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Adrenoceptor Blocking Agents. 2.[1] 2-(α-Hydroxyarylmethyl)-3,3-dimethylaziridines, a New Class of Selective β_2-Adrenoceptor Antagonists[2]

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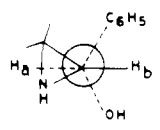
threo- and *erythro*-2-(α-hydroxybenzyl)-3,3-dimethylaziridines (**1a** and **1b**) and *threo*-2-[α-hydroxy(2-naphthyl)methyl]- and 2-[α-hydroxy(3,4-dichlorobenzyl)]-3,3-dimethylaziridines (**1d** and **1c**) have been prepared as conformationally restricted analogues of β-adrenoceptor blocking agents like dichloroisoproterenol (DCI) and pronethalol. The aziridine analogues **1** except possibly **1c** are competitive antagonists of isoproterenol-induced response on a guinea pig tracheal chain preparation and the order of potency is **1d** > **1a** ≥ **1b** > propranolol > **1c**. Unlike propranolol, these compounds have no effect on the isoproterenol-induced response on guinea pig auricles and no significant local anesthetic and antiarrhythmic activity. The aziridine analogues **1** represent the first of a new class of selective β_2-adrenoceptor blocking agents.

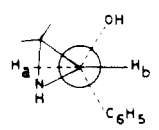
A number of 2-(α-hydroxyarylmethyl)-3,3-dimethylaziridines (**1**) have been synthesized and evaluated for β-adrenoceptor blocking activity in various pharmacological test models as these incorporate β-aryl-*N*-isopropylethanolamine[3]—a side chain present in β-sympathomimetics and β-adrenoceptor blocking agents—into a more rigid conformation having an additional chiral center and a reactive ethylenimine function.

Chemistry. The general method for the synthesis of **1** is outlined in Scheme I. Thus, aryl bromides **2** were converted to diarylcadmium **3** either via magnesium Grignard reagents or lithio compounds. Reaction of **3** with β,β-dimethylacryloyl chloride gave β,β-dimethyl acryloaranones **4**, which were converted to 2-aroyl-3,3-dimethylaziridines **7** either directly[4] by treatment with methanolic iodine and NH_3 or via the dibromo derivative **5**, which on condensation with methanolic NH_3 at room temperature gave **7**. If this reaction were carried out at 0 °C the dehydrohalogenated product **6** could be isolated, which on further treatment with methanolic NH_3 at room temperature gave **7**. Compounds **7** were difficult to purify because of their unstable nature and were used as such in the next step.

Reduction of 2-aroyl-3,3-dimethylaziridines **7** either with sodium borohydride in absolute methanol or with $LiAlH_4$ in dry ether gave one of the isomers of **1** in major amount. In the case of **1** (R = Ph), along with the major isomer **1a** (91.1%, mp 114 °C), a minor isomer **1b** (8.9%, mp 123 °C) was also isolated from the reaction mixture. The stereochemistry and major contributing rotamers for **1a** and



1a



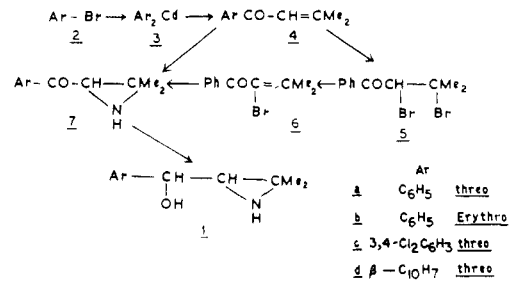
1b

1b were estimated on the basis of NMR, pyridine-induced NMR shifts, and dilution IR studies.

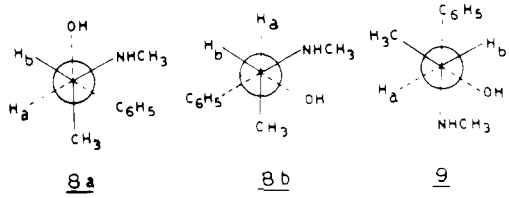
The NMR spectral data of **1a** and **1b** in solvents of diverse polarity are shown in Table I.

Thus both the isomers have similar J_{ab} values of ca. 8–9 Hz, which would indicate major contribution of conformations **1a** and **1b** having trans H_a and H_b with a dihedral

Scheme I

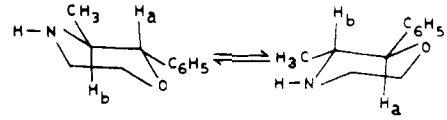


angle of ca. 160°. These conformations[5] are also favored on the basis of the minimum number of gauche interactions as compared to corresponding rotamers wth H_a and H_b gauche to each other. It is pertinent that in ephedrine (**8**) the rotamers **8a** and **8b** contribute significantly.[6] Thus in ephedrine the rotamers with larger gauche interactions



8a **8b** **9**

are stabilized by intramolecular hydrogen bonding. On the other hand, **1b** has minimum gauche interactions but no intramolecular hydrogen bonding. However, in the threo isomer **1a** the intramolecular hydrogen bonding stabilizes the favored rotamer having minimum gauche interactions. This situation is similar to ψ-ephedrine (**9**) and *trans*-2-phenyl-3-methylmorpholine (**10**). Indeed a comparison of δ_{H_a} and J_{ab} of **1a** and **1b** with ψ-ephedrine (**9**) and ephedrine (**8**) and *trans*- and *cis*-2-phenyl-3-



10

methylmorpholines (**10** and **11**) shows a remarkable similarity between **1**, **9**, and **10**, which have similar conformations (Table II).

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Table I. NMR[a] of 1a and 1b

	1a				1b			
Solvent	δ_{H_a}, ppm	δ_{H_b}, ppm	δ_{CH_3},[b] ppm	J_{ab}, Hz	δ_{H_a}, ppm	δ_{H_b}, ppm	δ_{CH_3},[b] ppm	J_{ab}, Hz
CCl_4	4.33	2.016	1.283 (1.249), 1.216	8				
$CDCl_3$	4.367	2.05	1.30 (1.266), 1.233	8	4.516	2.825	1.30 1.216	9.5
C_5D_5N	4.608	2.125	1.350 (1.225), 1.10	9	4.808	3.067	1.516 1.433	8
$(CD_3)_2SO$	4.062	1.775	1.225 (1.195), 1.166	9	4.362	2.546	1.175 1.108	9.5

[a] NMR spectra were recorded on Varian A-60D spectrometer at 10% concentration using Me_4Si as internal reference. [b] A singlet was obtained for each methyl group.

Table II. Comparison of NMR[a] of Aziridines 1a and 1b, ψ-Ephedrine (9), Ephedrine (8), and *trans*- and *cis*-2-Phenyl-3-methylmorpholines 10 and 11 in $CDCl_3$

Compd	δ_{H_a}, ppm	J_{ab}, Hz
1a	4.367	8
1b	4.516	9.5
9	4.16	8.23
8	4.70	4.07
10	4.00	8.80
11	4.80	2.99

[a] The δ_{H_a} and J_{ab} values for compounds 8-11 have been taken from the work of Portoghese.[6a]

The above stereochemical assignments for 1a annd 1b were further supported by pyridine-induced NMR shifts. It has been reported by Demarco et al.[7] that, in general, pyridine causes a vicinal, geminal, and 1,3-diaxial deshielding of groups in hydroxylic compounds. Further vicinal deshielding of a group is directly proportional to the dihedral angle it makes with the OH group. Thus the CH_3 groups in 1b would experience a greater pyridine-induced deshielding effect since these are gauche to the OH group as compared to 1a where the CH_3 groups are trans to the OH group. The pyridine-induced shift values for 1a and 1b (Table III) show a deshielding effect of ca. 0.2 ppm on the CH_3 in 1b while in 1a this is virtually unaffected.

A final proof for these stereochemical assignments was obtained by dilution IR studies.[8] A 0.75 M solution of 1a in tetrachloroethylene showed a bonded NH (3300 cm^{-1}), bonded OH (3175 cm^{-1}), and an intramolecular OH π bonding (3579 cm^{-1}).[9] The dilution experiments (0.005 M) showed OH π bonding (3579 cm^{-1}), bonded OH (3320 cm^{-1}), and bonded NH (3300 cm^{-1}), thus showing intramolecular hydrogen bonding. Definitive conclusions could not be derived from a similar study on 1b which retains water of crystallization tenaciously and this interfered with unambiguous IR assignments. However, at high dilution (0.005 M) 1b showed free OH (3630 cm^{-1}), OH π bonding (3574 cm^{-1}), and free NH (3350 cm^{-1}). Portoghese[6a] and Hyne[10] in independent NMR studies on ephedrine isomers have shown more powerful intramolecular hydrogen bonding for ψ-ephedrine as compared to ephedrine, which is in agreement with the results on 1a and 1b.

Thus, from the above data the higher melting isomer was assigned the erythro (1b) and the lower melting isomer was assigned the threo (1a) stereochemistry. These assignments are consistent with the physical properties like lower melting point and higher R_f value for intramolecularly hydrogen-bonded threo isomer 1a as compared to the erythro isomer 1b.

Wall et al.[11] have shown that the reduction of 1-cyclohexyl-2-phenyl-3-benzoylaziridine with $LiAlH_4$ or $NaBH_4$ gave predominently the erythro isomer, while Deyrup and Moyer[12] showed that $LiAlH_4$ reduction of 1-*tert*-butyl-2-benzoylaziridine gave the erythro isomer, but use of $NaBH_4$ gave threo and erythro isomers in a ratio of 7:3. On the other hand, Pierre et al.[13] showed that reduction of 1-*tert*-butyl-2-acetylaziridine with $LiAlH_4$ gave the threo isomer only, while in 1-methyl-2-*tert*-butyl-3-acetylaziridine, the stereochemistry of the reduction was dependent on the relative stereochemistry of 2,3-substituents. Okutani and Masuda[14] have shown that 1-cyclohexyl-2-benzoylaziridine on $NaBH_4$ reduction gave a mixture of *threo*- and *erythro*-carbinols in a ratio of 7:3. Thus the results obtained in this work show that if the nitrogen of aziridine ring is unsubstituted, the hydride reductions are more stereoselective and a rigid model[15] in which the hydride attack takes place from the less hindered side must be invoked.

Pharmacological Results. Compounds 1a–d (2.5 mg/kg iv) did not show any significant effect on mean arterial blood pressure, rate and amplitude of respiration, and heart rate of an anesthetized cat. Unlike propranolol, none of these compounds caused a reversal of the blood pressure response of isoproterenol. Compounds 1b and 1d potentiated the rise in blood pressure due to epinephrine and 1a and 1d potentiated the pressor phase of the response to isoproterenol, indicating weak cardiovascular β-adrenoceptor blocking activity of 1a, 1b, and 1d.

The order of β_2-adrenoceptor blocking activity of these compounds on guinea pig tracheal chain preparations as shown by pA_2 values and comparison with propranolol (Table IV) is 1d > 1a ≥ 1b > propranolol > 1c. The β_2-blocking activity of these compounds, except 1c, is competitive in nature as suggested by a parallel shift in

Table III. Pyridine-Induced Shifts in the NMR of 1a and 1b

	H_a		H_b		CH_3[a]	
	1a	1b	1a	1b	1a	1b
$\delta_{CDCl_3} - \delta_{C_5D_5N}$	−0.231	−0.292	−0.075	−0.242	+0.041	−0.217
$\delta_{CCl_4} - \delta_{C_5D_5N}$	−0.278		−0.009		+0.024	
$\delta_{(CD_3)_2SO} - \delta_{C_5D_5N}$	−0.546	−0.446	−0.35	−0.521	−0.03	−0.234

[a] The values denoting the midpoint of the two methyl singlets have been used to calculate the pyridine induced chemical shifts.

Table IV. Pharmacological Activity of 1a-d

Compd	% effect on blood pressure[a] (cat), 2.5 mg/kg iv			pA_2 on isolated preparations		Local anesthetic act. (guinea pig) at 0.1% concn
	Response to epinephrine[b]	Response to isoproterenol: Depressor phase	Response to isoproterenol: Pressor phase	Guinea pig tracheal chain[c,d]	Guinea pig auricles[d]	
1a	0	−10	+20	7.2086 ± 0.5139 (4)	4.365 (2)	+++
1b	+11.1	0	0	7.1914 ± 0.8723 (3)	3.4634 (2)	(−)
1c	0	0	−16	6.4001 ± 0.4614 (4)	4.7588 (2)	++++
1d	+62.0	−33	0	8.5168 ± 0.7533 (3)	3.4634 (2)	++
Propranolol	+45.0	−100	Reversal	6.6182 ± 1.6439 (4)	6.5962 (2)	+++++
Procaine	(−)	(−)	(−)	(−)	(−)	+++++

[a] 1a-d did not have a significant effect on mean arterial blood pressure, heart rate, and respiration. [b] 0, no effect; (−), not done. [c] Mean values ± SE calculated for 95% confidence intervels. [d] Figures in the parentheses show the number of experiments.

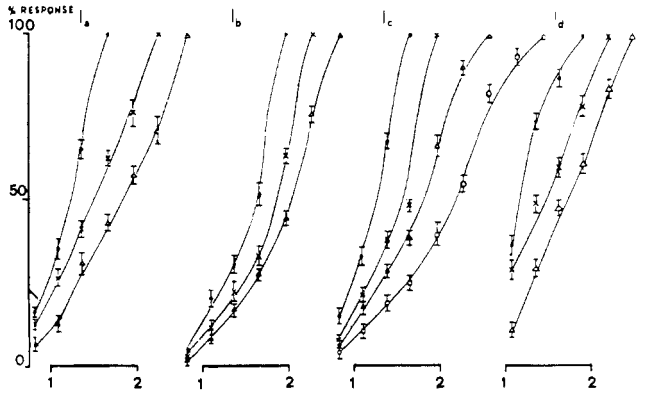

Figure 1. Log concentration–response curves of isoproterenol on isolated guinea pig tracheal chain preparations in the presence of **1a–d**. The abscissas represent the concentrations of isoproterenol: 1 is 1×10^{-5} M and 2 is 1×10^{-4} M isoproterenol. O---O are the control responses of the preparations to isoproterenol. I_a: responses to isoproterenol in the presence of (×---×) 1.376×10^{-7} M **1a** and (Δ---Δ) 2.752×10^{-7} M **1a**. I_b: responses to isoproterenol in the presence of (×---×) 3.44×10^{-8} M **1b** and (Δ---Δ) 1.376×10^{-7} M **1b**. I_c: responses to isoproterenol in the presence of (×---×) 5.868×10^{-7} M **1c**, (Δ---Δ) 1.173×10^{-6} M **1c**, and (□---□) 2.346×10^{-6} M **1c**. I_d: responses to isoproterenol in the presence of (×---×) 5.36×10^{-9} M **1d** and (Δ---Δ) 8.576×10^{-8} M **1d**.

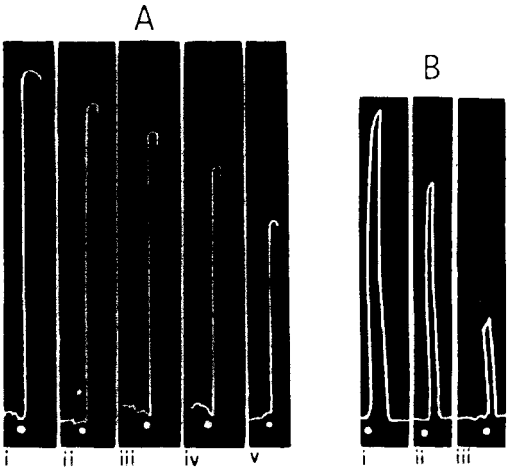

Figure 2. (A) Responses of an isolated guinea pig tracheal chain preparation to acetylcholine (0.72×10^{-8} M): control response (i), and responses in the presence of 1.470×10^{-7} M (ii), 2.94×10^{-7} M (iii), 5.88×10^{-7} M (iv), and 1.176×10^{-6} M (v), of **1c**. (B) Responses of isolated guinea pig ileum to acetylcholine (1.81×10^{-8} M): control response (i), and responses in the presence of 2.346×10^{-6} M (ii) and 9.384×10^{-6} M (iii), of **1c**.

the dose–response curves (Figure 1). The responses to isoproterenol recover within 30–60 min of washing away the antagonist. Moreover at 10^{-7} M concentration **1c** possesses an appreciable competitive type of cholinolytic activity on isolated guinea pig ileum and tracheal chain preparations (Figure 2); other compounds did not have this effect. It is possible that a rather poor activity of **1c** on the tracheal chain preparation is to some extent due to its cholinolytic action.

None of these compounds showed a β_1-adrenoceptor blocking activity on isolated guinea pig auricles and the pA_2 values for these compounds may be less than 5.0; the pA_2 for propranolol under the same experimental conditions is 6.59. Compounds **1a–d** also produced a negative inotropic effect.

It is apparent from the foregoing observations that **1a–d** except possibly **1c** are potent and specific β_2-adrenoceptor blocking agents and are devoid of any apparent β_1-blocking activity. Unlike propranolol, none of these compounds except **1c** showed any significant local anesthetic and antiarrhythmic activity. Further work to investigate this difference in the activities of **1c** as compared to **1a**, **1b**, and **1d** is in progress.

Discussion

The aziridines **1** have two important structural features, the reactive ethylenimine group and a new chiral center in the side chain, and it was expected that these compounds might act as irreversible β-adrenoceptor blocking agents. However, the results show that in guinea pig trachea at pA_2 dose levels, the preparations recover and the test compound can be washed away. On the other hand, in guinea pig auricles at concentrations of 10^{-5} M the preparations do not recover and this may be due to irreversible reaction of the compounds with the preparation. It is unlikely that specificity to β-receptors would be achieved at such a high concentration.

The new chiral center in the side chain will fix the orientation of the amino, hydroxyl, and isopropyl groups in relation to the aromatic ring. Studies on the preferred conformation of catecholamines and their α- and β-antagonists have been carried out in the solid state using x-ray analysis,[16] by NMR in solution,[17] and by MO calculations.[18] It has been shown[19] that the nitrogen is trans and gauche to aryl and hydroxyl groups, respectively. A study of the x-ray structure of isoproterenol,[16b] dichloroisoproterenol (DCI),[16a] and salbutamol, which are either β-adrenergic agonists or antagonists, has shown that the aromatic ring is inclined[19] at 72.9–84.1° to the plane of the ethylamine side chain and the bulky substituent on the nitrogen atom is on the same side as the aromatic group with an N–O distance of ca. 2.8 Å.

The approximate solution conformations of the threo isomers **1a**, **1c**, and **1d** as discussed earlier indicate that the nitrogen is gauche to the hydroxy and trans to the

aromatic group while in the erythro isomer **1b**, which is as potent as **1a** as the β_2-antagonist, the amino group is trans to the hydroxyl and gauche to the aromatic group. Thus while the rotamer contributions[6a] of **1a** are similar to ψ-ephedrine, in **1b** they are different from ephedrine. Thus, in order to explain the biological activity of **1b**, it may be necessary to assume a conformational perturbation of **1b** to ephedrine-like conformation at the receptor site, the energy barrier being small enough to permit this change. The biological activity of the threo isomers having ψ-ephedrine stereochemistry is an enigma. In the phenylethanolamine-type adrenergic agonists an *R* configuration[6a] at the hydroxyl group carbon is essential for activity and among ephedrine isomers D(−)-ephedrine (1*R*:2*S*) has some direct sympathomimetic action.[20] It was proposed[6a] that the inactivity of the D(−) ψ isomer (1*R*:2*R*) may be because of the orientation of the *C*-methyl group below the plane, which hinders effective interaction with the receptor. However, the results obtained in this study show that the ethylenimine C_2–C_3 bond, because of a rigid conformation, does not offer any effective steric barrier for the interaction of the threo isomers of **1** with β-receptors.

It is interesting to note[16d] that in 1-(3,5-dihydroxyphenyl)-2-[2-[3-(4-hydroxyphenyl)propylamino]]ethanol the diastereoisomer having *RR*/*SS* stereochemistry (Th-1165) is about 9–20 times more potent as a β_2-stimulant as compared to the other diastereoisomer having *RS*/*SR* stereochemistry (Th-1179) which points to a preferred orientation of the bulky substituent on the amino group to be on the same side as the aromatic ring. It has been shown in the present study that probably the threo isomers **1a**, **1c**, and **1d** have, and the erythro isomer **1b** can assume, such a conformation, and the locking of this conformation in a rigid ethylenimine structure may account for selective β_2-adrenergic antagonistic activity of these compounds.

Experimental Section

Melting points were taken by the capillary method and are uncorrected. The compounds were checked by IR on a Perkin-Elmer Infracord and/or by NMR on a Varian A-60D spectrometer using Me_4Si as reference; where the analyses are represented by symbols only, the values were found within ±0.4% of the theoretical values. The high dilution IR experiments were carried out on a Perkin-Elmer Model 337 spectrophotometer by using a NaCl cell of 25-mm thickness.

β,β-Dimethyl Acryloaranones (4). Method A (4a). $CdCl_2$ (9.93 g, 55 mM, dried at 110 °C for 8 h) was added to a stirred solution of C_6H_5MgBr [from Mg, 2.4 g (0.1 g-atom), and C_6H_5Br, 15.7 g (0.1 mol)] in Et_2O (150 mL) in 10 min. After the reaction mixture was refluxed for 1.5 h, Et_2O was distilled and replaced by thiophene-free C_6H_6 (100 mL). β,β-Dimethylacryloyl chloride[21] (11.95 g, 0.1 mol) was added to this suspension of Ph_2Cd in C_6H_6 under stirring. The reaction mixture was stirred and refluxed for 16 h, cooled, and decomposed by adding H_2O (50 mL) and aqueous H_2SO_4 (100 mL of 20%). The organic layer was separated and the aqueous layer extracted with C_6H_6. The combined C_6H_6 extracts were washed successively with H_2O, 10% aqueous $NaHCO_3$, and H_2O, dried (Na_2SO_4), and evaporated, and the residue was fractionated under reduced pressure: yield 85%; bp 72–74 °C (1 mm) [lit.[22] bp 102–104 °C (4 mm)].

Method B (4c and 4d). *n*-BuLi in hexane (53.3 mL of 2.25 M, 0.12 mol) was transferred to an N_2-swept three-neck flask containing Et_2O (50 mL). The flask was cooled (to −50 °C in the case of 3,4-$Cl_2C_6H_3Br$ and to −10 °C in the case of β-$C_{10}H_7Br$) and the appropriate bromo compound (0.1 mol) was added; the reaction mixture was stirred for 10 min and this solution of aryllithium was converted to acryloaranones as described in method A. **4c:** yield 30%; bp 148–150 °C (1.5 mm). Anal. ($C_{15}H_{14}O$) C, H. **4d:** yield 78%; bp 113–114 °C (0.5 mm). Anal. ($C_{11}H_{10}Cl_2O$) C, H.

2-Aroyl-3,3-dimethylaziridines (7). Method A. The dibromo compound **5** (9.6 g, 0.03 M) was added to MeOH (75 mL) saturated with dry NH_3 at 0 °C and the mixture was left in the ice chest for 18 h and evaporated in vacuo. The residue was taken in Et_2O, washed with H_2O, dried (Na_2SO_4), and evaporated and the residue was distilled in vacuo to give **6**: yield 3.4 g (47.4%); bp 92–93 °C (1 mm). Anal. ($C_{11}H_{11}BrO$) C, H.

6 (2.6 g, 0.011 M) in MeOH (5 mL) was added to MeOH (20 mL) saturated with NH_3 at 0 °C, stirred at 5 °C for 2 h and 25 °C for 72 h, and processed as above to give **7a** in 93% yield, which could be obtained directly from **5** in 62% yield by carrying out the reaction at 25 °C.

Method B. **4** (60 mM) was added to MeOH (180 mL) saturated with dry NH_3 at 0 °C and I_2 (15.24 g, 60 mM) in a minimum volume of warm MeOH was added under stirring. The color of I_2 was discharged after 6–7 h and the reaction mixture was further stirred at 25 °C for 20 h. Excess NH_3 was removed by passing N_2 through the reaction mixture. Finally the solvent was removed in vacuo and the residue was processed as in method A to give **7** in 52–55% yield. Compounds **7** were labile and could not be obtained in analytically pure form by distillation or chromatography.

***threo*- and *erythro*-2-(α-Hydroxybenzyl)-3,3-dimethylaziridine (1a and 1b).** Sodium borohydride (5 g) was added in small portions to a solution of 2-benzoyl-3,3-dimethylaziridine (5.0 g, 0.0285 M) in CH_3OH (100 mL) under cooling and stirring. The reaction mixture was further stirred for 4 h and then water (10 mL) was added and the reaction mixture was evaporated under reduced pressure. The crude product was taken in cold 5% aqueous AcOH and the neutral impurities were removed by washing with ether. The aqueous layer was made alkaline with 1 N NaOH and the product was extracted with ether. Concentration of the ether extract gave the major isomer **1a** (1.6 g). The residue was chromatographed on neutral Al_2O_3 (60 g) in benzene. Elution with benzene gave an additional amount of **1a** (1.4 g). Further elution with benzene gave the minor isomer **1b** (0.32 g).

1a crystallized from Et_2O–hexane: yield 3.0 g (60%); mp 114 °C. Anal. ($C_{11}H_{15}NO$) C, H, N.

1b crystallized from EtOAc–C_6H_6: yield 0.32 g (6.4%); mp 123 °C; crystallized as a monohydrate. Anal. Calcd for $C_{11}H_{15}NO{\cdot}H_2O$: C, 67.69; H, 8.71; N, 7.11. Found: C, 67.95; H, 8.38; N, 7.12. The structure of **1b** was further confirmed by a comparison of its mass spectrum with that of **1a**. Both gave a weak molecular ion peak at 177 and a base peak at M − 18.

Similarly, the following were prepared: **1c** [crystallized from DMF–H_2O; yield 71%; mp 173 °C. Anal. ($C_{15}H_{17}NO$) C, H, N] and **1d** [crystallized from Et_2O–hexane; yield 68%; mp 132 °C. Anal. ($C_{11}H_{13}Cl_2NO$) C, H, N].

Pharmacological Methods. The following experiments were carried out to study the pharmacological profile of these compounds.

1. The effect of compounds on mean arterial blood pressure and rate and amplitude of respiration was studied in a cat (2–3.5 kg, either sex) anesthetized with pentobarbital–sodium (30 mg/kg ip) by standard manometric technique. The electrocardiograph of a Model 410 "Tektronix" physiological monitor was used to monitor the heart rate.

2. The isolated guinea pig tracheal chain preparations were made and mounted in a bath containing 15 mL of Krebs bicarbonate ringer solution at 36.5 ± 0.5 °C and bubbled with oxygen containing 5% carbon dioxide according to the method of Castillo and deBeer.[23] The initial muscle tone was developed by acetylcholine and cumulative concentrations of isoproterenol were added and the pA_2 values for 15-min applications of the compounds were determined by a linear extrapolation method[24] to measure their β_2-adrenergic blocking activity and compared with that of propranolol.

3. The isolated guinea pig auricles were prepared by the standard method and placed in a bath containing 15 mL of oxygenated Lockes solution. The pA_2 values of the test compounds were determined in the presence of isoproterenol as an agonist and compared with propranolol as a measure of β_1-blocking activity.

4. Antiarrhythmic activity was tested on the electrically driven isolated guinea pig auricles according to the method of Dawes.[25]

5. Isolated guinea pig ileum was placed in a bath containing 15 mL of oxygenated Tyrode solution at 36.5 ± 0.5 °C; acetylcholine and histamine were used as standard spasmogens.

6. The guinea pig intradermal wheal method[26] was used for testing the local anesthetic activity with procaine and propranolol as standard drugs. The response to each of the six pinpricks made at intervals of 5 s was recorded as one plus for one negative response. Table IV shows an average of six such observations.

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Synthesis and Adrenergic Activity of Benzimidazole Bioisosteres of Norepinephrine and Isoproterenol[1]

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The concept of bioisosterism between benzimidazole and catechol was applied to the design and synthesis of benzimidazole analogues of norepinephrine, (*R,S*)-1-[5(6)-benzimidazolyl]-2-aminoethanol (**2**), and of isoproterenol, (*R,S*)-1-[5(6)-benzimidazolyl]-2-isopropylaminoethanol (**4**). Compound **2** was shown to be a partial bioisostere of norepinephrine, with direct agonist activity at the α-adrenergic receptor. The ED_{50} for **2** in contracting the guinea pig isolated aortic strip was determined to be 8.0×10^{-6} M. Compound **4** was shown to be a partial bioisostere of isoproterenol, with direct activity as a β-adrenergic agonist. The ED_{50} values for positive chronotropic and inotropic effects of **4** on the isolated guinea pig atrial preparation were determined to be 6.2×10^{-6} and 3.8×10^{-6} M, respectively. The ED_{50} for **4** on the isolated guinea pig tracheal preparation was determined to be 1.6×10^{-6} M. These results indicate that **4** shows greater selectivity for the β-2 adrenergic receptor than does isoproterenol. The chemical stability of benzimidazole, compared with that of catechol, suggests that benzimidazole bioisosteres of catecholamines may be of value as adrenergic drugs.

In prior studies of structure–activity relationships of compounds which have direct agonist activity at adrenergic receptors, emphasis has been placed on alterations in the ethanolamine side-chain portion of the basic catecholamine agonist. Replacement of the catechol portion of the molecule has met with limited success. We have been interested in the relationship between catechol and a possible nitrogen bioisostere, benzimidazole, especially as it relates to catecholamines.

Several 5(6)-substituted benzimidazoles have been synthesized and tested for adrenergic activity prior to our work in this area. Vaughan and Blodinger[3] reported the syntheses of two benzimidazole analogues of epinephrine, 1-[2-methyl-5(6)-benzimidazolyl]-2-methylaminoethanol and 1-[2-oxo-5(6)-benzimidazolyl]-2-methylaminoethanol. Both compounds were tested for bronchodilator activity, but neither was found to be active. Chodnekar et al.[4] synthesized 1-[2-oxo-5(6)-benzimidazolyl]-2-isopropylaminoethanol as a possible β-adrenergic blocking agent. They reported that an infusion of 100 μg/kg per minute of this compound produced a 35% inhibition of isoproterenol-induced tachycardia in the cat, indicating weak

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