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Selectivity in New β-Adrenergic Blocking Agents. (3-Amino-2-hydroxypropoxy)benzamides

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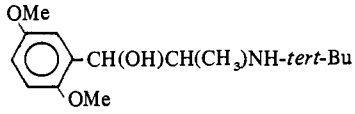
The β-adrenergic receptor blocking properties of new open-chain and lactam-type benzamido analogs of practolol (2) were investigated. These compounds display a competitive blocking activity on both vascular and myocardial β receptors. However, subtle structural changes in the aromatic moiety profoundly affected their organ specificity toward each of these receptors. Since all of the test compounds including practolol (2) share similar lipohydrophilic character, it may be concluded that their ability to selectively block either myocardial or vascular receptors depends primarily on electronic and steric factors.

It has been recently suggested that adrenergic β receptors may be classified into β-1 (*e.g.*, myocardial) and β-2 (*e.g.*, vascular) receptor subtypes.[1,2] The basis for this classification is the observed differences in sensitivity of adrenergic β receptors in various organs to β stimulants and the selective action of some β-adrenergic receptor blockers. With regard to selectivity, it appears that there exists at least three categories of β-receptor antagonists:[3] a group that selectively blocks vascular β receptors, represented by butoxamine (1); one that selectively blocks cardiac β receptors, represented by practolol (2); and one that blocks β receptors in all tissues ("nonselective" β blockers), represented by propranolol (3). Structure–activity relationships of numerous agonists and antagonists for the adrenergic β receptors have been extensively reviewed.[4–8] However, the organ specificity displayed by various β blockers is as yet poorly understood. In order to study in detail the possible implications of chemical structure on selectivity in β blockade, practolol (2) was chosen as a reference compound. This is because of the recognized importance of cardioselective β blockers in clinical practice. The present report is concerned with the syntheses and adrenergic β-blocking activity in the cardiovascular system of a series of benzamido analogs of practolol (2).



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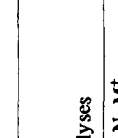
Chemistry. The open-chain (Table I, compounds **15–17**) and lactam-type (Table I, compounds **18** and **19**) benzamido analogs of practolol (2) were prepared in two steps: (a) reaction of epichlorohydrin with the corresponding substituted phenols, in the presence of a base, and (b) treatment of the resulting 1-aryloxy-2,3-epoxypropanes (Table II, compounds **9–14**) with the appropriate amine to give the desired (±)-1-amino-3-aryloxypropan-2-ols (Table I, compounds **15–19**). The starting materials for compounds **10–12**, namely, 4-hydroxybenzamide, 3-hydroxybenzamide, and 3,5-dihydroxybenzamide (α-resorcylamide), respectively, were prepared in high yield by aminolysis of the corresponding esters in aqueous ammonia at room temperature. The phenolic lactams, 2,3,4,5-tetrahydro-7-hydroxy-1*H*-2-benzazepin-1-one[9] (7) and 2,3-dihydro-8-hydroxy-1,4-benzoxazepin-5(4*H*)-one (8) (the starting materials for compounds **13** and

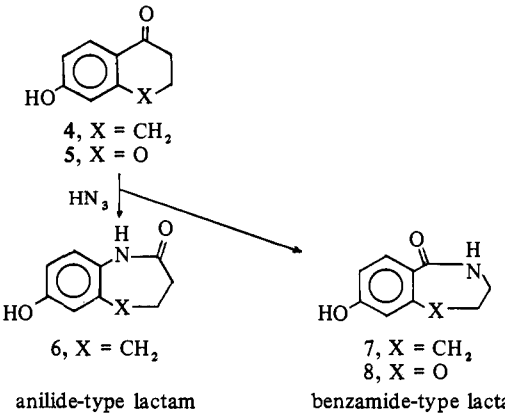
†This work forms part of a Ph. D. thesis to be submitted by M. Erez to the Tel Aviv University Medical School.

Table I. DL-1-Aryloxy-3-isopropylaminopropan-2-ols, $ROCH_2CH(OH)CH_2NH$-*i*-Pr

No.	R	Mp, °C	Crystn solvent	Formula	Analyses	R_f values[a]			"pA_2"[b]		Vascular/ myocardial ED ratio
						A	B	C	Myocardial	Vascular	
15[c]	4-$PhCONH_2$	152–154	Toluene	$C_{13}H_{20}N_2O_3$	C, H, N, M^+	0.36	0.42	0.32	5.68 (526 μg/kg)	5.76 (439 μg/kg)	0.8
16[c]	3-$PhCONH_2$	117–118	*i*-PrOH–hexane	$C_{13}H_{20}N_2O_3$	C, H, N, M^+	0.36	0.42	0.34	6.26 (139 μg/kg)	6.73 (47 μg/kg)	0.3
17		113–114	*i*-PrOH	$C_{19}H_{33}N_3O_5$	C, H, N, M^+	0.25	0.32	0.20	>10 mg/kg	>10 mg/kg	
18		158–159	Toluene	$C_{16}H_{24}N_2O_3$	C, H, N, M^+	0.36	0.45	0.32	4.80 (4.65 mg/kg)	5.74 (531 μg/kg)	0.1
19		115–117	*i*-PrOH–Et_2O	$C_{15}H_{22}N_2O_4$	C, H, N, M^+	0.35	0.41	0.31	5.33 (1.37 mg/kg)	4.92 (3.52 mg/kg)	2.6
2	4-$PhNHCOCH_3$					0.38	0.48	0.34	6.79 (43 μg/kg)	5.30 (1.33 mg/kg)	31
3	1-Naphthyl								7.15 (18.3 μg/kg)	7.70 (5.2 μg/kg)	0.3

[a]Developer A: NH_4OH (sp gr 0.89)–MeOH, 3.5:96.5 by volume. Developer B: NH_4OH (sp gr 0.89)–MeOH, 7:93 by volume. Developer C: *n*-BuOH–AcOH–H_2O, 4:2:1 by volume. [b]Values are the average of three determinations. For explanation, see Experimental Section. [c]German Patents 1,936,693 (1969) [*Chem. Abstr.*, **72**, 111099v (1970)] and 2,106,509 (1970) [*Chem. Abstr.*, **75**, 140515v (1971)].

14, respectively), were prepared by the Schmidt reaction with 6-hydroxy-1-tetralone[10] (**4**) and 7-hydroxychroman-4-one[11] (**5**), respectively.

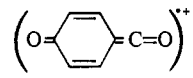


The electron-releasing effect of the 6-hydroxy group in position para to the carbonyl group of 6-hydroxy-1-tetralone (**4**) was found in our experiments to predominate over the steric effect. Consequently, alkyl migration in the course of Schmidt rearrangement was favored, leading to the formation of 2,3,4,5-tetrahydro-7-hydroxy-1*H*-2-benzazepin-1-one (**7**) as the major product (*ca.* 90%) in the mixture of the two possible isomeric benzazepinones (**6** and **7**). The benzamide-type lactam **7** was easily separated from other reaction products. The high ratio of alkyl/aryl migration in our procedure (carried out in methanesulfonic acid as the acidic medium) contrasts with recent results by others (*ca.* 40% for 93% H_2SO_4 and *ca.* 60% for trichloroacetic acid).[9] These differences in migration aptitudes could be attributed to the nature of the various acid media employed in the Schmidt reaction. In the present case methanesulfonic acid was chosen as the catalyst-solvent, in order to avoid simultaneous sulfonation of the phenolic ring. In the case of the Schmidt reaction with 7-hydroxychroman-4-one (**5**), the combined electron-releasing effects of the hydroxyl group and etheral oxygen atom (para and ortho to the carbonyl group, respectively) led to the almost exclusive formation of 2,3-dihydro-8-hydroxy-1,4-benzoxazepin-5(4*H*)-one (**8**), as a result of alkyl migration. In this connection, it has been argued that, in the Schmidt rearrangement of chromanones, only electronic effects prevail.[12]

The structures of the phenolic lactams **6–8** were established unequivocally by nmr and mass spectrometry. The nmr spectrum of the benzamide-type lactam **7** revealed the participation of the NH hydrogen in spin–spin coupling of the C-3 methylene protons, which was abolished by deuterium exchange. On the other hand, the nmr spectrum of the anilide-type lactam **6** showed an unresolved multiplet in the region δ 1.8–2.7, integrating for 6 protons (CH_2-3, CH_2-4, CH_2-5), which remained unchanged after the addition of deuterium oxide. The nmr spectrum of **8** showed a quartet-like multiplet centered at δ 3.44 (2 H, CH_2-3, methylene adjacent to the NH function of the lactam group), which upon addition of deuterium oxide collapsed to a triplet (J = 5 Hz) as expected from a benzamide-type lactam structure.

Another useful tool for the differentiation of benzamide from anilide-type lactams was the fragmentation pattern of these isomers by electron impact. The benzamide-type phenolic lactams **7** and **8** show two prominent peaks of *m/e* 120 (**20**) and 121 (**21**). On the other hand, the strongest peak (100%) in the mass spectrum of the anilide-type phenolic lactam **6** is of *m/e* 122 (**22**).

Reaction of the substituted phenols with epichlorohydrin



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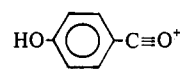

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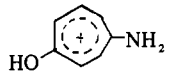

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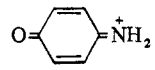

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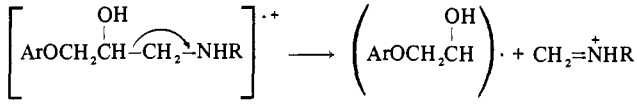
to yield the corresponding 1-aryloxy-2,3-epoxypropanes (Table II, compounds **9–14**) was carried out with a large excess of epichlorohydrin in order to avoid the formation of bis-1,3-aryloxypropan-2-ols.[13] The epoxypropane derivatives of the benzazepinones **6** and **7**, in contrast to the phenolic precursors, could be differentiated into anilide- and benzamide-type lactams on the basis of the ir absorption band of the lactam carbonyl, 1690 and 1670 cm^{-1}, respectively. The strongest peak (100%) in the mass spectra of the 1-aryloxy-2,3-epoxypropanes was in all cases the molecular peak (M^+) with the exception of compound **9** with *m/e* 108 (100%) (**23**). Opening of the epoxide ring in compounds **9–14** to yield the 1-amino-3-aryloxypropan-2-ols was carried out with a large excess of the appropriate amine (*i*-$PrNH_2$). In this way, the formation of tertiary amines as a result of further reaction of the *sec*-amino alcohol products with another molecule of the epoxide[14] was avoided. In agreement with previous data on mass spectra of similar compounds,[15] the strongest peak (100%) in the mass spectra of 1-aryloxy-3-isopropylaminopropan-2-ols (compounds **2**, **15–19**) was *m/e* 72 (**24**). This fragment could only be derived from α cleavage to the nitrogen atom of secondary alcohols, in analogy with the cleavage of simple aliphatic amines.[16]



24, R = *i*-Pr (*m/e* 72)

Pharmacological Activity and Structure-Activity Relationships. Compounds **15**, **16**, **18**, and **19** produced a parallel shift to the right of the log dose–response curves due to isoproterenol-induced tachycardia and vasodilatation, with no depression of the maximum response. These compounds therefore display a competitive and reversible β-adrenergic blockade. Compound **17** was devoid of β-adrenergic blocking activity on either myocardial or vascular receptors even at doses as high as 10 mg/kg. For comparison, propranolol (**3**) is a potent β-adrenergic receptor blocker with a definite though weak selectivity toward vascular receptors [ED(vascular)/ED(myocardial) = 0.3]. Practolol (**2**), on the other hand, is a weaker β blocker which, however, displays a pronounced selective action on cardiac β receptors [ED(vascular)/ED(myocardial) = 31]. These findings are in agreement with published data.[8] Reversal of the amide group of practolol (**2**) in the benzamido analogs markedly reduced the β-adrenergic blocking activity on myocardial receptors. Within this series of compounds, the open-chain benzamides (compounds **15** and **16**) are more potent blockers of myocardial receptors than the lactams (compounds **18** and **19**). The inactivity of compound **17** may be attributed to an unfavorable spatial arrangement of the amino alcohol side chains. In compound **15**, the mere reversal of the amide group from an anilide (as in practolol) to a benzamide type, resulted in a complete loss of cardiac selectivity [reversal of ED(vascular)/ED(myocardial) from 31 to 0.8]. This change in pharmacological activity could be attributed to electronic factors associated with the electron-releasing effect of the acetamido group, as compared with the electron-withdrawing effect of the benzamido group. Replacement of a methylene group in compound **18** with an oxygen atom, to give a benzoxazepine derivative (compoung **19**), reversed once again the selectivity from vascular to myocardial [ED(vascular)/ED(myocardial) change from 0.1 to 2.6]. It should be emphasized that none of the observed changes in pharmacological activities were accompanied by changes in the lipohydrophilic character of the compounds studied. This was estimated from their R_f values in tlc[17] (Table I) which were very close in all cases.

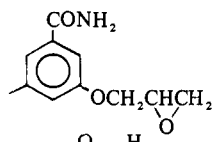
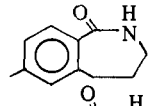
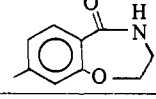
In conclusion, at this stage, the results reported in this study support the view that the organ specificity (selectivity) displayed by blockers of β-adrenergic receptors may be attributed to intrinsic differences among these blockers such as molecular shape and size and charge distribution. Further studies to confirm this hypothesis are now in progress.

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 Infracord Model 337 spectrophotometer equipped with a NaCl prism. Nmr spectra were taken on a Varian H-100 spectrometer for 5–10% solutions in either $CDCl_3$ or pyridine (d_5) containing TMS as an internal standard. Mass spectra were taken with an Hitachi Perkin-Elmer RMU-6 instrument, the

Table II. 1-Aryloxy-2,3-epoxypropanes

$ROCH_2CH(O)CH_2$

No.	R	Mp, °C	Crystn solvent	Formula	Analyses
9	4-$PhNHCOCH_3$	118	*i*-PrOH	$C_{11}H_{13}NO_3$	C, H, N, M^+
10	4-$PhCONH_2$	145–146	EtOAc	$C_{10}H_{11}NO_3$	C, H, N, M^+
11	3-$PhCONH_2$	105–107	EtOAc	$C_{10}H_{11}NO_3$	C, H, N, M^+
12		125–126	*i*-PrOH	$C_{13}H_{15}NO_5$	C, H, N, M^+
13		137–138	Toluene	$C_{13}H_{15}NO_3$	C, H, N, M^+
14		119	C_6H_6-CCl_4 (1/1)	$C_{12}H_{13}NO_4$	C, H, N, M^+

samples being introduced directly into the ion source through a vacuum-lock, electron energy 70 eV, electron current 20 μA, source temperature 170–200°, secondary electron multiplier as the detector. Tlc's were performed on silica gel G precoated plates, layer thickness 0.25 mm (E. Merck, Germany) and spots detected by exposure to I_2 vapor. Reaction products were checked routinely 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 ±0.2% of the theoretical values.

Pharmacology. β-Adrenergic blocking activity was evaluated in cats of either sex (2.5–3.5 kg) anesthetized with chloralose (80 mg/kg iv). Spontaneous respiration was assisted by the insertion of a tracheal cannula. The cats were vagotomized bilaterally and their aortic blood pressure and heart rate were recorded continuously. Electrocardiograms (lead 2) were obtained from needle electrodes inserted into the skin. Drugs were administered through a catheter in the femoral vein. Control dose-response curves to isoproterenol-induced tachycardia and vasodilatation were established (dose range *ca.* 0.06–0.60 μg/kg). Then, a saline solution of a given test compound was administered iv, on a 0.5 log dose schedule (0.01–10.00 mg/kg), at 15–20-min intervals. Isoproterenol was administered at 5–10-min intervals before and after each dose of any of the various test compounds. Dose-response curves were drawn for the positive chronotropic and vasodepressor effects of isoproterenol after individual doses of each of the test compounds. Quantitative evaluation of isoproterenol antagonism on myocardial and vascular β-adrenergic receptors was performed by determination of "pA_2" values.[18] "pA_2" is defined as the negative logarithm of the molar dose of an antagonist injected into animals on a weight basis that doubles the dose of the agonist required to achieve a given effect. The "pA_2" values thus derived from whole animals' experiments are assumed to be analogous to pA_2 values derived from isolated organ preparations and to be related to the concentration of the antagonist at its site of action. The dose ratio x of equiactive doses of isoproterenol obtained in the presence and in the absence of a given antagonist was calculated for each test compound from the log dose–response curve. Plotting $\log (x - 1)$ against the negative logarithm of the molar dose of each of the test compounds (**15**, **16**, **18**, and **19**) injected per kilogram of body weight ("pAx") resulted in a straight line with intercept "pA_2." The "pA_2" values determined in this way for each new test compound and the relative intensity of β blockade in myocardium and blood vessels [ED(vascular)/ED(myocardial)ratio] are shown in Table I. For comparison, "pA_2" values and relative intensity of β blockade of two reference drugs, practolol (**2**) and propranolol (**3**), are also included.

Chemistry. 2,3,4,5-Tetrahydro-7-hydroxy-1*H*-2-benzazepin-1-one[9] (7). To a stirred solution of 6-hydroxy-1-tetralone[10] (**4**) (6.5 g, 0.04 mol) in methanesulfonic acid (140 ml) cooled to 6–12° was added sodium azide (3.4 g, 0.052 mol) in portions over 1 hr with constant stirring and cooling. After the evolution of N_2 had ceased, the reaction mixture was stirred at room temperature overnight and then poured onto crushed ice. A tarry material was filtered off and the filtrate neutralized with sodium bicarbonate. The product (4.60 g, mp 200–230°) separated from the aqueous solution in relatively pure form (>80% according to tlc). The aqueous phase was extracted exhaustively with EtOAc. Evaporation of the dried extract left a mixture (1.7 g, *ca.* 1/1 ratio according to tlc) of the two isomeric benzazepinones **6** and **7**. The total yield of the benzamide-type phenolic lactam **7** was 80%. Recrystallization of the relatively pure product that separated as the first crop from water gave an analytical compound: mp 244–245° (lit.[9] mp 238–239°); ir (KBr) 1640 cm^{-1} (C=O lactam); *m/e* 147 (100%); R_f 0.46 ($CHCl_3$–MeOH, 8:2); nmr (pyridine-d_5) δ 1.79 (multiplet, 2 H, CH_2-4), 2.72 (triplet, 2 H, J = 7 Hz, CH_2-5), 3.07 (multiplet, 2 H, CH_2-3), collapsing to a triplet centered at δ 3.07 (J = 7 Hz) following deuterium exchange. *Anal.* ($C_{10}H_{11}NO_2$) C, H, N.

The anilide-type isomer **6** gave mp 241–245° dec (EtOH) (lit.[9] mp 244–245°); ir (KBr) 1640 cm^{-1} (C=O lactam); *m/e* 122 (100%); R_f 0.50 ($CHCl_3$–MeOH, 8:2); nmr (pyridine-d_5) δ 1.8–2.7 (multiplet, 6 H, CH_2-3, CH_2-4, CH_2-5).

2,3-Dihydro-8-hydroxy-1,4-benzoxazepin-5(4*H*)-one (8). 7-Hydroxychroman-4-one[11] (**5**) (8.2 g, 0.05 mol) in methanesulfonic acid (150 ml) was treated with sodium azide (4.2 g, 0.065 mol) in exactly the same manner as for 1-tetralone (**4**). After the usual work-up the product was obtained in an analytical form (7.5 g, 84% yield): mp 224–225° (H_2O); ir (KBr) 1650 cm^{-1} (C=O lactam); *m/e* 121 (100%); R_f 0.44 ($CHCl_3$–MeOH, 8:2); nmr (pyridine-d_5) δ 3.44 (multiplet, 2 H, CH_2-3), collapsing to a triplet centered at δ 3.44 (J = 5 Hz) following deuterium exchange, 4.25 (triplet, 2 H, J = 5 Hz, CH_2-2). *Anal.* ($C_9H_9NO_3$) C, H, N.

General Procedure for Preparation of 1-Aryloxy-2,3-epoxypropanes (9–14). The appropriate phenol (5 mmol), dissolved in H_2O (*ca.* 10 ml) containing NaOH (6 mmol), was added slowly into a large excess of epichlorohydrin (100 mmol) dissolved in MeOH (15 ml), with stirring, at room temperature. At the end of the reaction (overnight for compounds 9–12; 3–4 days for compounds 13 and 14), the reaction mixture was evaporated *in vacuo* to remove the excess of epichlorohydrin and of the MeOH. The residue was taken into EtOAc and the extract washed with H_2O and dried ($MgSO_4$). Evaporation of the dried extract, followed by crystallization of the residue from appropriate solvents, furnished the analytically pure products. Yields were above 90% in all cases.

General Procedure for Preparation of 1-Amino-3-aryloxypropan-2-ols (15–19). The epoxides (compounds 9–14) in *i*-PrOH were added slowly into a large excess of *i*-$PrNH_2$, while stirring (amine/epoxide molar ratio, 50–100/1). The reaction mixture was left at room temperature for 1–2 days and then evaporated to dryness *in vacuo*. The resulting amino alcohols (1-aryloxy-3-isopropylaminopropan-2-ols, compounds 15–19) were crystallized to constant melting points. Yields of the amino alcohols were almost quantitative in all cases.

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