1-[[4-(2-Chlorophenyl)-2-(4-chlorophenyl)-1,3-dioxolan-2-yl]methyl]-1*H*-imidazole Nitrate (47). A solution of 9 (37.6 g, 0.093 mol) in dry DMF (500 mL) was refluxed with imidazole (33.5 g, 0.5 mol) for 3 days. After cooling, the reaction mixture was diluted with water and extracted with ether. The organic layer was dried ($MgSO_4$), and the nitrate salt formed by the addition of a small excess of 65% HNO_3. The precipitated salt was filtered and recrystallized from EtOH/*i*-Pr_2O to yield 17.9 g (44%) of **47**, mp 183.3 °C.

Method B. *cis*- and *trans*-1-[[4-[(4-Bromophenyl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-2-yl]methyl]-1*H*-imidazole Ethanedioate (73). A solution of 3-(4-bromophenyl)-1,2-propanediol (27.5 g, 0.12 mol), the *p*-toluenesulfonate of 1-[(2,4-dichlorophenyl)acetyl]imidazole (42.7 g, 0.1 mol), and *p*-TosOH·H_2O (3 g) in benzene (400 mL) and 1-butanol (200 mL) was refluxed with azeotropic removal of water. After completion, the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (300 mL), washed with 6 N NaOH solution, dried ($MgSO_4$), and filtered. After evaporation of the solvent, the residue was purified by column chromatography on SiO_2 (eluent $CHCl_3$/MeOH, 99:1). The resulting oily product was dissolved in CH_3CN/*i*-Pr_2O and a slight excess of oxalic acid was added. The formed precipitate was collected and recrystallized from CH_3CN to give 23.3 g (36%) of **73**, mp 128.8 °C.

Acknowledgment. The authors thank Dr. M. Janssen for helpful suggestions and discussion of the manuscript and the "Instituut tot Aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw" for financial support.

β-Adrenergic Blocking Agents. 21. *threo*-1-(Aryloxy)-3-(alkylamino)butan-2-ols

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Received April 8, 1981

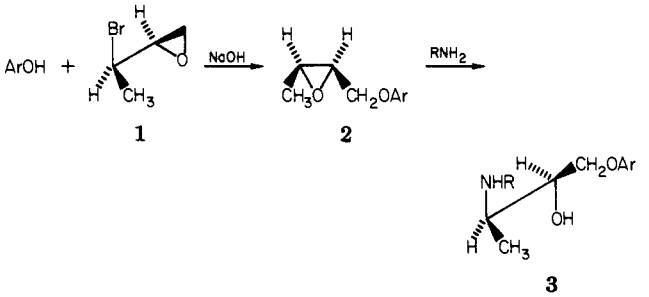
The synthesis and structure–activity relationships of a series of *threo*-1-(aryloxy)-3-(alkylamino)butan-2-ols are discussed. These compounds are less potent β-adrenoreceptor antagonists than the corresponding 1-(aryloxy)-3-(alkylamino)propan-2-ols. The data presented indicate that, unlike the arylethanolamine series, substitution of an alkyl group on the carbon atom α to the amino function on the oxypropanolamine side chain does not necessarily lead to enhanced vascular (β_2) selectivity.

Two structural features which are essential for a β-adrenergic receptor antagonist are an aromatic ring and an ethanolamine side chain. Crowther and Smith[1] showed that the introduction of an oxymethylene group between the aromatic ring and the ethanolamine side chain gave rise to even more potent β-adrenoreceptor antagonists. The effects on biological activity of introducing alkyl groups on the carbon atom α to the amino group in the ethanolamine series have been well documented.[2,3] However, with the exception of work by Howe[4] on propranolol analogues (mixtures of threo and erythro isomers) and a recent publication by Shtacher and co-workers,[5] little has been reported on the biological consequences of similar alkyl group substitutions in the (aryloxy)propanolamine series. The published biological work has been mainly devoted to studies on the threo α-methyl analogues of propranolol and practolol.[6,7] We report herein the synthesis of a series of *threo*-(aryloxy)butanolamines and discuss their structure–activity relationships.

Chemistry. The introduction of a methyl group α to the nitrogen atom on the side chain of an (aryloxy)-propanolamine gives rise to erythro and threo forms of the compound. We have developed a synthetic route which affords the erythro and threo isomers of the (aryloxy)butanolamines in a stereospecific manner.[8] The threo isomers are most conveniently prepared by the base-promoted reaction of the *threo*-oxirane **1** with the corresponding phenol (Scheme I). In practice, the *cis*-1-(aryloxy)-2,3-epoxybutanes formed were not purified but were characterized by NMR and reacted directly with the corresponding amine. A representative preparation is included under Experimental Section.

Pharmacology. β-Adrenoreceptor blocking potency was estimated in vivo using the previously described cat

Scheme I



preparation.[9] The results listed in Tables I–III 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 iv). The degree (percent) 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

(1) A. F. Crowther and L. H. Smith, *J. Med. Chem.*, 11, 1009 (1968).
(2) H. Corrodi, H. Persson, A. Carlsson, and J. Roberts, *J. Med. Chem.*, **6**, 751 (1963).
(3) D. K. Phillips, *Handb. Exp. Pharmacol.*, **54**(1), 3 (1980).
(4) R. Howe, *J. Med. Chem.*, **12**, 642 (1969).
(5) G. Shtacher, R. Rubinstein, and P. Somani, *J. Med. Chem.*, **21**, 678 (1978).
(6) B. Levy, *Br. J. Pharmacol.*, **49**, 514 (1973).
(7) J. D. Fitzgerald and S. R. O'Donnell, *Clin. Exp. Pharmacol. Physiol.*, **5**, 579 (1978).
(8) H. Tucker, *J. Org. Chem.*, **44**, 2943 (1979).
(9) J. D. Fitzgerald and S. R. O'Donnell, *Br. J. Pharmacol.*, **43**, 222 (1971).

0022-2623/81/1824-1364$01.25/0

Table I. *threo*-1-(Substituted-phenoxy)-3-(alkylamino)butan-2-ols

no.	R	R_1	mp, °C	crystn solvent	salt	yield,[a] %	emp formula	anal.	dose, mg/kg, giving 50% inhibn of tachycardia[c]	inhibn, %, of depressor response
1	2-CN	*i*-Pr	175–178	EtOAc-EtOH-petrol[d]	HCl	7	$C_{14}H_{21}ClN_2O_2$	C, H, N	32	11
2	2-CN	*t*-Bu	178–181	EtOAc-EtOH	HCl	2	$C_{15}H_{23}ClN_2O_2$	C, H, N	NA	
3	2 CH=CHCN	*i*-Pr	207–208	MeOH-Et_2O	$(COOH)_2$	5[b]	$C_{18}H_{24}N_2O_6$	C, H, N	18	39
4	2 CH=CHCN	*t*-Bu	207–209	EtOH-Et_2O	HCl	9[b]	$C_{17}H_{23}ClN_2O_2$	C, H, N, Cl	NA	
5	2-OCH_2CH=CH_2	*i*-Pr	56–59	petrol[d]	base	4	$C_{16}H_{25}NO_3$	C, H, N	363	66
6	2-CH_2CH=CH_2	*i*-Pr	oil		base	2	$C_{16}H_{25}NO_2$	C, H, N	636	100
7	4-PhCH_2O	*i*-Pr	129–130	EtOH-butanone	base	5	$C_{20}H_{27}NO_3$	C, H, N	NA	
8	3-Me	*i*-Pr	102–103	EtOAc	HCl	53	$C_{14}H_{24}ClNO_2$	C, H, N	600	47
9	4-Me	*i*-Pr	115–118	EtOH	$(COOH)_2$, $0.5H_2O$	60	$C_{16}H_{25}NO_6 \cdot 0.5H_2O$	C, H, N	NA	
10	3,4-Cl_2	*i*-Pr	179–182	H_2O	$0.5(COOH)_2$	2[b]	$C_{14}H_{20}Cl_2NO_4$	C, H, N, Cl	NA	
11	2	*i*-Pr	232–234	EtOH-Et_2O	2HCl	1[b]	$C_{20}H_{26}Cl_2N_2O_2S \cdot 0.5EtOH$	C, H, N, Cl	NA	
12	2	*i*-Pr	137–140	EtOH-petrol	base	12	$C_{16}H_{23}N_5O_2$	C, H, N	151	11

[a] Yield based on epoxide. [b] Yield based on phenol. [c] NA indicates that the compound was inactive when dosed at 200 (μg/kg)/min for 30 min. [d] Petroleum ether, bp 60–80 °C.

β_1 (cardiac) as opposed to β_2 (vascular) receptors. Mean log ED_{50} values 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

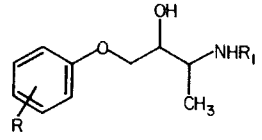
The introduction of a methyl group on the carbon atom α to the nitrogen atom in the oxypropanolamine side chain leads to an overall reduction in cardiac β-blocking potency of some 10- to 12-fold compared with the parent (aryloxy)propanolamines, which is in agreement with the findings of Howe and of Shtacher on a more limited group of compounds. In many (aryloxy)propanolamine series, replacement of the isopropylamino group by the *tert*-butylamino group frequently results in increased potency.[10] However, for these *threo*-(aryloxy)butanolamines, with the exception of compound **30**, the *tert*-butylamino analogues are inactive; compare compounds **1** and **2**, **3** and **4**, **19** and **20**, **21** and **22**, **36** and **37**, **44** and **45**, and **46** and **47**. This is especially surprising for compounds **2** and **4**, given the relatively high potency of their corresponding isopropylamino analogues **1** and **3**. An examination of molecular models shows that the methyl group and the *tert*-butyl group together form a large lipophilic envelope which totally encloses the nitrogen atom and the lack of β-antagonist activity could be attributable to the inability of the nitrogen atom to interact with its binding site on the receptor. In other respects, factors affecting potency parallel those found for other series of ring-substituted 1-phenoxy-3-[(isopropyl or *tert*-butyl)amino]propanols,[11] (aryloxy)butanolamines with substituents in the ortho and meta positions are active (**1**, **3**, **5**, **6**, **8**, and **12**), while the para-substituted analogues are, in the main, inactive (**7**, **9**, and **10**).

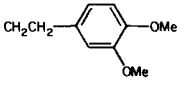
All the 4-amide substituted derivatives are inactive with the exception of compounds **18**, **19**, **21** (which have low potency), and **33** (Table II). It is assumed that the cardioselectivity of 4-amide substituted (aryloxy)propanolamines results from an interaction between the amide group and some additional binding site on the receptor,[12] and it is possible that the inactivity in this series is a consequence of additional unfavorable steric conformational effects in the side chain caused by introduction of the methyl group. The ortho position is less sensitive to steric bulk than the para position[12] and this is illustrated by compound **29**, which is more potent that the reference cardioselective β-antagonist, practolol (**50**).

There is evidence that α-methyl substitution in antagonists of the arylethanolamine series enhances β_2 selectivity;[3,13] our results show that this is not necessarily so for the (aryloxy)propanolamine series, since of the substituted phenoxy(alkylamino)butanols in Table I, compounds **1** and **12** show a degree of cardioselectivity, **3**, **5**, and **8** are nonselective, and there are indications that α-methyl alprenolol **6** has some β_2 selectivity. All the active amide derivatives listed in Table II are cardioselective (**18**, **19**, **21**, **29**, and **33**). Among the bicyclic (aryloxy)butanolamines in Table III there are no cardioselective com-

(10) H. Tucker, *J. Med. Chem.*, **23**, 1122 (1980).
(11) A. F. Crowther, D. J. Gilman, B. J. McLoughlin, L. H. Smith, R. W. Turner, and T. M. Todd, *J. Med. Chem.*, **12**, 638 (1969).
(12) L. H. Smith, *J. Appl. Chem. Biotechnol.*, **28**, 201 (1978).
(13) B. Levy and B. E. Wilkenfeld, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **29**, 1362 (1970).

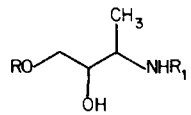
Table II. *threo*-1-(Amide-substituted-phenoxy)-3-(alkylamino)butan-2-ols



no.	R	R_1	mp, °C	crystn solvent	salt	yield,[a] %	emp formula	anal.	dose, mg/kg, giving 50% inhibn of tachycardia[c]	inhibn, %, of depressor response
13	4-$NHCOCH_3$	H	142–145	*n*-BuOAc–EtOH	base	4	$C_{12}H_{18}N_2O_3$	C, H, N	NA	
14	4-$NHCOCH_3$	Et	84–86	EtOAc	base	9	$C_{14}H_{22}N_2O_3$	C, H, N	NA	
15	4-$NHCOCH_3$	*i*-Pr	117	butanone	base	10	$C_{15}H_{24}N_2O_3$	C, H, N	NA	
16	4-$NHCOCH_3$	*t*-Bu	137–138.5	butanone	base	34	$C_{16}H_{26}N_2O_3$	C, H, N	NA	
17	4-$NHCOCH_3$	$+CH_2OH$	oil		base	3	$C_{16}H_{26}N_2O_4$	C, H, N	NA	
18	4-$NHCOCH_2CH_3$	Et	102–104	EtOAc	base	3	$C_{15}H_{24}N_2O_3$	C, H, N	1884	15
19	4-$NHCOCH_2CH_3$	*i*-Pr	oil		base	27	$C_{16}H_{26}N_2O_3$	C, H, N	908	0
20	4-$NHCOCH_2CH_3$	*t*-Bu	124–125	EtOAc	base	3	$C_{17}H_{28}N_2O_3$	C, H, N	NA	
21	2-NO_2, 4-$NHCOCH_2CH_3$	*i*-Pr	95–99	EtOAc–petrol[d]	base	4	$C_{16}H_{25}N_3O_5$	C, H, N	1116	31
22	2-NO_2, 4-$NHCOCH_2CH_3$	*t*-Bu	98–100	EtOAc	base	3	$C_{17}H_{27}N_3O_5$	C, H, N	NA	
23	4-CH_2CONH_2	Et	113–114	EtOAc	base	1	$C_{14}H_{22}N_2O_3 \cdot 0.25H_2O$	C, H, N	NA	
24	4-CH_2CONH_2	*i*-Pr	128–131	*i*-PrOH	base	3	$C_{15}H_{24}N_2O_3$	C, H, N	NA	
25	4-CH_2CONH_2	*t*-Bu	87	EtOAc–petrol[d]	base	8	$C_{16}H_{26}N_2O_3$	C, H, N	NA	
26	4-CH_2CONH_2		88–92	EtOH–petrol[d]	base	9	$C_{22}H_{30}N_2O_5$	C, H, N	NA	
27	2-$CH_2CH{=}CH_2$, 4-CH_2CONH_2	*t*-Bu	133–135	H_2O	0.5$(COOH)_2$, H_2O	18[b]	$C_{20}H_{31}N_2O_5 \cdot H_2O$	C, H, N	NA	
28	2-F, 4-CH_2CONH_2	*t*-Bu	96–98	EtOAc	base	23	$C_{16}H_{25}FN_2O_3$	C, H, N	NA	
29	2-$OCH_2CONHMe$	*i*-Pr	184–186	EtOH–Et_2O	HCl	10[b]	$C_{16}H_{27}ClN_2O_4$	C, H, N	107	23
30	2-$OCH_2CONHMe$	*t*-Bu	175–176.5	EtOH–Et_2O	HCl	22[b]	$C_{17}H_{29}ClN_2O_4$	C, H, N	1255	28
31	2-OEt, 4-$CH_2NHCOCH_2CH_3$	*i*-Pr	oil		base	2[b]	$C_{19}H_{32}N_2O_4$	C, H, N	NA	
32	2-Cl, 4-$CONHCH_2CH(CH_3)_2$	*i*-Pr	152–156	EtOH–Et_2O	HCl	1[b]	$C_{18}H_{30}Cl_2N_2O_3$	C, H, N	NA	
33	2-Cl, 4-NHCONH-*n*-Bu	*i*-Pr	200–202	MeOH–Et_2O	0.5$(COOH)_2$	20	$C_{19}H_{31}ClN_3O_5$	C, H, N	472	0

[a–c] See corresponding footnotes in Table I.

Table III. Bicyclic *threo*-(Aryloxy)-3-(alkylamino)butan-2-ols



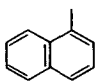
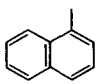
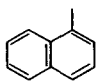
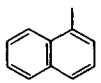
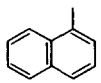
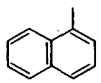
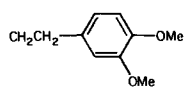
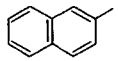
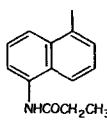
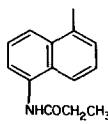
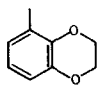
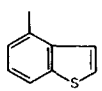
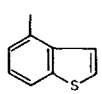
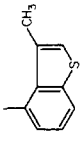
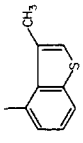
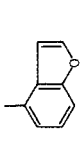
no.	R	R_1	mp, °C	crystn solvent	salt	yield,[a] %	emp formula	anal.	dose, μg/kg, giving 50% inhibn of tachycardia[c]	inhibn, %, of depressor response
34		H	102	EtOAc-petrol[d]	base	20	$C_{14}H_{17}NO_2$	C, H, N	640	55
35		Et	156–158	MeOH-EtOAc	$(COOH)_2$	50	$C_{18}H_{23}NO_6$	C, H, N	750	87
36		*i*-Pr	216	EtOH-Et_2O	HCl	71	$C_{17}H_{24}ClNO_2$	C, H, N	744	52
37		*t*-Bu	189	EtOH-Et_2O	HCl	15	$C_{18}H_{26}ClNO_2$	C, H, N, Cl	NA	
38		*i*-Bu	183–185	EtOH	HBr	19	$C_{18}H_{26}BrNO_2$	C, H, N, Br	NA	
39			176–178	butanone	HCl, $0.5H_2O$	18[b]	$C_{24}H_{29}ClNO_4 \cdot 0.5H_2O$	C, H, N, Cl	NA	
40		*i*-Pr	206–210	MeOH-H_2O	$0.5(COOH)_2$	24	$C_{18}H_{24}NO_4$	C, H, N	NA	
41		*i*-Pr	106–110	benzene-petrol[d]	base	13	$C_{20}H_{28}N_2O_3$	C, H, N	NA	
42		*t*-Bu	204–208	EtOAc-EtOH	HCl	13	$C_{21}H_{31}ClN_2O_3$	C, H, N	NA	
43		*i*-Pr	152–154	*n*-butyl acetate	$0.5(COOH)_2$	3	$C_{16}H_{24}NO_6$	C, H, N	825	100
44		*i*-Pr	198–200	EtOH-Et_2O	HCl	6[b]	$C_{15}H_{22}ClNO_2S$	C, H, N	283	94
45		*t*-Bu	oil		$(COOH)_2$	4[b]	$C_{18}H_{25}NO_6S$	C, H, N	NA	

Table III (*Continued*)

no.	R	R_1	mp, °C	crystn solvent	salt	yield,[a] %	emp formula	anal.	dose, μg/kg, giving 50% inhibn of tachycardia[c]	inhibn, %, of depressor response
46		*i*-Pr	244–246	EtOH–H_2O	HCl	6[b]	$C_{16}H_{24}ClNO_2S$	C, H, N	1744	100
47		*t*-Bu	238–242	EtOH–EtOAc	HCl	7	$C_{17}H_{26}ClNO_2S$	C, H, N	NA	
48		*i*-Pr	186–189	EtOAc–EtOH	HCl	16	$C_{15}H_{22}ClNO_3$	C, H, N	395	68
49 (propranolol)									62	85
50 (practolol)									167	8
51 (oxprenolol)									30	58

[a–d] See corresponding footnotes in Table I.

pounds, but there is a tendency toward β_2 selectivity with compounds **35**, **43**, **44**, **46**, and **48**. In agreement with the findings of O'Donnell[9] and Levy[6] α-methylpropranolol (**36**) is nonselective in this cat test. Preliminary results with *erythro*-α-methylpropranolol show that it is more potent than the threo analogue **36** by a factor of 2 and resembles propranolol in its β_2 activity.[14,15]

Shtacher and co-workers have shown that replacement of the isopropylamino group by the 3,4-dimethoxyphenethylamino group in phenoxybutanolamine derivatives is accompanied by a shift from vascular selectivity to cardioselectivity; however, introduction of this 3,4-dimethoxyphenethylamino group into the α-methyl analogues of propranolol and atenolol (compounds **39** and **26**) gave inactive compounds.

In conclusion, we have found that the main biological consequence of methyl substitution on the carbon atom α to the nitrogen atom in a series of (aryloxy)propanolamines is an overall reduction in β-adrenoreceptor blocking potency and, in contrast to the arylethanolamine series, this does not necessarily result in enhanced vascular β_2 receptor antagonist activity. Interestingly, the *threo*-3-(*tert*-butylamino)-1-(aryloxy)butanolamines are mainly inactive, possibly because of unfavorable steric interactions about the nitrogen atom.

Experimental Section

All melting points were obtained using an Electrothermal melting point apparatus and are uncorrected. Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. NMR data were consistent with the structures and were recorded either on a Varian HA-100 or a Varian A-60 instrument using tetramethylsilane as the internal standard.

***cis*-1-(3-Tolyloxy)-2,3-epoxybutane.** A solution of *m*-cresol (7.0 g, 0.65 mol) in dimethoxyethane (10 mL) was added to a stirred solution of sodium hydroxide pellets (2.9 g, 0.075 mol) in water (70 mL). After 5 min, a solution of *threo*-3-bromo-1,2-epoxybutane (12.7 g, 0.084 mol) in dimethoxyethane (10 mL) was added, and the reaction mixture was stirred at ambient temperature for 72 h. The reaction mixture was extracted with petroleum ether (bp 60–80 °C; 3 × 50 mL), and the combined petroleum ether extracts were washed with 2 N NaOH solution (2 × 25 mL) and water (4 × 25 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was distilled under reduced pressure to give *cis* 1-(3-tolyloxy)-2,3-epoxybutane: bp 98–100 °C (0.9 mm); yield 6.95 g (60%); ^1H NMR ($CDCl_3$) δ 1.3–1.37 (d, 3 H, CH_3) 2.32 (s, 3 H, CH_3), 3.02–3.35 (m, 2 H, epoxide protons), 4.05–4.1 (d, 2 H, CH_2), 6.62–7.3 (m, 4 H, aromatic protons).

***threo*-1-(3-Tolyloxy)-3-(isopropylamino)butan-2-ol Hydrochloride (8).** A mixture of *cis*-1-(3-tolyloxy)-2,3-epoxybutane (2.7 g, 0.015 mol), water (10 mL), and isopropylamine (10 mL, 0.12 mol) was heated under reflux for 2 h. The reaction mixture was concentrated and the residue partitioned between 2 N HCl (50 mL) and ethyl acetate (25 mL). The acid layer was separated and basified with NaOH. This basic solution was extracted with chloroform (3 × 25 mL), and the combined chloroform extracts were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the oily residue was shaken with ethereal HCl. The solid hydrochloride was crystallized from ethyl acetate at −20 °C to give **8**: mp 102–103 °C; yield 2.2 g (53%). Anal. ($C_{14}H_{24}ClNO_2$), C, H, N, Cl.

Acknowledgment. The author thanks Dr. J. D. Fitzgerald, Dr. J. Wale, and J. Carter for providing the biological activity, J. Gourlay and J. Coope for their expert chemical support, and C. J. Howarth for providing analytical data.

(14) M. H. Todd, *Pharmacologist*, 18, 138 (1976).
(15) Unpublished results from these laboratories.