 h at 0 °C and 1–5 h at 25 °C. A few drops of H_2O were added and the mixture was concentrated in vacuo, taken up in ether, washed with 10% NaOH, and dried ($MgSO_4$). Removal of the solvent resulted in recovery of 14.0 g of crude bromohydrin. A solution of the bromohydrin and freshly distilled *tert*-butylamine (10.95 g, 0.15 mol) in EtOH (50mL) was heated under reflux for 44 h. The reaction mixture was concentrated, taken up in ether, and extracted with 10% HCl. The aqueous phase was washed with ether, cooled in an ice bath, made basic with 20% NaOH, and extracted with $CHCl_3$. Both the ether layer and $CHCl_3$ layer were found by TLC to contain product. The layers were separately dried ($MgSO_4$), and the residues were individually chromatographed on silica gel (500 g) using EtOAc–MeOH–Et_3N (94:3:3) as the eluting solvent. From the ether extract was recovered 3.3 g of **5h**, while the $CHCl_3$ extract gave 1.2 g of **5h**. The combined oil was converted to its HCl salt by addition of an ethereal solution of the amine to a saturated solution of anhydrous HCl in diethyl ether. The recrystallization solvent, yield, and melting point for this product and other compounds **5** and **6**, which were prepared by a similar procedure, are given in Table I.

Binding Assay. The ability of each compound to bind to β-adrenergic receptors of C6-2B astrocytoma cells was tested essentially as previously described by Terasaki and Brooker.[8] A 2×10^{-2} M solution of each compound (**5a–j**) was prepared in 1 mL of a 1:1 solution of 5 mmol of HCl and 95% EtOH. Serial dilutions were then made in 5 mmol HCl and each compound was tested at a wide range of concentrations (10^{-5} to 10^{-10} mol). The C6-2B astrocytoma cells in growth medium (Ham's F-10, 1 mL/well) were added to the culture plates at 37 °C, and 50 μL of blocker was added, followed by 50 μL of [^{125}I]HYP (6.5 fmol, approximately 20 000 cpm/well). The plates were incubated for 1.5 h. The reaction was terminated by replacing the medium with buffered salt solution (130 mmol of NaCl, 4 mmol of KCl, 0.6 mmol of $MgSO_4$, 0.3 mmol of $CaCl_2$, 5 mmol of H_3PO_4, adjusted to pH 7.5 with NaOH) containing 0.1 mmol of (±)-propranolol. The cells were washed 3 times at 21 °C with the buffered salt solution (containing propranolol) over a period of 0.3 h. The cells were dissolved in 1 mL of 0.2 N NaOH and quantitatively transferred to a glass tube and counted for 1 min in a Beckman Gamma 300 Counter.

Guinea Pig Preparations. On a few occassions, some of the test compounds appeared to be weak agonists immediately upon addition to the bath. However, such effects were not observed consistently with any of the compounds, and addition of isoproterenol to the bath was not begun until the preparation base line had returned to normal.

Isolated Atrial Preparations. The isolated spontaneously beating guinea pig atrial preparation was used for evaluation of β_1 receptors blocking activity.[9] Following a 0.5-h equilibrium of the atria in Krebs–Ringer bicarbonate solution (40 mL, 37 °C, oxygenated with 95% O_2–5% CO_2), isoproterenol was added to the bath in a cumulative fashion. Individual doses of isoproterenol were added after the maximal response (increase in rate) was obtained to the preceding dose. After achieving maximal increase

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in atrial rate, the preparation was washed, allowing to reequilibrate, and a second isoproterenol dose–response curve was obtained. Preliminary experiments revealed that the initial isoproterenol dose–response curve was displaced to the left relative to subsequent curves. The second curve was used as a control. After the preparation was washed and was allowed to reequilibrate, 1 μg of (±)-propranolol and 10 μg of **5a–j** or **6a–e** were individually added to the bath and, after 0.25 h, another isoproterenol dose–response curve was obtained. The extent to which this curve was displaced to the right of the control curve was taken as a measure of β_1-receptor antagonist activity. In all cases, curves obtained after addition of test compounds were parallel to and achieved the same maximum value as control curves.

Isolated Tracheal Strips. The isolated guinea pig tracheal strip was used for evaluation of β_2-receptor blocking activity.[9,10] Carbachol (10^{-5} mol) was added to the tissue bath to produce maximal contraction of tracheal smooth muscle 0.25 h prior to addition of the first aliquot of isoproterenol. The effect of carbachol was shown to persist for more than 1 h. Cumulative dose–response curves for isoproterenol, in the presence and absence of 1 μg of (±)-propranolol or 10 μg of compounds **5a–j** or **6a–e** were determined in a manner analagous to that described for isolated atria. In this case, the degree to which the antagonist blocked isoproterenol-induced relaxation of the tracheal smooth muscle was taken as a measure of β_2-receptor antagonist activity. In all cases, curves obtained after addition of test compounds were parallel to and achieved the same maximum value as control curves.

Results were plotted using linear regression (log dose vs. probit of percent of response) and the EC_{50} was determined from these plots.

Acknowledgment. T.L.L. and M.B.C. thank the Institute for Cardiovascular Studies (University of Houston), Eli Lilly and Co. (Indianapolis, IN), and American Heart Association (Texas Affiliate, Inc.) for financial support. The authors express their appreciation to Cynthia Blizzard, Peter Tarbutton, and Margaret Saul for their assistance in collecting biological data.

Retinoic Acid Analogues with Ring Modifications. Synthesis and Pharmacological Activity

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Analogues of retinoic acid that have their major modifications in the 5,6 double bond and 4-methylene group regions of the β-cyclogeranylidene ring have been synthesized as potential agents for the treatment and prevention of epithelial cancer. These modifications were intended to reduce retinoid toxicity by lowering the effective treatment dose because the major metabolic deactivation pathway would be inhibited. Ethyl (*E*)-3,7-dimethyl-9-(*exo*-2-bicyclo[2.2.1]-heptyl)-2,4,6,8-nonatetraenoate (**7**), ethyl (*E*)-3,7-dimethyl-9-(2,2,6-trimethylbicyclo[4.1.0]hept-1-yl)-2,4,6,8-nonatetraenoate (**18**), (*E*)-1-(4-carbethoxyphenyl)-2-methyl-4-(2,2,6-trimethylbicyclo[4.1.0]hept-1-yl)-1,3-butadiene (**28**), (*E*)-retinoic acid-*4,4,18,18,18-d*$_5$ (**39**), and ethyl (*E*)-3,7-dimethyl-9-(3,3-ethano-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (**47**) displayed moderate to excellent activity in an assay for the inhibition of tumor promoter-induced mouse epidermal ornithine decarboxylase.

The reversal or prevention of the transformation of epithelial cells to a neoplastic state by both natural and synthetic retinoids is well established by both in vitro and in vivo experiments.[1] Unfortunately, the dose level of retinoids necessary for therapeutic effectiveness can also produce toxic side effects.[2] However, dose levels could be reduced if the metabolic deactivation of these compounds were reduced or eliminated. A major pathway for metabolic deactivation is allylic oxidation at the 4_R position[3] of the β-cyclogeranylidene ring of the retinoid skeleton.[4] Interference with this hydrogen-abstraction process may therefore produce less toxic and more effective retinoids. We have undertaken the design and synthesis of retinoid analogues that have their major modifications in the region of the $5,6_R$ double bond to reduce the allylic nature of the 4_R protons (**7**, **18**, and **28**) or that have substituents replacing the 4_R protons (**39** and **47**).

The $5,6_R$ bond of norbornyl analogue **7** is saturated. This compound was proposed as an analogue of the labile, but active, 2-norbornenylretinoid **9**[5] and 5,6-dihydro-

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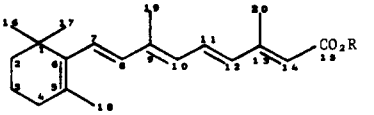
(3) For structural comparisons, standard retinoid numbering has been used:



Similar proton and carbon atoms in the analogues have been denoted by the subscript R. Aryl carbon atoms have been denoted in the spectral tabulations as 1′ and 6′. The position bearing the polyene substituent is numbered 1′ and the remaining positions are numbered in the direction of lowest numerical assignment to the other substituents. The norbornyl ring has also been numbered 1′ to 7′ following standard numbering.

(4) (a) Roberts, A. B.; Nichols, N. D.; Newton, D. L.; Sporn, M. B. *J. Biol. Chem.* **1979**, *254*, 6296. (b) Roberts, A. B.; Lamb, L. C.; Sporn, M. B. *Arch. Biochem. Biophys.* **1980**, *199*, 374.

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