Notes

Cardioselectivity as a Function of Molecular Structure in β-Adrenoceptor Blocking Agents of the 1-(Para-substituted aryloxy)-3-(isopropylamino)propan-2-ol Type[1]

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The relationship between molecular structure and cardioselectivity is described in the 1-(para-substituted aryloxy)-3-(isopropylamino)propan-2-ol type of β-adrenoceptor blocking agents. Cardioselectivity in the aforementioned series requires that the aromatic substitution in the position para to the amino alcohol side chain will have a minimal linear length of 5.0 Å. Highest cardioselectivity is obtained when this para substituent is a rigid group coplanar with the aromatic ring. This may result from steric hindrance for binding at the β_2-adrenoceptor subtype which does not occur in the β_1 subtype. Evidence in favor of this suggestion was obtained by the finding that the trans isomer of 1-[4-(1-propenyl)-2-methoxyphenoxy]-3-(isopropylamino)propan-2-ol is cardioselective ($\beta_1/\beta_2 = 25$), whereas the cis isomer is β_2 selective ($\beta_1/\beta_2 = 0.1$).

β-Adrenoceptor blocking agents are being used increasingly in the treatment of angina pectoris, arrhythmias, and hypertension.[4] It is desirable that the drugs will block selectively β-adrenoceptors in the heart (β_1) with little or no activity on bronchial or vascular (β_2) receptors.[5]

A number of cardioselective β-adrenoceptor blocking agents of the aryloxypropanolamine type are known to date, most of which contain a substituent para to the amino alcohol side chain.[4] However, detailed structural requirements for cardioselectivity in these compounds appear to be lacking. Practolol (**1**), a prototype of the cardioselective β-adrenoceptor blocking agents,[6] was therefore taken as a model for establishing these requirements. The only structural feature in **1** which is different or absent in other nonselective β-adrenoceptor blocking agents that share the same basic skeleton is its *p*-acetamido group. Modifications were therefore made in this substituent as follows: (1) reversal of the amide function, (2) cyclization of the amides to benzamide and anilide type of lactams, (3) replacement of the amide function by alkyl groups, and (4) replacement of the amide function by rigid cis and trans (1-propenyl) isomers.

The results of these modifications indicate that cardioselectivity in 1-(para-substituted aryloxy)-3-(isopropylamino)propan-2-ols is due to spatial properties of the para substituents.

Chemistry. The various aryloxypropanolamines (**1**–**12**, Table I) reported herein were prepared from the corresponding substituted phenols by condensation with epichlorohydrin and subsequent amination with isopropylamine.[7]

The substituted phenols were either prepared according to literature directions cited below or obtained from commercial sources.

The starting material for *cis*-**11** and *trans*-**10** isomers of 1-[4-(1-propenyl-2-methoxyphenoxy)]-3-(isopropylamino)propan-2-ol was 1-hydroxy-2-methoxy-4-propenylbenzene which was obtained commercially and itself consists of a mixture of cis and trans isomers in a ratio of 1:3, respectively. These latter (isoeugenol) isomers were separated quantitatively by GLC[8] and identified by NMR. The AB part of ABX_3 pattern of the isoallyl group in the region of δ 5.0–6.5 ppm, which belongs to the vinylic protons, was identical with the patterns of *cis*- and *trans*-isoeugenols known in the literature.[8]

The ketalic phenol precursor of **12** was obtained by ketalization of 3-(4-hydroxyphenyl)propan-2-one.[9] Ketalization was achieved under acidic catalysis in two ways: (a) the azeotropic distillation with benzene as a solvent and *p*-TosOH as catalyst (ethylene glycol was used here in much higher proportion than usual due to its role as solvent for the phenol and in order to reduce polymerization), and (b) ketalization at room temperature in chloroform, with H_2SO_4 as a catalyst in the presence of 4Å molecular sieves. The ketalization reaction was monitored by IR, following the disappearance of the carbonyl absorption (1700 cm^{-1}).

Examination of the fragmentation pattern of compound **12** revealed similar dominancy of the functional groups (i.e., the dioxolane and amino alcohol side chains) in mass spectrometry.

Pharmacological Activity and Structure–Activity Relationships. A systematic analysis was carried out of the relative contribution made to the cardioselective properties of practolol by steric and electronic factors as well as by lipophilicity of the compounds.

In order to assess the contribution of the electronic factor, the NH and CO in the amide function of practolol were interchanged. The resulting "reversed" practolol (compound **2**) exhibits a high degree of cardioselectivity. When tested in vitro on rat atria (β_1) and on rat stomach fundus (β_2) preparations, the ratio of pA_2 values (β_1/β_2) for this compound was 275.[10]

The benzamide **2** was also found to be cardioselective in vivo.[10,11] This derivative, **2**, with an electron-withdrawing group, is even more cardioselective than the electron-donating, anilide isomer—practolol (**1**) (Table I). This suggests that the cardioselectivity of practolol is not determined by electron distribution in the molecule. Interchange of the NH and CO in the amide function of compounds **1** and **2** did not alter cardioselectivity. Therefore, H bonding between these moieties and the receptor does not appear to be essential for selectivity.

The importance of the spatial location of the N-substituent was examined by cyclization of the amide function in **1** and **2** to the corresponding lactams **4** and **6** and their heterocyclic analogues **5** and **7**. None of these compounds was significantly selective. In view of this, it was concluded that the conformation of the amide function is important

† Deceased March 23, 1978. We wish to dedicate this article to the memory of Dr. Shtacher.

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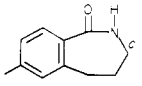
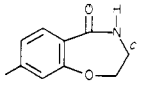
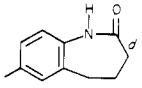
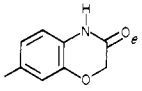
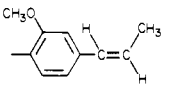
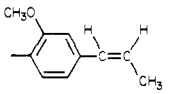
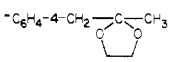
Table I. *dl*-(1-Aryloxy)-3-(isopropylamino)propan-2-ol, $ROCH_2CH(OH)CH_2NH$-*i*-Pr

no.	R	mp, °C	crystn solvent	formula (analyses)	pA_2 value[a] β_1 (atria) (chronotropism)	pA_2 value[a] β_2 (fundus)	β_1/β_2 act. ratio[b]
1	$-C_6H_4$-4-$NHCOCH_3$[c]				6.47	4.33	138
2	$-C_6H_4$-4-$CONHCH_3$[c]	free base, 154-155	MeEtCO	$C_{14}H_{22}N_2O_3$ (C, H, N, M^+)	5.44	3.00	275
3	$-C_6H_4$-4-$CONH_2$[c]				5.00	4.80	1.6
4					3.87	4.09	0.6
5					4.74	4.34	2.5
6		free base, 105-107	toluene	$C_{16}H_{24}N_2O_3$ (C, H, N, M^+)	5.0[f]	5.0[f]	1
7		free base, 120-121	*i*-PrOH-Et_2O	$C_{14}H_{20}N_2O_4$ (C, H, N, M^+)	5.6[f]	5.5[f]	1.3
8	$-C_6H_4$-4-$CH_2CH_2CH_3 \cdot HCl$	117-118	EtOH-Et_2O	$C_{15}H_{26}NO_2Cl$ (C, H, N, M^+)	7.60	6.80	6.5
9	$-C_6H_4$-4-CH_2CH_3	free base, 69-71	*n*-hexane	$C_{14}H_{23}NO_2$ (C, H, N, M^+)	7.20	7.50	0.5
10		free base, 85-87	cyclohexane	$C_{16}H_{25}NO_3$ (C, H, N, M^+)	7.30	5.90	25
11		free base, 77-78	cyclohexane	$C_{16}H_{25}NO_3$ (C, H, N, M^+)	6.70	7.70	0.1
12		free base, 81-82	Et_2O-C_6H_{14} (4:1)	$C_{17}H_{27}NO_4$ (C, H, N, M^+)	<3.5[g]	<3.5	

[a] Values are the average of three to eight determinations, except for compounds **6** and **7**, and are within ±0.1. [b] β_1/β_2 activity ratio refers to the ratio of antagonistic potency of compounds on stomach strip to that of heart rate of isolated atria. [c] See ref 7 and 10. [d] Prepared from the corresponding phenolic benzazepinone which was obtained as a minor product together with its benzamido isomer from Schmidt reaction of 6-hydroxy-1-tetralone.[7] [e] Prepared from 2,3-dihydro-7-hydroxy-1,4-benzisoxazin-3-one which in turn was prepared according to the literature.[14] [f] Values are results of in vivo test in anesthesized cats: β_1 refers to the myocardial effect and β_2 to the vascular effect (ref 7). [g] Agonistic activity of 10^{-8}-10^{-9} M, blocked by propranolol.

in conferring cardioselectivity. The amide function in **1** and **2**, like in other secondary amides, exists almost exclusively in the transoid conformation.[12] The lactams, on the other hand, obviously exist in the cisoid conformation. This suggests that a factor in determining cardioselectivity of **1** and **2** is a minimal distance of the amidomethyl group from the aromatic ring, as determined here by the transoid conformation.

To test this assumption **8** and **9**, in which the amido group was replaced by alkyl groups of varying lengths, were synthesized.

These compounds are structurally similar to the compounds 1-[4-(2-methoxyethyl)phenoxy]-3-(isopropylamino)propan-2-ol (H93/26 or metoprolol) and its hydroquinonic analogue H87/67 reported by Ablad et al.[13]

Although the propyl-substituted compound **8** was cardioselective (β_1/β_2 = 6.5), whereas **9** was not, nevertheless it was much less so than practolol (**1**, β_1/β_2 = 140).

This finding may be interpreted as resulting from the high flexibility of the propyl substituent which makes it adaptable for interaction with β_2 receptors, in contrast to the more rigid amide function of practolol.

In an attempt to confirm this assumption, *cis*- and *trans*-isoeugenol derivatives **10** and **11** were synthesized. In these compounds the acetamide group of practolol is substituted by a rigid 1-propenyl side chain with a preferred conformation coplanar with the aromatic ring.

The 1-propenyl group has two geometric isomers, of which the trans isomer is analogous in its steric structure to that of practolol (**1**) and its "reversed" analogue **2**. Its methyl group is fixed at 5.0 Å from the aromatic ring. In the cis isomer the distance between the methyl group and the aromatic ring is 4.2 Å.

The pharmacological results are in agreement with the aforementioned assumption. The trans isomer **10** (β_1/β_2 = 25) was about 250 times more cardioselective than the cis isomer **11** (β_1/β_2 = 0.1). The marked difference in organ selectivity between the cis and trans isomers is primarily due to a 63-fold decrease in affinity of the trans isomer to β_2 receptors, accompanied by a fourfold increase in its affinity to β_1 receptors.

The pharmacological behavior of the *cis*-**11** and *trans*-**10** isomers also strongly suggests that lipophilicity is not an essential factor in determining the cardioselectivity in practolol derivatives.

In conclusion, cardioselectivity in the para-substituted aryloxypropanolamine type of β-adrenoceptor blocking agents appears to be the result of a steric factor. The steric tolerance of the β_2-adrenoceptor subtype is more limited than that of the β_1 adrenoceptors in that they apparently

cannot accommodate rigid para substituents with a linear length exceeding 5.0 Å.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. IR spectra were recorded in KBr disks on a Perkin-Elmer grating infrared spectrophotometer Model 257. NMR spectra were taken on a Jeol C-60HL spectrometer for 10% solutions in either $CDCl_3$ or CCl_4 containing Me_4Si as an internal standard. Mass spectra were taken with a Hitachi Perkin-Elmer RMU-6 instrument, the samples being introduced directly into the ion source through a vacuum lock, electron energy 70 eV, electron current 20 μA, source temperature 150–350 °C, secondary electron multiplier as the detector. TLC's were performed on either neutral aluminum oxide precoated plates (Al F, 0.25 mm, Riedel-De Haen AG, Germany) or silica gel precoated plates (Si F, Riedel-De Haen, AG, Germany), both containing fluorescent indicator. Spots were detected by UV light at 254 nm and by exposure to I_2 vapor. Preparative gas chromatography of cis and trans isomers of isoeugenol was carried out on a Varian 90P GC instrument with thermal conductivity detector (column, Apiezon L 20% on Chromosorb W, AW, DMCS, 80–100 mesh). Helium was used as a carrier, column temperature 180 °C, detector and injector temperature 230 °C.

Reaction products were routinely analyzed by IR, NMR, and mass spectrometry and by TLC. All compounds showed the expected spectral characteristics. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical results.

Pharmacology. β_1-Blocking activity was determined on isolated rat atria.[10] β_2-Blocking activity was determined on isolated rat stomach fundus.[10] The rationale for using this organ rather than tracheal or vascular muscle is the relative simplicity of the test and its clear distinction from β_1 responses.

Chemistry. 2-(4′-Hydroxybenzyl)-2-methyl-1,3-dioxolane (16). Ketalization of 3-(4′-hydroxyphenyl)propan-2-one was accomplished in two ways.

(a) 3-(4′-Hydroxyphenyl)propan-2-one (2.40 g, 16 mmol) was dissolved in 120 mL of benzene, and ethylene glycol (36 mL, 640 mmol) and p-TosOH–H_2O (710 mg) were added. Following azeotropic distillation of the reaction mixture (72 h), the benzene layer was separated, washed with water, dried ($MgSO_4$), and evaporated. The ketalic product (1.65 g, 53% yield), obtained as a colorless viscous oil, lacked the carbonyl absorption at 1700 cm^{-1}. The product was used without further purification in the reaction with epichlorohydrin.

(b) 3-(4′-Hydroxyphenyl)propan-2-one (2.50 g, 17 mmol) was dissolved in a chloroform–ethylene glycol mixture (20:40 mL, respectively), and 4 Å molecular sieves and 1 mL of concentrated H_2SO_4 were added. The reaction mixture was stirred at room temperature for 7 days. The mixture was then extracted with ether, washed with $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated. The resulting ketalic product was obtained in 77% yield (2.5 g).

1-Aryloxy-2,3-epoxypropanes. The epoxypropanes were prepared according to published procedures.[7] The compounds were purified by column chromatography on neutral alumina grade II. The eluting solvents were mixtures of petroleum ether (bp 40–60 °C) and chloroform. Solid products were recrystallized: 1-(7′-oxy-2′,3′-dihydro-3′-oxo-1′,4′-benzisoxazinyl)-2,3-epoxypropane, mp 164–166 °C, C, H, N, M^+; 1-[4′-(*N*-carboxamidomethyl)phenoxy]-2,3-epoxypropane, mp 108–109 °C (toluene), C, H, N, M^+.

The final aryloxypropanolamines were prepared by the addition of isopropylamine to 1-(aryloxy)-2,3-epoxypropanes by the general method described before.[7]

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References and Notes

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(2) (a) This work forms part of a Ph.D. Thesis submitted by M. Erez to Tel-Aviv University Medical School; (b) The Institute for Clinical Physiology and Bio-Medical Engineering, Beilinson Medical Center, Petah-Tikva, Israel.
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Antiallergic Activity of Tetracyclic Derivatives of Quinoline-2-carboxylic Acids. 1

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Substitution of 1,4-dihydro-4-oxoquinoline-2-carboxylic acid by acetyl, benzoyl, and phenylsulfonyl substituents was found to enhance activity in the rat passive cutaneous anaphylaxis assay. A further increase in activity, to equipotency with DSCG, was achieved by incorporation of the 8-benzoyl moiety into a tetracyclic structure to give 1,4-dihydro-4,11(1*H*,11*H*)-dioxoindeno[1,2-*b*]quinoline-2-carboxylic acid (**20**). In contrast, the reverse isomer **19** was found to have little activity.

Reports[1-3] describing the antiallergic activity of quinoline-2-carboxylic acids (**1**) lead us to report on a parallel series of investigations within our laboratories. Following the introduction of disodium cromoglycate (DSCG, **2**),[4]

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