

**$\beta_1$ -Selective Adrenoceptor Antagonists. 2. 4-Ether-Linked Phenoxypropanolamines**

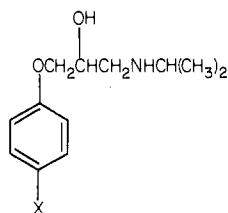
Peter J. Machin,\*† David N. Hurst,† Rachel M. Bradshaw,† Leslie C. Blaber,‡ David T. Burden,‡ Allison D. Fryer,‡ Rosemary A. Melarange,† and Celia Shivdasani†

Chemistry and Pharmacology Departments, Roche Products Limited, Welwyn Garden City, Hertfordshire AL7 3AY, United Kingdom. Received January 17, 1983

A series of 4-substituted phenoxypropanolamines was prepared and examined for  $\beta$ -adrenoceptor activity. Some of the compounds, especially the [4-[2-[[2-(4-fluorophenyl)ethyl]oxy]ethoxy]phenoxy]propanolamines (14, 15, and 24), showed potent  $\beta_1$ -blockade with virtually no  $\beta_2$ -blockade at doses over a 1000 times greater. The compounds also possessed partial agonist activity. Structure-activity relationships are discussed, and conclusions are drawn about the binding sites on  $\beta$ -adrenoceptors.

The use of  $\beta$ -adrenoceptor antagonists is now widely established in the treatment of essential hypertension. However, although cardioselective blockade appears to be of theoretical advantage, in practice the selectivity shown at low doses by the currently available agents is probably lost at the higher doses commonly used in patients.<sup>1,2</sup> Thus, the ideal cardioselective  $\beta$ -blocker should show potent blockade of the  $\beta_1$ -receptors with no blockade of  $\beta_2$ -receptors at the doses used for treating hypertension. A modicum of partial agonist activity may also be desirable to protect against cardiac depression under conditions of low sympathetic drive.

It has been suggested<sup>3</sup> that cardioselectivity is conferred on (aryloxy)propanolamines substituted in the para position by groups capable of binding to an additional site on  $\beta_1$ -adrenoceptors. Comparison of a number of cardioselective agents of this type, e.g., atenolol (1),<sup>4</sup> practolol (2),<sup>5</sup>

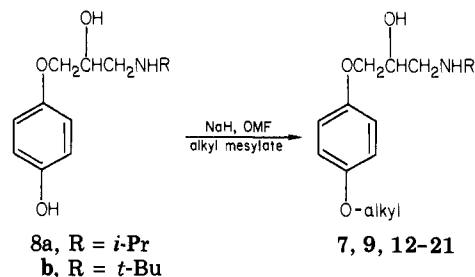
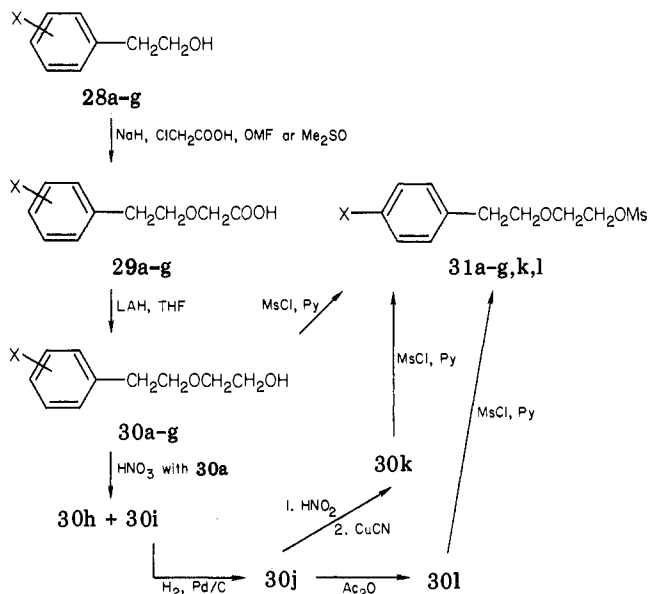


- 1, X = CH<sub>2</sub>CONH<sub>2</sub>
- 2, X = NHCOCH<sub>3</sub>
- 3, X = CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>-*c*-C<sub>3</sub>H<sub>5</sub>
- 4, X = CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>
- 5, X = OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>
- 6, X = CH<sub>2</sub>CH<sub>2</sub>NHCOOCH<sub>3</sub>
- 7, X = *p*-OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>O-C<sub>6</sub>H<sub>4</sub>-OCH<sub>2</sub>CH(OH)CH<sub>2</sub>NHCH(CH<sub>3</sub>)<sub>2</sub>

betaxolol (3),<sup>6</sup> metoprolol (4),<sup>7</sup> H87/07 (5),<sup>7</sup> and pamtolol (6),<sup>8</sup> reveals a number of different functional groups, all of which have in common a heteroatom, either oxygen or nitrogen, three or four atoms distant from the aromatic ring. The binary phenoxypropanolamine (7), which also fulfills these apparently simple requirements for cardioselectivity, was prepared as part of a different approach<sup>9</sup> to  $\beta$ -blockers. Biological evaluation of 7 did indeed reveal potent, cardioselective  $\beta$ -blockade, though of short duration of action on oral administration.<sup>10</sup> This report describes the synthesis and biological evaluation of compounds designed to optimize the in vivo profile shown by 7. Systematic modification of the para substituent in 7 has led to a series of [4-[2-(2-arylethoxy)ethoxy]phenoxy]propanolamines,<sup>11</sup> some of which exhibit highly potent, cardioselective  $\beta$ -blockade combined with a modicum of partial agonist activity.

**Chemistry.** Two general methods were used for the synthesis of the para-substituted phenoxypropanolamines

Scheme I

Scheme II<sup>a</sup>

<sup>a</sup> See Tables II and III for substituents X.

described in Table I. Method A, shown in Scheme I, involved alkylation of a (4-hydroxyphenoxy)propanolamine (8) with the appropriate alkyl mesylate to give compounds 7, 9, and 12-21. The alkylation was effected with sodium

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- (4) Barrett, A. M.; Carter, J.; Fitzgerald, J. D.; Hull, R.; Le Count, D. *Br. J. Pharmacol.* 1973, 48 340P.
- (5) Dunlop, D.; Shanks, R. G. *Br. J. Pharmacol.* 1968, 32, 201.
- (6) Boudout, J. P.; Cavero, I.; Fenard, S.; Lefevre-Borg, F.; Manoury, P.; Roach, A. G. *Br. J. Pharmacol.* 1979, 66, 445P.
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- (8) Carruthers, S. G.; Hosler, J. P.; Pentikainen, P.; Azarnoff, D. L. *Chim. Pharmacol. Ther.* 1978, 24, 168.
- (9) Kierstead, R. W.; Faraone, A.; Mennona, F.; Mullin, J.; Guthrie, R. W.; Crowley, H.; Simko, B.; Blaber, L. C. *J. Med. Chem.* preceding paper in this issue.
- (10) Blaber, L. C., unpublished results.
- (11) Machin, P. J., European Patent Application EP 41 233, 1981.

\* Chemistry Department.

† Pharmacology Department.

Table I

compd	R	R <sup>1</sup>	X	Y	R <sup>2</sup>	mp, °C	salt	crystn solvent	method	yield, %	emp formula	anal.	β-antagonism: ED <sub>50</sub> , μg/kg		β-agonism: ED <sub>30</sub> , μg/kg
													inhibn of tachycardia	inhibn of depressor response	increase in heart rate
7 <sup>a</sup>	see structure in text					152-154	2HCl	EtOH	A	71	C <sub>28</sub> H <sub>46</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>7</sub>	C, H, N, Cl	52	>10 000	5
9	<i>i</i> -Pr	H	O	O	H	109-111	(COOH) <sub>2</sub>	EtOH	A	80	C <sub>24</sub> H <sub>33</sub> NO <sub>9</sub>	C, H, N	41	> 5000	17
10	<i>i</i> -Pr	H		O	H	117-120	HCl	<i>i</i> -PrOH	B	75	C <sub>22</sub> H <sub>32</sub> ClNO <sub>4</sub>	C, H, N	68	924	>1000
11	<i>i</i> -Pr	H			H	81-83	HCl	EtOAc	B	50	C <sub>22</sub> H <sub>32</sub> ClNO <sub>3</sub>	C, H, N	163	> 2000	>1000
12	<i>i</i> -Pr	H	O		H	105-107	HCl	<i>i</i> -PrOH	A	51	C <sub>22</sub> H <sub>32</sub> ClNO <sub>4</sub>	C, H, N	15	>5000	20
13	<i>t</i> -Bu	H	O		H	87-88	HCl	EtOH-Et <sub>2</sub> O	A	30	C <sub>23</sub> H <sub>34</sub> ClNO <sub>4</sub>	C, H, N, Cl	18	979	22
14	<i>i</i> -Pr	H	O		F	88-92	HCl	<i>i</i> -PrOH	A	50	C <sub>22</sub> H <sub>31</sub> ClFNO <sub>4</sub>	C, H, N, Cl, F	3	>2000	37
14a <sup>b</sup>	<i>i</i> -Pr	H	O		F	107-110	fumarate	<i>i</i> -PrOH	A	39	C <sub>26</sub> H <sub>34</sub> FNO <sub>8</sub>	C, H, N, F	4	>2000	19
14b <sup>c</sup>	<i>i</i> -Pr	H	O		F	109-110	fumarate	<i>i</i> -PrOH	A	39	C <sub>26</sub> H <sub>34</sub> FNO <sub>8</sub>	C, H, N	> 2000	>2000	>1000
15	<i>t</i> -Bu	H	O		F	101-106	hydrogen maleate	<i>i</i> -PrOH	A	56	C <sub>22</sub> H <sub>36</sub> FNO <sub>8</sub>	C, H, N	2	>2000	24
16	<i>i</i> -Pr	H	O		CH <sub>3</sub>	104-106	HCl	<i>i</i> -PrOH	A	50	C <sub>23</sub> H <sub>34</sub> ClNO <sub>4</sub>	C, H, N	66	>2000	22
17	<i>i</i> -Pr	H	O		Cl	99-101	HCl	EtOAc	A	57	C <sub>22</sub> H <sub>31</sub> Cl <sub>2</sub> NO <sub>4</sub>	C, H, N	627	>2000	32
18	<i>i</i> -Pr	H	O		OCH <sub>3</sub>	99-101	HCl	<i>i</i> -PrOH	A	77	C <sub>23</sub> H <sub>34</sub> ClNO <sub>5</sub>	C, H, N	344	>2000	9
19	<i>i</i> -Pr	H	O		SCH <sub>3</sub>	98-101	HCl	EtOAc	A	41	C <sub>23</sub> H <sub>34</sub> ClNO <sub>4</sub> S	C, H, N	174	>2000	42
20	<i>i</i> -Pr	H	O		CN	94-98	(COOH) <sub>2</sub>	EtOH	A	24	C <sub>25</sub> H <sub>32</sub> N <sub>2</sub> O <sub>8</sub>	C, H, N	654	>2000	32
21	<i>i</i> -Pr	H	O		NHCOCH <sub>3</sub>	92-96	HCl	MeCN	A	50	C <sub>24</sub> H <sub>35</sub> ClN <sub>2</sub> O <sub>5</sub>	C, H, N	> 2000	>2000	29
22	<i>i</i> -Pr	2-CH <sub>3</sub>	O		H	85-87	HCl	EtOAc	B	27	C <sub>23</sub> H <sub>34</sub> ClNO <sub>4</sub>	C, H, N	572	>2000	57
23	<i>i</i> -Pr	2-Cl	O		H	82-84	HCl	<i>i</i> -PrOH	B	48	C <sub>22</sub> H <sub>31</sub> Cl <sub>2</sub> NO <sub>4</sub>	C, H, N, Cl	25	834	16
24	<i>i</i> -Pr	2-F	O		F	77-80	TsOH	<i>i</i> -PrOH	B	48	C <sub>29</sub> H <sub>37</sub> F <sub>2</sub> NO <sub>7</sub> S	C, H, N, F, S	1	>2000	45
25	<i>i</i> -Pr	3-F	O		F	74-76	HCl	<i>i</i> -PrOH	B	38	C <sub>22</sub> H <sub>30</sub> ClF <sub>2</sub> NO <sub>4</sub>	C, H, N, Cl, F	1	>2000	>1000
atenolol													91	2130	>1000
metoprolol													250	>2000	>1000

<sup>a</sup> S,S isomer, [α]<sub>D</sub><sup>20</sup> - 21.6° (MeOH, c 0.5). <sup>b</sup> S isomer, [α]<sub>D</sub><sup>20</sup> - 11.6° (H<sub>2</sub>O, c 1.0). <sup>c</sup> R isomer, [α]<sub>D</sub><sup>20</sup> + 12.0° (H<sub>2</sub>O, c 1.0).

Table II

$\text{X}-\text{C}_6\text{H}_4-\text{CH}_2\text{CH}_2\text{OH} \rightarrow \text{X}-\text{C}_6\text{H}_4-\text{CH}_2\text{CH}_2\text{OCH}_2\text{COOH}$   
 28  29

compd	X	mp, °C	crystn solvent	reaction solvent	yield, %	emp formula	anal.
29a	H	46-48	EtOAc-hexane	DMF	85	C <sub>10</sub> H <sub>12</sub> O <sub>3</sub>	C, H
29b	F	82-85	methylcyclohexane	DMF	79	C <sub>10</sub> H <sub>11</sub> F <sub>3</sub> O <sub>3</sub>	C, H, F
29c	CH <sub>3</sub>	65-67	methylcyclohexane	DMF	84	C <sub>11</sub> H <sub>14</sub> O <sub>3</sub>	C, H
29d	Cl	75-77	EtOAc-hexane	DMF	91	C <sub>10</sub> H <sub>11</sub> ClO <sub>3</sub>	C, H
29e	OCH <sub>3</sub>	82-84	toluene	Me <sub>2</sub> SO	79	C <sub>11</sub> H <sub>14</sub> O <sub>4</sub>	C, H
29f	SCH <sub>3</sub> <sup>a</sup>	58-60	toluene-hexane	Me <sub>2</sub> SO	46	C <sub>11</sub> H <sub>14</sub> O <sub>3</sub> S	C, H
29g	OCH <sub>2</sub> Ph <sup>b</sup>	87-89	EtOAc-hexane	Me <sub>2</sub> SO	76	C <sub>17</sub> H <sub>18</sub> O <sub>4</sub>	C, H

<sup>a</sup> Precursor 28f prepared by the method in ref 14. <sup>b</sup> Precursor 28g prepared by the method in ref 15.

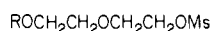
Table III

$\text{X}-\text{C}_6\text{H}_4-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$

compd	X	mp or bp (mm), °C	crystn solvent	chromatogr solvent	yield, <sup>a</sup> %	emp formula	anal.
30a	H	140-142 (15) <sup>b</sup>			92		
30b	4-F	101-104 (0.5)			91	C <sub>10</sub> H <sub>13</sub> FO <sub>2</sub>	C, H, F
30c	4-CH <sub>3</sub>			CHCl <sub>3</sub>	88	C <sub>11</sub> H <sub>16</sub> O <sub>2</sub>	C, H
30d	4-Cl			CHCl <sub>3</sub>	43	C <sub>10</sub> H <sub>13</sub> ClO <sub>2</sub>	C, H
30e	4-OCH <sub>3</sub>			CHCl <sub>3</sub>	96	C <sub>11</sub> H <sub>16</sub> O <sub>3</sub>	C, H
30f	4-SCH <sub>3</sub>			CHCl <sub>3</sub>	54	C <sub>11</sub> H <sub>16</sub> O <sub>3</sub> S	C, H
30g	4-OCH <sub>2</sub> Ph	30-32		CHCl <sub>3</sub>	86	C <sub>17</sub> H <sub>20</sub> O <sub>3</sub>	C, H
30h	2-NO <sub>2</sub> <sup>c</sup>			Et <sub>2</sub> O-hexane (1:1)	12	C <sub>10</sub> H <sub>13</sub> NO <sub>4</sub>	C, H, N
30i	4-NO <sub>2</sub> <sup>c</sup>			Et <sub>2</sub> O-hexane (1:1)	41	C <sub>10</sub> H <sub>13</sub> NO <sub>4</sub>	C, H, N
30j	4-NH <sub>2</sub> <sup>d</sup>	140-142	EtOH		100	C <sub>10</sub> H <sub>16</sub> ClNO <sub>2</sub>	C, H, N
30k	4-CN			CHCl <sub>3</sub>	61	C <sub>11</sub> H <sub>13</sub> NO <sub>2</sub>	C, H, N
30l	4-NHCOCH <sub>3</sub>	71-74	EtOAc		89	C <sub>12</sub> H <sub>17</sub> NO <sub>3</sub>	C, H, N

<sup>a</sup> Yield based on the previous step. <sup>b</sup> Literature<sup>16</sup> bp 140-142 °C (15 mm). <sup>c</sup> Separated by column chromatography. <sup>d</sup> Characterized as the hydrochloride.

hydride in DMF, an excellent base-solvent pair, which consistently gave clean products. Compounds 7 and 14a were prepared from the *S* isomer<sup>12</sup> of 8a, while 14b was prepared from the *R* isomer of 8a. All the other phenoxypropanolamines were racemic. The alkyl mesylates were obtained as follows. The dimesylate (26)<sup>13</sup> of 2,2'-

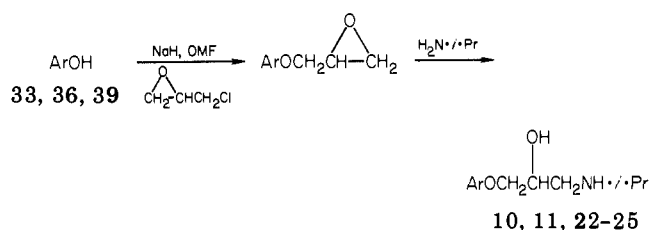


26, R = Ms

27, R = Ph

oxybis[ethanol] was used for compound 7 and also, by reaction with sodium phenoxide, provided the mesylate (27) required for 9. The remaining mesylates (31) were prepared as illustrated in Scheme II. The substituted phenethyl alcohols (28), which were either commercially available or prepared by literature methods,<sup>14,15</sup> were reacted with chloroacetic acid using sodium hydride in DMF or Me<sub>2</sub>SO to give ethoxyacetic acids (29) (Table II). Reduction to the alcohols (30) (Table III) was carried out with lithium aluminum hydride. This two-step procedure was found to be superior to the one-step reaction of phenethyl alcohol with ethylene oxide reported<sup>16</sup> for the synthesis of 30a. However, alcohols 30k and 30l were not available by this route because of the incompatibility of

Scheme III



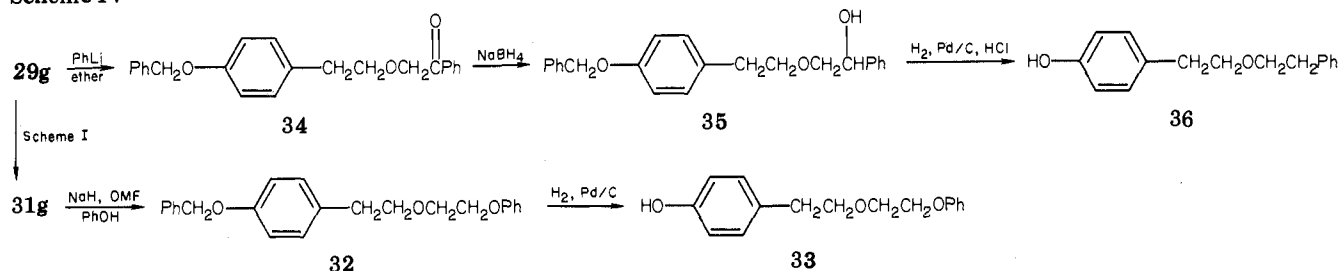
the substituents with the hydride reducing agent. These compounds were prepared by nitration of 30a according to the method of Woodburn and Stuntz<sup>17</sup> as used for phenethyl alcohol. After chromatographic separation of the isomers, the 4-nitro derivative 30i was hydrogenated to the amine 30j. Sandmeyer reaction with cyanide converted 30j to nitrile 30k, and acetylation of 30j gave amide 30l. The mesylates 31, obtained from 30 with mesyl chloride in pyridine, were not purified but used directly for the subsequent alkylation reactions.

The second general route, method B (Scheme III), used the classical phenol-epoxide-amino alcohol sequence for the preparation of the 4-alkyl-substituted analogues 10 and 11 and the disubstituted phenoxypropanolamines 22-25 (Table I). The reactions with excess epichlorohydrin were carried out in DMF with sodium hydride. These conditions gave efficient and essentially quantitative conversion to the epoxides, which were used without purification for the reactions with isopropylamine. The phenols used as

- (12) Schroeter, H.; Carlsson, E. L.; Persson, N. H. A.; Samuelsson, G. B. R.; Wetterlin, K. I. L. German Patent 2503751, 1975.  
 (13) Ulrich, H.; Grabhoefer, H.; Mueller, H.; Posse, R. F.; Reckziegel, E. German Patent 1138314, 1962; *Chem. Abstr.* 1963, 58, 3535d.  
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 (15) Manoury, P. M. J.; Cavero, I. A. G.; Majer, H.; Guidicelli, P. R. L. German Patent 2649605, 1977.  
 (16) Halasz, A. *Bull. Soc. Chim. Fr.* 1941, 8, 170.

- (17) Woodburn, H. M.; Stuntz, C. F. *J. Am. Chem. Soc.* 1950, 72, 1361.

## Scheme IV



starting materials were obtained as follows. Phenols **33** and **36** required for **10** and **11**, respectively, were prepared from a common acetic acid precursor (**29g**) as illustrated in Scheme IV. After conversion to the mesylate **31g**, alkylation with sodium phenoxide gave the triether **32**, which on hydrogenolysis afforded phenol **33**. The strategy adopted for phenol **36** proved necessary when the classical approach via the Williamson ether synthesis, i.e., in this case, reaction of a phenethyl alkoxide with a phenethyl halide or sulfonate, failed due to styrene formation. Thus, treatment of **29g** with excess phenyllithium gave the ketone **34**, which was reduced with sodium borohydride to the alcohol **35**. Hydrogenolysis under acidic conditions conveniently removed both the benzyl protecting group and the benzylic alcohol function to furnish **36**.

The Baeyer-Villiger reaction has been used<sup>18</sup> in  $\beta$ -blocker chemistry for the efficient introduction of oxygen functions into aromatic rings. We have used this reaction to prepare 4-alkoxy analogues unambiguously substituted in the 2- and 3-positions (Scheme V). Reaction of the known 4-hydroxybenzaldehyde or acetophenones **37** with the alkyl mesylates **31** or benzyl bromide gave ethers **38** and **40**, respectively. Compounds **38** were treated with 3-chloroperbenzoic acid followed by deacylation to liberate phenols **39a,d**. Similarly, **40** were converted to phenols **41**, which, after alkylation with mesylates **31** to give **42**, were debenzylated to afford phenols **39b,c**. Reaction of phenols **39** according to method B gave analogues **22-25**.

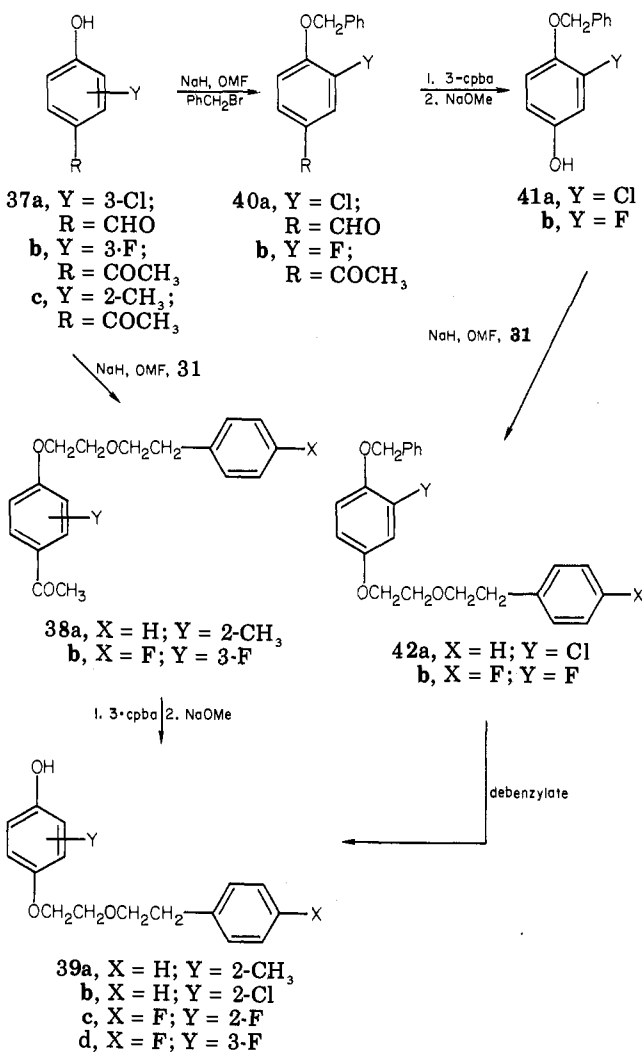
**Pharmacology.** Compounds were tested for  $\beta$ -adrenoceptor blocking and partial agonist activities in anesthetized rats. The results for blockade are expressed as the dose of test compound (given intravenously) required to inhibit by 50% the tachycardia ( $\beta_1$ ) and vasodepressor response ( $\beta_2$ ) produced by a submaximal dose of isoprenaline. The agonist activity is expressed as the dose of test compound (given intravenously) required to increase heart rate by 30 beats/minute. The results are shown in Table I.

## Discussion

A major objective of this work has been to synthesize  $\beta_1$ -antagonists that will show no  $\beta_2$ -blockade in man at doses likely to be encountered in hypertensive therapy. For this reason, attempts were made to measure  $ED_{50}$  values in animals at both types of  $\beta$ -receptor, and an outstanding feature of the activities shown in Table I is that with the exception of compounds **10**, **13**, and **23**, all the analogues showed little or no  $\beta_2$ -blockade at doses as high as, and in some cases considerably higher than, 2 mg  $kg^{-1}$  iv.

With regard to  $\beta_1$ -blockade, the potent activity shown by the binary compound **7** was improved as follows. Bearing in mind that **7** is the biologically active *S* isomer<sup>19</sup>

## Scheme V



whereas the other compounds, except **14a,b**, are racemic, replacement of the second oxypropanolamine group by a hydrogen atom as in compound **9** led to some increase in potency. Further simplification of structure **7** showed that compounds which did not possess an oxygen link to the  $\beta$ -blocker ring, i.e., **10** and **11**, were less potent than those with the oxygen link, i.e., **9** and **12**. This probably reflects a greater preference for a three-atom link between the middle oxygen atom and the  $\beta$ -blocker ring rather than a change in lipophilicity or overall substituent size. The best of these simplified structures is **12**, the [4-[2-(phenethyl-oxy)ethoxy]phenoxy]propanolamine, with a  $\beta_1$   $ED_{50}$  value of 15  $\mu g$   $kg^{-1}$ . This structure was used as a basis for further optimization.

The phenethyl group was substituted in the para position by a variety of groups reflecting divergent electronic, lipophilic, and steric properties, i.e., compounds **14-21**. However, only the steric factor produced any discernible

(18) Nelson, W. L.; Burke, T. R., Jr. *J. Med. Chem.* 1979, 22, 1082.

(19) Wasson, B. K.; Gibson, W. K.; Stuart, R. S.; Williams, H. N. R.; Yates, C. H. *J. Med. Chem.* 1972, 15, 651, and references therein.

trend, highlighted by the fact that only those analogues, 14 and 15, with the smallest possible substituent, fluorine, showed greater potency over 12 with ED<sub>50</sub> values around 3 μg kg<sup>-1</sup>. The other analogues with substituents larger than fluorine and hydrogen were generally much less potent.

The effects of extra substituents in the β-blocker ring were also investigated, although only a few analogues were prepared. Despite reports<sup>20,21</sup> of increased potency produced by ortho substituents, the introduction of an *o*-methyl group, as in analogue 22, considerably reduced potency in our compounds. Halogen substituents had little effect on β<sub>1</sub>-blockade in our series; the *o*-chloro analogue 23 and both fluoro analogues 24 and 25 showed only small changes in potency from the parent compounds 12 and 14, respectively. Replacement of the *N*-isopropyl group by a *tert*-butyl group, consistently found to improve potency in a series of 4-ureido-substituted β-blockers,<sup>21</sup> had little effect on β<sub>1</sub>-blockade, cf. 13 and 15, but did produce some weak β<sub>2</sub>-antagonism in one of the compounds, 13.

The steric requirement<sup>19</sup> of β-receptors for the correct absolute configuration of the oxypropanolamine side chain was confirmed by 14a, the *S*-(-) enantiomer of 14, in which all the activity resided. The *R*-(+) isomer, 14b, as expected, was essentially inactive as both an agonist and antagonist.

The overriding requirement for partial agonist activity is quite clearly the presence of an oxygen atom in the para position of the β-blocker ring with the detailed nature of the alkyl group on the oxygen having only marginal influence on the level of this activity. In the two examples where the oxygen is not present, 10 and 11, no agonist activity is found, whereas the phenol (8a) itself is the potent cardioselective agonist, prenalaterol.<sup>22</sup> The one exception to this rule is the *m*-fluoro analogue 25, which has only weak agonist activity. Presumably, the powerfully electron-withdrawing fluorine atom is sufficiently close to reduce the electron density on the para oxygen atom below the level required to activate the receptor. Similar effects on agonist activities of fluorocatecholamines have been reported<sup>23</sup> recently.

Thus, a number of conclusions can tentatively be drawn about the nature of β-receptors and their respective binding sites. Firstly, the hypothesis<sup>3</sup> that there is an additional binding site on cardiac β-receptors with which an appropriately positioned heteroatom can interact is supported by the potent cardioselective blockade shown by some of the compounds described herein. Secondly, our results are consistent with the suggestion<sup>24</sup> that there may be a second additional binding site, in the form of a lipophilic cleft, on or near the β<sub>1</sub>-adrenoceptor. It has been postulated<sup>24</sup> that there is an interaction between this cleft and the terminal cycloalkyl ring in a recently reported series of cardioselective thiazole β-blockers. A similar interaction could also occur with the terminal aryl ring in our compounds contributing to the potent cardioselective blockade we have observed. Thirdly, the suggestion<sup>25</sup> that the β<sub>2</sub>-receptor has difficulty in accommodating molecules with large para substituents is supported by the almost

total lack of activity at the β<sub>2</sub>-receptor shown by our compounds.

In summary, a number of [4-[2-[[2-(4-fluorophenyl)ethyl]oxy]ethoxy]aryloxy]propanolamines, specifically compounds 14, 15, and 24, have shown excellent potency as β<sub>1</sub>-adrenoceptor antagonists in the rat, with a desirable level of partial agonist activity, while showing virtually no β<sub>2</sub>-blockade at doses over 1000 times higher than the ED<sub>50</sub> values at the β<sub>1</sub>-receptors. These three compounds have been selected for further biological studies with a view to evaluating the most promising candidate in man.

### Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were obtained on a Pye-Unicam SP1000 spectrophotometer. NMR spectra were obtained on a Varian T-60 or XL-100 spectrometer with tetramethylsilane as internal reference. Each purified product had IR and NMR spectra compatible with its structure and was homogeneous by TLC. Microanalyses were within ±0.4% of the theoretical values for the elements measured. DMF was dried over 4Å molecular sieves. Sodium hydride (50% in oil) was washed with hexane before use. General workup procedures involved washing all organic extracts with water, drying over sodium sulfate and filtering prior to evaporation. Chromatography was carried out with Merck silica gel 60.

**Preparation of Substituted (Aryloxy)-3-(isopropylamino)- and -(*tert*-butylamino)-2-propanols (Table I). Method A.** The general conditions given below were followed for compounds 7, 9, and 12–21. A solution of 1-(isopropylamino)- or 1-(*tert*-butylamino)-3-(4-hydroxyphenoxy)-2-propanol (20 mmol) in 20 mL of DMF was treated with 0.96 g (20 mmol) of sodium hydride, and the mixture was stirred for 5 min. The appropriate mesylate 26 (10 mmol), 27 (20 mmol), or 31 (20 mmol) was added, and the mixture was stirred at 60 °C for 30 min. The solvent was evaporated, and the residue was partitioned between 2 N NaOH solution and dichloromethane. Workup afforded the free base of the product, which was converted to the salt as follows. The amine was dissolved in ethanol and treated with ethanolic HCl or an ethanolic solution of the appropriate organic acid. After evaporation, the residue was triturated with ether, filtered off, and recrystallized to give pure (aryloxy)propanolamine salt.

**Method B.** The general conditions given below were followed for compounds 10, 11, and 22–25. A solution of the appropriate phenol 33, 36, or 39 (12 mmol) in 50 mL of DMF was treated with 0.58 g (12 mmol) of sodium hydride, and the mixture was stirred for 5 min. After the addition of 10 mL of epichlorohydrin, the mixture was stirred at 60 °C for 30 min to complete alkylation. The excess reagent and solvent were evaporated under reduced pressure, and the residue was partitioned between ethyl acetate and water. Workup gave the epoxide, which was used without further purification. TLC usually indicated a single material, and crude yields were greater than 90%. The epoxide was dissolved in 50 mL of ethanol containing 15 mL of isopropylamine, and the solution was allowed to stand at room temperature for 18 h. Evaporation of the solvent gave the free base, which was converted to its salt as described in method A.

**2,2'-Oxydiethyl bis(methanesulfonate) (26)** was prepared according to the literature<sup>13</sup> in 53% yield.

**2-(2-Phenoxyethoxy)ethyl Methanesulfonate (27).** Phenol (2.82 g, 30 mmol) in 50 mL of DMF was treated with 1.44 g (30 mmol) of sodium hydride, and the mixture was stirred for 5 min. To this was added 7.86 g (30 mmol) of 26, and the mixture was stirred at 60 °C for 30 min. The solvent was evaporated, and the residue was partitioned between ethyl acetate and 2 N NaOH solution. Workup afforded crude material, which was purified by chromatography with chloroform-hexane (4:1) to give 3.9 g (50%) of 27 as a colorless oil: NMR (CDCl<sub>3</sub>) δ 7.4–6.7 (5 H, m), 4.3 (2 H, m), 4.1 (2 H, m), 3.8 (4 H, m), 3.00 (3 H, s). This material was used without further purification for the preparation of 9.

**2-(2-Arylethoxy)acetic Acids (29a–g; Table II).** The appropriate phenethyl alcohol (28; 50 mmol) in 100 mL of DMF or Me<sub>2</sub>SO (see Table II) was treated with 4.8 g (100 mmol) of sodium hydride, and the mixture was stirred at 60 °C for 10 min. Following the addition of 4.73 g (50 mmol) of chloroacetic acid, the

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reactions in DMF were kept at 60 °C for 30 min while the slower reactions requiring Me<sub>2</sub>SO were heated to 80 °C for 3 h. The cooled mixture was either evaporated to remove solvent (DMF) or poured directly into water (Me<sub>2</sub>SO). After partitioning between water and ether, the aqueous phase was acidified to pH 1 with dilute HCl and extracted with ethyl acetate. Workup and recrystallization gave pure product (29a-g). [[2-(4-Fluorophenyl)ethyl]oxy]acetic acid (29b) afforded the following spectral data as an example of this class of compounds: IR (Nujol) 1725 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>) δ 10.5 (1 H, s), 7.4–6.7 (4 H, m), 4.10 (2 H, s), 3.75 (2 H, t, *J* = 7 Hz), 2.90 (2 H, t, *J* = 7 Hz).

**2-(2-Arylethoxy)ethanols (30a-g; Table III).** A solution of 29 (40 mmol) in 50 mL of THF was added dropwise over 10 min to an ice-cold suspension of 1.54 g (40 mmol) of lithium aluminum hydride in 50 mL of THF. After the addition was complete, the mixture was stirred at room temperature for 30 min. Excess reducing agent was destroyed by the Steinhardt method,<sup>26</sup> and the inorganic solids were filtered off and washed well with THF. The filtrates were evaporated to give the crude ethanols (30a-g), which were purified either by distillation or by chromatography (chloroform). 2-[[2-(4-Fluorophenyl)ethyl]oxy]ethanol (30b) afforded the following spectral data as an example of this class of compounds: IR (film) 3420, 1220 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>) δ 7.35–6.75 (5 H, m), 3.9–3.4 (6 H, m), 2.85 (2 H, t, *J* = 7 Hz), 2.43 (1 H, s).

**Preparation of 2-[[2-(2-Nitrophenyl)ethyl]oxy]ethanol (30h) and 2-[[2-(4-Nitrophenyl)ethyl]oxy]ethanol (30i).** A 12-mL quantity of acetyl chloride was added dropwise to 20.75 g (125 mmol) of 30a over 5 min, and then the solution was evaporated under reduced pressure at 50 °C for 30 min. The residual acetate was added dropwise over 10 min to 100 mL of fuming nitric acid at -20 to -15 °C and then stirred for a further 30 min before being poured onto ice and extracted with ether. The ether extracts were washed with water and 20% K<sub>2</sub>CO<sub>3</sub> solution and worked up to give crude nitrated acetate. The yellow oil was heated to reflux in 150 mL of 2% HCl in ethanol for 1 h, and the solution was evaporated to dryness. The products were separated by chromatography with ether-hexane (1:1). The first component off the column provided 3.1 g (12%) of 30h as a pale yellow oil: NMR (CDCl<sub>3</sub>) δ 7.9–7.7 (1 H, m), 7.6–7.1 (3 H, m), 3.9–3.4 (6 H, m), 3.18 (2 H, t, *J* = 6 Hz), 2.20 (1 H, br s). Anal. (C<sub>10</sub>H<sub>13</sub>NO<sub>4</sub>) C, H, N. The second component off the column afforded 10.9 g (41%) of 30i as a pale yellow oil: NMR (CDCl<sub>3</sub>) δ 8.16 (2 H, d, *J* = 9 Hz), 7.41 (2 H, d, *J* = 9 Hz), 3.77 (2 H, t, *J* = 6 Hz), 3.7–3.4 (4 H, m), 3.00 (2 H, d, *J* = 6 Hz), 2.28 (1 H, br s). Anal. (C<sub>10</sub>H<sub>13</sub>NO<sub>4</sub>) C, H, N.

**2-[[2-(4-Aminophenyl)ethyl]oxy]ethanol (30j).** A solution of 10.6 g (50 mmol) of 30i in 300 mL of ethanol was hydrogenated over 0.5 g of 10% Pd/C catalyst at room temperature and pressure. The theoretical uptake was achieved in 75 min, and after removal of the catalyst, the solvent was evaporated to give 9.0 g (100%) of 30j as a colorless oil. The amine was fully characterized as the crystalline hydrochloride, mp 140–142 °C (from ethanol). Anal. (C<sub>10</sub>H<sub>16</sub>ClNO<sub>2</sub>) C, H, N.

**4-[2-(2-Hydroxyethoxy)ethyl]benzoxonitrile (30k).** A solution of 3.25 g (66 mmol) of NaCN in 5 mL of water was added to a stirred suspension of 2.48 g (25 mmol) of CuCl in 10 mL of water, and the resulting solution was left to cool. Meanwhile, a solution of 1.4 g (20 mmol) of NaNO<sub>2</sub> in 4 mL of water was added dropwise to 3.61 g (20 mmol) of 30j in 5 mL of concentrated HCl and 20 g of ice, maintaining the temperature between 0 and 5 °C. The resulting solution of the diazonium salt was neutralized by the addition of Na<sub>2</sub>CO<sub>3</sub> (ca. 1.2 g) in a small volume of water. This solution was then added dropwise over 20 min with vigorous stirring to a two-phase mixture of the CuCN solution and 20 mL of toluene. The mixture was allowed to warm to room temperature then heated at 50 °C for 5 min. After cooling, the mixture was worked up with ethyl acetate, and the residual brown oil was purified by chromatography with chloroform to give 2.48 g (65%) of 30k: IR (film) 3440, 2230 cm<sup>-1</sup>. Anal. (C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub>) C, H, N.

**N-[4-[2-(2-Hydroxyethoxy)ethyl]phenyl]acetamide (30l).** A mixture of 0.91 g (5 mmol) of 30j and 5 mL of acetic anhydride

was heated at 80 °C for 90 min and then evaporated to dryness. The residue was dissolved in 50 mL of ethanol containing sodium ethoxide (from 0.3 g of sodium hydride) and was left for 20 min. The solution was acidified with ethanolic HCl and evaporated to dryness. The solid residue was extracted with boiling ethyl acetate, the extracts were evaporated to dryness, and the product was recrystallized from ethyl acetate to give 0.99 g (89%) of 30l, mp 71–74 °C. Anal. (C<sub>12</sub>H<sub>17</sub>NO<sub>3</sub>) C, H, N.

**2-(2-Arylethoxy)ethyl Methanesulfonates (31a-g,k,l).** To the appropriate alcohol 30 (20 mmol) dissolved in 50 mL of pyridine was added 2.3 g (20 mmol) of mesyl chloride, and the solution was stirred for 30 min. The solvent was evaporated, and the residue was partitioned between ethyl acetate and dilute HCl. Workup gave the oily mesylates (31a-g,k,l), which were used without further purification. TLC usually indicated a single material, and crude yields were generally higher than 85%. As an example of this class of compounds, 2-[[2-(4-fluorophenyl)ethyl]oxy]ethyl methanesulfonate (31b) gave the following spectra: IR (film) 1350, 1175 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>) δ 7.25–6.7 (4 H, m), 4.25 (2 H, m), 3.6 (4 H, m), 2.87 (3 H, s), 2.78 (2 H, t, *J* = 7 Hz).

**1-(Benzyloxy)-4-[2-(2-phenoxyethoxy)ethyl]benzene (32).** A solution of sodium phenoxide made from 0.71 g (7.5 mmol) of phenol and 0.36 g (7.5 mmol) of sodium hydride in 15 mL of DMF was treated with 1.9 g (5.4 mmol) of 31g, and the mixture was stirred at 60 °C for 45 min. The solvent was evaporated, and the residue was partitioned between ethyl acetate and 2 N NaOH solution. Workup and recrystallization from ethanol gave 1.63 g (89%) of 32, mp 54–56 °C. Anal. (C<sub>23</sub>H<sub>24</sub>O<sub>3</sub>) C, H.

**4-[2-(2-Phenoxyethoxy)ethyl]phenol (33).** A solution of 1.0 g (2.9 mmol) of 32 in 60 mL of ethanol-ethyl acetate (1:1) was hydrogenated over 50 mg of 10% Pd/C catalyst at room temperature and pressure. Workup in the usual manner gave, after recrystallization from carbon tetrachloride, 0.66 g (90%) of 33, mp 62–64 °C. Anal. (C<sub>16</sub>H<sub>18</sub>O<sub>3</sub>) C, H.

**2-[[2-[4-(Benzyloxy)phenyl]ethyl]oxy]acetophenone (34).** A solution of 4.94 g (18 mmol) of 29g in 100 mL of ether was added over 10 min to a solution of phenyllithium (52 mmol; prepared in situ) in 80 mL of ether, and the mixture was stirred for a further 30 min. Excess reagent was quenched carefully with water, and the etheral extracts were washed with saturated NaHCO<sub>3</sub> solution. Workup gave a crude product, which was purified by chromatography with chloroform-hexane (3:1) to afford 3.1 g (49%) of 34, mp 35–38 °C. Anal. (C<sub>23</sub>H<sub>22</sub>O<sub>3</sub>) C, H.

**α-[[2-[4-(Benzyloxy)phenyl]ethyl]oxy]methyl]benzyl Alcohol (35).** Reduction of 2.6 g (7.5 mmol) of 34 in 100 mL of ethanol was effected with 0.5 g of sodium borohydride. Evaporation of the solvent, followed by partition of the residue between dilute HCl and ethyl acetate, gave, after workup, 2.6 g (100%) of 35. A small sample was recrystallized from hexane-ethyl acetate, mp 50–52 °C. Anal. (C<sub>23</sub>H<sub>24</sub>O<sub>3</sub>) C, H.

**4-[2-[2-(Phenylethyl)oxy]ethyl]phenol (36).** A solution of 2.1 g (6 mmol) of 35 in 150 mL of ethanol containing 1 mL of concentrated HCl was hydrogenated over 100 mg of 10% Pd/C catalyst. After 2 equiv of hydrogen had been absorbed, the catalyst was filtered off, and then the filtrates were evaporated. The crude product was dissolved in carbon tetrachloride, dried, and filtered. The filtrate was evaporated, and the residue was recrystallized from hexane to give 0.67 g (46%) of 36, mp 64–66 °C. Anal. (C<sub>16</sub>H<sub>18</sub>O<sub>2</sub>) C, H.

**2-Methyl-4'-[2-[(2-Phenylethyl)oxy]ethoxy]acetophenone (38a).** A solution of 2.25 g (15 mmol) of 4'-hydroxy-2'-methylacetophenone (37c) in 30 mL of DMF was alkylated by reaction with 0.72 g (15 mmol) of sodium hydride and 3.66 g (15 mmol) of mesylate 31a at 60 °C for 45 min. Workup in the usual manner afforded a crude product, which was purified by chromatography with chloroform-hexane (3:2) to give 2.5 g (56%) of 38a as an oil. Anal. (C<sub>19</sub>H<sub>22</sub>O<sub>3</sub>) C, H.

The following alkylations were carried out in a similar manner. **3'-Fluoro-4'-[2-[[2-(4-fluorophenyl)ethyl]oxy]ethoxy]acetophenone (38b).** 3'-Fluoro-4'-hydroxyacetophenone (37b)<sup>27</sup> and 31b afforded, after chromatography with chloroform-hexane (4:1), 38b (63%) as an oil. Anal. (C<sub>18</sub>H<sub>16</sub>F<sub>2</sub>O<sub>3</sub>) C, H.

**3-Chloro-4-(benzyloxy)benzaldehyde (40a).** 3-Chloro-4-

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hydroxybenzaldehyde (37a)<sup>28</sup> and benzyl bromide afforded, after recrystallization from ethanol, 40a (78%), mp 88–89 °C (lit.<sup>28</sup> mp 94 °C).

4'-(Benzyloxy)-3'-fluoroacetophenone (40b). 3'-Fluoro-4'-hydroxyacetophenone (37b) and benzyl bromide afforded, after recrystallization from ethyl acetate–hexane, 40b (73%), mp 82–85 °C. Anal. (C<sub>15</sub>H<sub>13</sub>FO<sub>2</sub>) C, H.

1-(Benzyloxy)-2-chloro-4-[2-[(2-phenylethyl)oxy]ethoxy]benzene (42a). The phenol 41a and mesylate 31a afforded, after chromatography with chloroform, 42a (64%) as an oil. Anal. (C<sub>23</sub>H<sub>23</sub>ClO<sub>3</sub>) C, H.

1-(Benzyloxy)-2-fluoro-4-[2-[(4-fluorophenyl)ethyl]oxy]ethoxy]benzene (42b). The phenol 41b and mesylate 31b afforded, after recrystallization from ethanol, 42b (74%), mp 33–35 °C. Anal. (C<sub>23</sub>H<sub>22</sub>F<sub>2</sub>O<sub>3</sub>) C, H.

4-[2-[(2-Phenylethyl)oxy]ethoxy]-2-cresol (39a). A solution of 5.9 g (20 mmol) of 38a in 80 mL of dichloromethane containing 3.91 g (20 mmol) of 3-chloroperbenzoic acid was allowed to stand at room temperature for 5 days. The mixture was washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and saturated NaHCO<sub>3</sub> solution and then worked up. The crude ester was dissolved in 250 mL of methanol containing 2.25 g (40 mmol) of NaOMe for 1 h before evaporation of the solvent. The residue was partitioned between 2 N HCl and dichloromethane. Workup and chromatography over silica with chloroform–hexane (1:1) gave 3.3 g (61%) of 39a as an oil. Anal. (C<sub>17</sub>H<sub>20</sub>O<sub>3</sub>) C, H.

The following Baeyer–Villiger reactions were carried out in a similar manner.

4-[2-[(4-Fluorophenyl)ethyl]oxy]ethoxy]-3-fluorophenol (39d). Acetophenone 38b afforded, after chromatography with chloroform, 39d (50%) as an oil. Anal. (C<sub>16</sub>H<sub>16</sub>F<sub>2</sub>O<sub>3</sub>) C, H.

4-(Benzyloxy)-3-chlorophenol (41a). Benzaldehyde 40a afforded, after recrystallization from hexane, 41a (60%), mp 55–58 °C. Anal. (C<sub>13</sub>H<sub>11</sub>ClO<sub>2</sub>) C, H.

4-(Benzyloxy)-3-fluorophenol (41b). Acetophenone 40b afforded, after recrystallization from methylcyclohexane, 41b (57%), mp 80–82 °C. Anal. (C<sub>13</sub>H<sub>11</sub>FO<sub>2</sub>) C, H.

2-Chloro-4-[2-[(2-phenylethyl)oxy]ethoxy]phenol (39b). A solution of 4.3 g (11 mmol) of 42a in 20 mL of 48% HBr–acetic acid was stirred for 30 min. The solution was evaporated to dryness, and the residue was partitioned between 2 N NaOH and ether. The aqueous phase was acidified with concentrated HCl and extracted with ethyl acetate. Workup and chromatography with chloroform gave 2.06 g (76%) of 39b as an oil. Anal. (C<sub>23</sub>H<sub>23</sub>ClO<sub>3</sub>) C, H.

2-Fluoro-4-[2-[(4-fluorophenyl)ethyl]oxy]ethoxy]phenol (39c). A solution of 1.2 g (3.1 mmol) of 42b in 50 mL of ethanol–ethyl acetate (1:1) was hydrogenated over 50 mg of 10% Pd/C catalyst to give, after workup and recrystallization from ethyl acetate–hexane, 0.8 g (87%) of 39c, mp 41–42 °C. Anal. (C<sub>16</sub>H<sub>16</sub>F<sub>2</sub>O<sub>3</sub>) C, H.

**Pharmacological Methods.** β-Adrenoceptor antagonism was measured in rats anesthetized with pentobarbitone sodium (75 mg/kg, ip). The rats were bilaterally vagotomized, and the trachea was cannulated. Isoprenaline (0.1 μg/kg) and test compounds dissolved in saline were administered through a polyethylene catheter into the right femoral vein, and the blood pressure was recorded from the left carotid artery by means of a Bell and Howell 4-422 transducer connected to a Grass Model 79D recorder. Heart

rate was recorded with a tachograph triggered from the arterial pulse. Five minutes after injection of isoprenaline, the test compound was injected, and heart rate and blood pressure were recorded. The procedure was repeated with cumulative doses of test compound up to, in most cases, a maximum dose of 2 mg/kg. The test was carried out in six rats for each compound, and the percentage blockade of both isoprenaline responses for each dose was calculated. The ED<sub>50</sub> values (defined as the dose producing 50% reduction of the control isoprenaline response) and 95% confidence limits were calculated from the log dose–response relationship established by linear regression.<sup>29</sup> Statistical analysis of the results showed that the 95% confidence limits for the ED<sub>50</sub> values averaged 30% (standard deviation 14%).

β-Adrenoceptor agonism was measured by the method of Barrett and Carter<sup>30</sup> in rats anesthetized with pentobarbitone sodium (75 mg/kg, ip) treated 20–24 h previously with reserpine (5 mg/kg, ip). Single doses of test compound were administered into the tail vein, and up to 20 animals were used, depending on activity. Blood pressure and heart rate were recorded as above. A dose–response relationship was established, and an ED<sub>30</sub> value (defined as the dose producing a 30 beats/min increase in heart rate) and 95% confidence limits were calculated as above. Statistical analysis of the results showed that the 95% confidence limits for the ED<sub>30</sub> values averaged 60% (standard deviation 37%).

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**Registry No.** (S,S)-7, 86901-76-0; (S,S)-7-HCl, 86901-77-1; (S)-8a, 57526-81-5; (R)-8a, 58165-85-8; (±)-8a, 62340-37-8; (±)-8b, 86901-78-2; (±)-9-(COOH)<sub>2</sub>, 86901-80-6; (±)-10, 86901-81-7; (±)-10-HCl, 86901-82-8; (±)-11, 86901-83-9; (±)-11-HCl, 86901-84-0; (±)-12, 86901-85-1; (±)-12-HCl, 86901-86-2; (±)-13, 86901-87-3; (±)-13-HCl, 86901-88-4; (±)-14, 86941-24-4; (±)-14-HCl, 86941-25-5; 14a fumarate, 86901-89-5; 14b fumarate, 86901-91-9; (±)-15 hydrogen maleate, 86901-93-1; (±)-16, 86921-31-5; (±)-16-HCl, 86901-94-2; (±)-17, 86901-95-3; (±)-17-HCl, 86901-96-4; (±)-18, 86901-97-5; (±)-18-HCl, 86901-98-6; (±)-19, 86901-99-7; (±)-19-HCl, 86902-00-3; (±)-20-(COOH)<sub>2</sub>, 86902-02-5; (±)-21, 86902-03-6; (±)-21-HCl, 86902-04-7; (±)-22, 86902-05-8; (±)-22-HCl, 86902-06-9; (±)-23, 86902-07-0; (±)-23-HCl, 86902-08-1; (±)-24-TsOH, 86902-10-5; (±)-25, 86902-11-6; (±)-25-HCl, 86902-12-7; 26, 34604-52-9; 27, 86902-13-8; 28a, 60-12-8; 28b, 7589-27-7; 28c, 699-02-5; 28d, 1875-88-3; 28e, 702-23-8; 28f, 81227-89-6; 28g, 61439-59-6; 29a, 81228-03-7; 29b, 81228-04-8; 29c, 81228-05-9; 29d, 81228-08-2; 29e, 81228-07-1; 29f, 81228-06-0; 29g, 86902-14-9; 30a, 74121-91-8; 30b, 81228-11-7; 30c, 81228-12-8; 30d, 81228-15-1; 30e, 81228-14-0; 30f, 81228-13-9; 30g, 86902-15-0; 30h, 86902-16-1; 30i, 86902-17-2; 30j-HCl, 86902-18-3; 30k, 86902-19-4; 30l, 86902-20-7; 31a, 81228-17-3; 31b, 81228-18-4; 31g, 86902-21-8; 32, 86902-22-9; 33, 86902-23-0; 34, 86902-24-1; 35, 86902-25-2; 36, 86902-26-3; 37a, 2420-16-8; 37b, 403-14-5; 37c, 875-59-2; 38a, 81227-98-7; 38b, 81228-00-4; 39a, 81227-91-0; 39b, 81228-24-2; 39c, 81227-92-1; 39d, 81227-93-2; 40a, 66422-84-2; 40b, 81227-99-8; 41a, 86902-27-4; 41b, 81228-25-3; 42a, 81227-97-6; 42b, 81227-96-5; epichlorohydrin, 106-89-8; chloroacetic acid, 79-11-8; sodium phenoxide, 139-02-6; benzyl bromide, 100-39-0.

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