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β-Adrenergic Blocking Agents. 17. 1-Phenoxy-3-phenoxyalkylamino-2-propanols and 1-Alkoxyalkylamino-3-phenoxy-2-propanols

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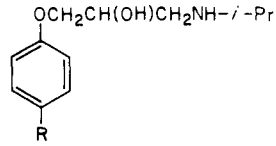
The synthesis is described of a series of derivatives of 1-phenoxy-3-phenoxyalkylamino-2-propanols and 1-alkoxyalkylamino-3-phenoxy-2-propanols. The compounds were investigated for their β-adrenoceptor blocking properties and many showed a surprising degree of cardioselectivity when tested in vivo in anesthetized cats for their effects on an isoproterenol-induced tachycardia and depressor response. The structure–activity relationship shown by this series of compounds is related to that of known cardioselective analogues and a possible reason for their cardioselectivity is discussed.

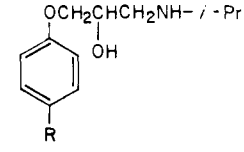
Several cardioselective β-adrenoceptor blocking agents are now available for clinical use and an examination of their structures reveals certain common features. From our previously described work[1-4] it has become apparent that a *p*-amidic substituent in the aryl ring of an aryloxypropanolamine will confer cardioselectivity (structure I).



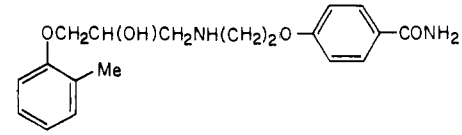
I, R = NHCOR′, NHCONHR′, CONHR′, or CH_2CONHR'; R′ = H, alkyl, or aryl substituents

Other workers[5,6] have found cardioselectivity with nonamidic, para-substituted aryloxypropanolamines, e.g., the para-substituted analogue of oxprenolol II and metoprolol III.

More recently, it was shown[7] that cardioselectivity was obtained by replacing the isopropyl or *tert*-butyl substituent with an aryloxyalkyl group in which the aryl ring had a *p*-amidic substituent; this work led to the development of tolamolol (IV).



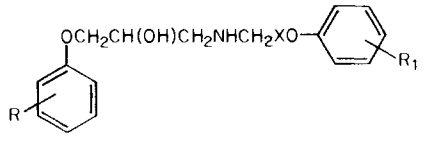
II, R = $-OCH_2CH{=}CH_2$
III, R = $-CH_2CH_2OCH_3$



IV

Working along similar lines, other workers[8] replaced the isopropyl or *tert*-butyl substituent with a 3,4-dimethoxyphenethyl moiety. The best compound, V, of this series

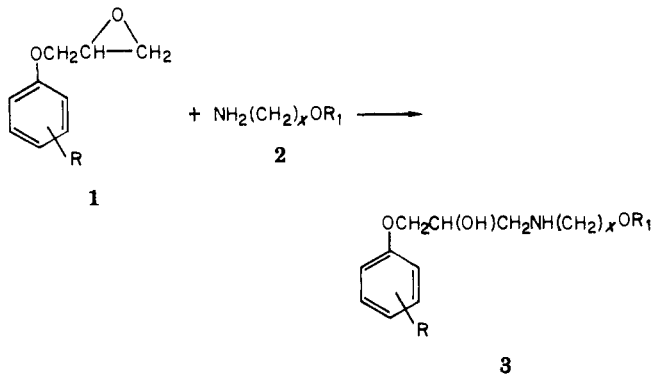
Table I. 1-Substituted Phenoxy-3-substituted Phenoxyalkylamino-2-propanols



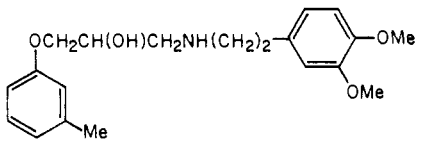
No.	R	R_1	X	Mp, °C	Crystn solvent	Yield,[a] %	Emp formula	Dose, μg/kg, giving 50% inhibn of tachycardia[c]	Inhibn, %, of depressor response[c]
4	H	H	CH_2	115–117	EtOAc	11	$C_{17}H_{21}NO_3 \cdot 0.5H_2O$	54	0
5	H	H	$(CH_2)_2$	191–193	EtOH	3	$C_{18}H_{24}ClNO_3$	239	0
6	H	H	$-CH(CH_3)-$	80–82	c-C_6H_{12}	30	$C_{18}H_{23}NO_3$	51	0
7	H	2-OH	CH_2	209–210	EtOH	2	$C_{17}H_{22}ClNO_4$	22	0
8	H	2-CH_3	CH_2	98–100	EtOAc	20	$C_{18}H_{23}NO_3$	31	0
9	H	3-CH_3	CH_2	166–168	*i*-PrOH	18	$C_{18}H_{24}ClNO_3$	116	29
10	H	4-CH_3	CH_2	112–113	c-C_6H_{12}	10	$C_{18}H_{23}NO_3$	179	0
11	H	2-*n*-C_3H_7	CH_2	154–156	*i*-PrOH	21	$C_{22}H_{29}NO_7 \cdot 0.5H_2O$	833	0
12	H	2-$CH_2CH{=}CH_2$	CH_2	163–166	EtOH	14	$C_{22}H_{27}NO_7$	750	33
13	H	2-OCH_3	CH_2	132–134	EtOH	25	$C_{20}H_{25}NO_6$	63	0
14	H	2-OCH_3	$(CH_2)_2$	117–119	EtOH	34	$C_{21}H_{27}NO_8 \cdot H_2O$	721	15
15	H	2-OCH_3	$-CH(CH_3)-$	106–108	EtOAc	9	$C_{21}H_{27}NO_8$	14	0
16	H	4-OCH_3	CH_2	104–106	EtOAc	7	$C_{18}H_{23}NO_4$	64	0
17	H	2,6-OCH_3	CH_2	138–140	EtOH	18	$C_{21}H_{27}NO_9$	2259	0
18	H	2-Cl	CH_2	150–152	EtOH	14	$C_{19}H_{22}ClNO_7 \cdot 0.5H_2O$	821	71
19	H	3-Cl	CH_2	171–172	EtOH	22	$C_{17}H_{21}ClNO_3$	375	36
20	H	4-Cl	CH_2	124–125	c-C_6H_{12}	14	$C_{17}H_{20}ClNO_3$	80	0
21	H	2-F	CH_2	154–155	*i*-PrOH	12	$C_{17}H_{20}FN$	81	0
22	H	4-F	CH_2	111–113	c-C_6H_{12}	13	$C_{17}H_{20}FNO_3$	29	58
23	H	2,6-Cl_2	CH_2	154–156	EtOH	19	$C_{19}H_{21}Cl_2NO_7$	402	11
24	H	2-Cl,6-CH_3	CH_2	168–170	EtOH	17	$C_{20}H_{24}ClNO_7$	90	79
25	H	4-$OCH_2C_6H_5$	CH_2	118–120	*n*-PrOH	28	$C_{24}H_{27}NO_4$	534	0
26	H	2,3-CH=CHCH=CH-	CH_2	168–169	*i*-PrOH	12	$C_{21}H_{24}ClNO_3$	231	0
27	2-CH_3	H	CH_2	125–127	*i*-PrOH	4	$C_{18}H_{24}ClNO_3$	284	12
28	3-CH_3	H	CH_2	156–158	*i*-PrOH	3	$C_{18}H_{24}ClNO_3$	1756	33
29	4-CH_3	H	CH_2	110–112	EtOAc–petr ether[b]	5	$C_{18}H_{23}NO_3$	Inactive	
30	2-OCH_3	H	CH_2	164–165	EtOH	11	$C_{20}H_{25}NO_8$	527	0
31	2-OCH_3	2-OCH_3	CH_2	118–120	EtOH–Me_2CO	26	$C_{21}H_{27}NO_9 \cdot H_2O$	539	60
32	4-$OCH_2C_6H_5$	H	CH_2	114–116	EtOAc	28	$C_{24}H_{27}NO_4$	Inactive	
33	4-OH	H	CH_2	154–156	EtOAc	60	$C_{17}H_{21}NO_4$	31	78
34	2-Cl	H	CH_2	175–177	H_2O	15	$C_{19}H_{22}ClNO_7$	1106	38
35	2-Br	H	CH_2	202–204	EtOH–H_2O	6	$C_{18}H_{21}BrNO_5$	300	0
36	Tolamolol							133	81

[a] Yield based on epoxide. [b] Bp 60–80 °C. [c] See Pharmacology section for description of method.

Scheme I



showed cardioselectivity and was chosen for clinical evaluation.



V

The features conferring cardioselectivity to structures I–V were either para substitution of the aryl ring of an aryloxypropanolamine or replacement of the isopropyl or *tert*-butyl groups with a substituted aromatic ring attached to the nitrogen atom by a suitable side chain.

We report here on extension of our work on cardioselective β-adrenoceptor blockers, adding further structure–activity information to the above observations. This work is complementary to that quoted above[7,8] but differs with respect to the aromatic substitution pattern of the aryloxyalkyl groups and by the replacement of these groups by simple alkoxyalkyl groups.

A surprising finding was the large number of compounds within the series which blocked the isoproterenol-induced tachycardia with little or *no* effect on the isoproterenol depressor response in our in vivo cat screen.

Chemistry. The compounds were prepared by the well-described method[9] of reacting a 1,2-epoxy-3-(substituted phenoxy)propane with the appropriate amine, as illustrated in Scheme I. The Experimental Section is therefore limited to a typical preparation, which is included for convenience, and to the preparation of the hydroxy analogues 7 and 33 which incorporate a hydrogenation procedure. The various substituted phenoxy and alkoxyethylamines were prepared by standard synthetic routes, all of which are adequately described in the literature.

Pharmacology. β-Adrenoceptor blocking potency was estimated in vivo using the previously described cat preparation.[10] The results given in Tables I and II are expressed as the total dose, infused over a period of 30 min, causing a 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 μg/kg dosed iv). The degree (%) of blockade of the vasodepressor response at that dose level is also given. The relative potencies of these two systems give some indication of selectivity for β-1 (cardiac) as opposed to β-2 (vascular) receptors. Mean log ED_{50}'s were calculated for each compound on the basis of two or three tests and the standard errors of the means were computed. On the average these mean values had an error of 30%.

Discussion

In this study our objective was to determine the effects on potency and cardioselectivity of replacing the isopropyl

Table II. 1-Alkoxyalkylamino-3-substituted Phenoxy-2-propanols

No.	R	R_1	x	Mp, °C	Crystn solvent	Yield,[a] %	Emp formula	Dose, μg/kg, giving 50% inhibn of tachycardia[c]	Inhibn, % of depressor response[c]
37	H	CH_3	2	145–147	EtOH	20	$C_{14}H_{19}NO_7$	130	0
38	H	C_2H_5	2	140–142	EtOAc–EtOH	77	$C_{14}H_{22}NO_5$	47	10
39	H	C_2H_5	3	139–140	EtOAc–EtOH	20	$C_{16}H_{27}NO_7$	66	0
40	4-OH	CH_3	2	165–167	EtOAc–EtOH	70	$C_{13}H_{20}NO_6$	118	0
41	2-CN	CH_3	2	75–76	EtOAc–EtOH	41	$C_{13}H_{18}N_2O_3$	198	0
42	2-NO_2	CH_3	2	94–95	EtOAc	26	$C_{12}H_{18}N_2O_5$	293	29
43	2-NO_2	C_2H_5	3	128–130	EtOAc–EtOH	20	$C_{16}H_{24}N_2O_5$	566	0
44	2-NO_2	i-C_3H_7	2	113–115	EtOAc–EtOH	28	$C_{16}H_{24}N_2O_5$	195	0
45	4-Cl	CH_3	2	55–57	Petr ether[b]	58	$C_{12}H_{18}ClNO_3$	Inactive	
46	2,3-CH=CHCH=CH-	CH_3	2	70–72	Petr ether[b]	18	$C_{16}H_{21}NO_3$	Inactive	

[a] Yield based on epoxide. [b] Bp 60–80 °C. [c] See Pharmacology section for description of method.

or *tert*-butyl groups of a β-adrenoceptor blocking compound with a variety of nonamidic substituted aryloxyalkyl substituents and further to decide whether the aryl ring itself was necessary for cardioselectivity. An inspection of the biological data in Tables I and II shows that in this series the structure–activity relationships differ markedly from those observed in previously described series of aryloxypropanolamines where the nitrogen atom was substituted with a small branched alkyl group. Thus, in an analogous series comprising compounds **4**, **27**, **29**, **30**, and **32–35**, substitution in the ortho position of the phenyl ring of the phenoxypropanolamine moiety decreased the potency but the compounds were cardioselective (e.g., compounds **27**, **30**, **34**, and **35**); substitution in the para position either gave inactive compounds (e.g., **29** and **32**) or active but nonselective compounds (e.g., **33**).

These findings were in contrast to those relating to the isopropyl and *tert*-butyl analogues where ortho substitution gave an increase in potency and para substitution gave a decrease in potency but generally conferred cardioselectivity.[11]

An examination of the alkoxyalkyl substituents (R_1, Table II) showed that potency and selectivity improved in parallel with the increase in lipophilicity of the terminal substituents; thus, compounds **38** and **44** were more potent than their analogues **37** and **42**, while all of them were cardioselective. With compounds carrying the aryloxyalkyl substituent, it proved difficult to correlate potency and selectivity with substituents in the aryl ring (R_1, Table I). There appeared, however, to be some correlation between potency and lipophilicity; thus, ortho substituents with low lipophilicity, in general, gave potent and selective compounds (e.g., **7**, **8**, **13**, and **21**), while substituents of higher lipophilicity were much less potent but were still cardioselective (e.g., compounds **11**, **12**, **23**, **25**, and **26**). The *p*-fluoro compound **22** was potent but not selective.

We were surprised by the large number of compounds in this series which showed cardioselectivity and in particular that this selectivity appeared to be insensitive to the steric bulk and lipophilicity of the groups attached to the side-chain oxygen atom; thus, both the α-naphthyloxyethyl and the methoxyethyl analogues **26** and **27** were cardioselective. Furthermore, in contrast to an earlier report,[7] these results indicate that an amidic substituent in the aryloxyalkyl group is not a major requirement for selectivity.

A consideration of previous findings that an ethyleneoxy linking group between the nitrogen atom and the aryl ring gave optimum potency and selectivity[7] and that a propyl linking group lowered potency and selectivity[8] (i.e., where the O atom of the ethyleneoxy link is replaced by a methylene group) together with our own results has led us to postulate that it is the oxygen atom itself which plays a major role in the determination of selectivity.

Experimental Section

Chemistry. All melting points were obtained using an Electrothermal capillary melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

General Methods. 1-(2-Methoxyphenoxy)-3-(2-methoxyphenoxyethylamino-2-propanol Oxalate (31). A mixture of 1-(2-methoxyphenoxy)-2,3-epoxypropane (1.8 g, 0.01 mol), 2-(2-methoxyphenoxy)ethylamine hydrochloride (2.05 g, 0.01 mol), NaOH (0.4 g, 0.01 mol), H_2O (4.0 mL), and *n*-PrOH was heated under reflux for 6 h. The mixture was evaporated to dryness and the residue was extracted with 2 N HCl (25 mL) and ether (25 mL), the acid phase was basified with 18 N NaOH (5 mL), and the mixture was extracted with EtOAc. The EtOAc phase was dried ($MgSO_4$) and evaporated to dryness, the residue was dissolved in Me_2CO (25 mL) and the solution was added to a solution of oxalic acid (1.25 g, 0.01 mol) in 25 mL of Me_2CO. The mixture was filtered and the solid residue was crystallized from a mixture of equal volumes of EtOH and Me_2CO: yield 1.2 g (26%); mp 118–120 °C. Anal. ($C_{21}H_{21}NO_9 \cdot H_2O$) C, H, N.

1-(2-Hydroxyphenoxyethylamino)-3-phenoxy-2-propanol Hydrochloride (7). A mixture of 1-phenoxy-2,3-epoxypropane (1.5 g, 0.01 mol), 2-(2-benzyloxyphenoxy)ethylamine hydrochloride (2.8 g, 0.01 mol), NaOH (0.4 g, 0.01 mol), H_2O (2.5 mL), and *n*-PrOH (50 mL) was heated under reflux for 18 h. The mixture was evaporated to dryness, the residue was dissolved in EtOH (85 mL) and 11 N HCl (5 mL), and the solution was hydrogenated over 5% Pd/C at room temperature and atmospheric pressure until uptake ceased. The mixture was filtered, the filtrate evaporated to dryness, and the residue was crystallized from EtOH: yield 0.06 g (2%); mp 209–210 °C. Anal. ($C_{17}H_{22}ClNO_4$) C, H, N.

1-(4-Benzyloxyphenoxy)-3-phenoxyethylamino-2-propanol (32). A mixture of 1-(4-benzyloxyphenoxy)-2,3-epoxypropane (5.12 g, 0.02 mol), phenoxyethylamine hydrochloride (3.5 g, 0.02 mol), NaOH (0.8 g, 0.02 mol), H_2O (5 mL), and *n*-PrOH (50 mL) was heated under reflux for 18 h. The mixture was cooled and filtered and the solid residue was dissolved in $CHCl_3$ (50 mL), filtered to remove NaCl, and evaporated to dryness. The solid residue was crystallized from EtOAc: yield 2.2 g (28%); mp 114–116 °C. Anal. ($C_{24}H_{27}NO_4$) C, H, N.

1-(4-Hydroxyphenoxy)-3-phenoxyethylamino-2-propanol (33). The benzyloxy derivative **32** (1.7 g, 0.0043 mol) in MeOH (35 mL) and HOAc (5 mL) was hydrogenated over 5% Pd/C at room temperature and atmospheric pressure until uptake ceased. The mixture was filtered, the filtrate was evaporated to dryness, and the residue was stirred with a mixture of EtOAc (25 mL), H_2O (25 mL), and $NaHCO_3$ (8.4 g, 0.1 mol). The EtOAc phase was dried ($MgSO_4$) and evaporated under reduced pressure, and the residue was crystallized from EtOAc: yield 0.8 g (60%); mp 154–156 °C. Anal. ($C_{17}H_{21}NO_4$) C, H, N.

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