28717-34-2; **14**, 7361-61-7; **15**, 1082-57-1; **16**, 526-36-3; **17**, 38941-33-2; **18**, 36067-72-8; **19**, 84-22-0; **20**, 76833-41-5; **21**, 65955-46-6; **22**, 715-83-3; **23**, 59-42-7; **24**, 57101-49-2; **25**, 37571-84-9; **26**, 82013-55-6; **27**, 68593-96-4; **28**, 74938-11-7; **29**, 64309-39-3; **30**, 83964-56-1; **31**, 59939-16-1; **32**, 15327-38-5; **33**, 39478-90-5; **34**, 5051-62-7; **35**, 1491-59-4; prazosin, 19216-56-9; phentolamine, 50-60-2; dihydroergotamine, 511-12-6; clozapine, 5786-21-0; cornynanthine, 483-10-3; azapetine, 146-36-1; yohimbine, 146-48-5; piperoxane, 59-39-2; tolazoline, 59-98-3; mianserin, 24219-97-4; rauwolscine, 131-03-3.

β_1-Selective Adrenoceptor Antagonists. 3. 4-Azolyl-Linked Phenoxypropanolamines

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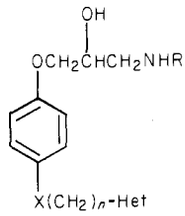
A series of 4-substituted phenoxypropanolamines has been prepared and examined for β-adrenoceptor activity. The 4-substituents, di- and triazole ring systems connected to the phenoxy ring by different length chains, were chosen as a means of introducing cardioselectivity. This has been achieved, especially in the 1-[4-[(4-chloropyrazol-1-yl)methoxy]phenoxy]-3-(isopropylamino)-2-propanol (**11**), the 4-[(2*H*-1,2,3-triazol-2-yl)methoxy] analogue (**21**), and the 4-[2-(2*H*-1,2,3-triazol-2-yl)ethoxy] analogue (**22**), which show potent β_1-blockade with selectivity ratios in excess of 100:1. Structure–activity relationships are discussed, and the optimum position of the heteroatom in the 4-substituent is defined.

The preceding papers[1,2] in this series describe the synthesis and β-blocking activities of variously substituted (aryloxy)propanolamines and support the contention[2,3] that a heteroatom suitably positioned in a 4-substituent is necessary to produce both potent and cardioselective β-blockade.

Although, in general, the more potent agents are those with oxygen functions in the 4-substituent, we wished to find an alternative functionality that could achieve the same interaction with the β_1-receptor. Since this interaction is likely to involve the lone pairs of electrons on the oxygen atom, a situation was sought in which a nitrogen atom lone pair was available in similar fashion. Having excluded simple amines because of protonation at physiological pH and amides because of delocalization over the carbonyl system, we considered the possibility that the pyridinic nitrogen atoms in diazoles and triazoles closely fulfilled the requirement. Consequently, we have synthesized a series of phenoxypropanolamines (**1–26**)[4] sub-

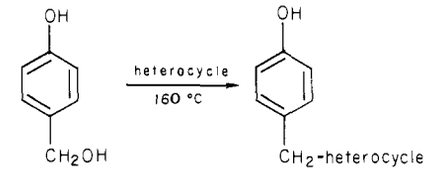


1–26, R = *i*-Pr, *t*-Bu; X = O, S; *n* = 1-3; Het = pyrazoles, triazoles, benzoazoles

stituted in the 4-position by groups incorporating di- and triazole rings.[5] The use of one of the ring nitrogen atoms as the point of attachment to the chain afforded easy synthetic access to molecules with variable heteroatom position and basicity. This paper describes their synthesis and evaluation as β-adrenoceptor antagonists.

Chemistry. All but two of the oxypropanolamines listed in Table I were obtained by the classical phenol–epoxide–amino alcohol sequence using the conditions described previously.[2] The phenol starting materials were prepared by the following general methods (A–E).

Scheme I. Method A



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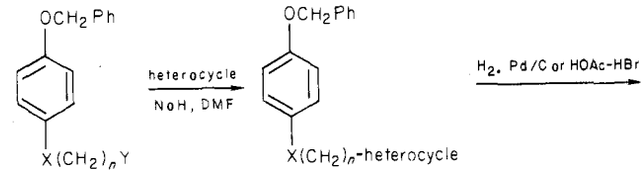
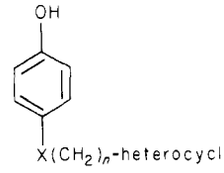
Scheme II. Method B



28, Y = OMs; *n* = 2
29, X = O; Y = Br; *n* = 2
30, X = O; Y = Br; *n* = 3

31, *n* = 2
32, X = O; *n* = 2
33, X = O; *n* = 3



34, *n* = 2
35, X = O; *n* = 2
36, X = O; *n* = 3

† Chemistry Department.
‡ Pharmacology Department.

(1) Kierstead, R. W.; Faraone, A.; Mennona, F.; Mullin, J.; Guthrie, R. W.; Crowley, H.; Simko, B.; Blaber, L. C. *J. Med. Chem.* **1983**, *26*, 1561.
(2) Machin, P.; Hurst, D. N.; Bradshaw, R. M.; Blaber, L. C.; Burden, D. T.; Fryer, A. D.; Melarange, R. A.; Shivdasani, C. *J. Med. Chem.* **1983**, *26*, 1570.
(3) Smith, L. H. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 201.
(4) Machin, P. British Patent Application 8 035 997, 1980.

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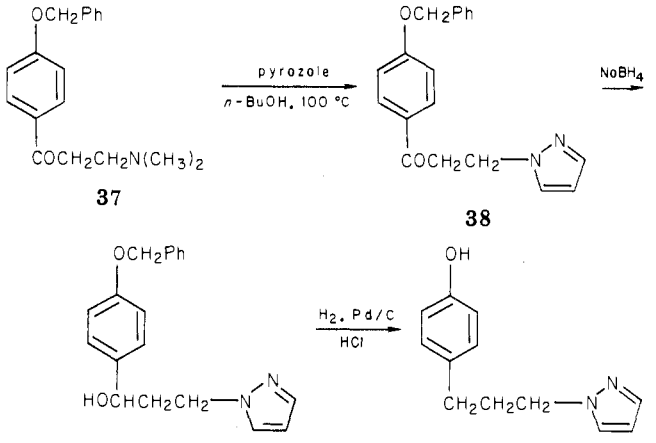
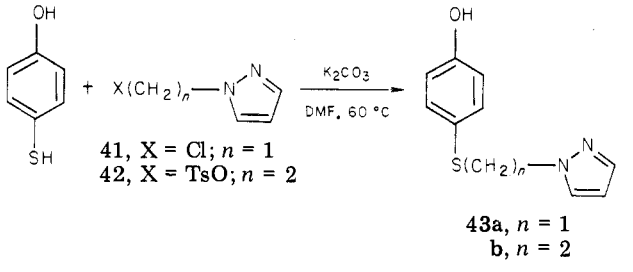
Scheme III. Method C

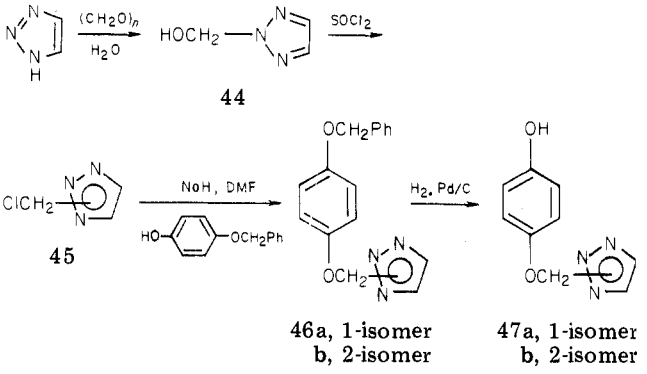


Scheme IV. Method D



Thermal coupling[6] of heterocycles with 4-hydroxybenzyl alcohol gave the methylene-linked phenols (**27**) (method A, Scheme I). The ethylene (**34**), oxyethylene (**35**), and oxypropylene (**36**) linked phenols were prepared by alkylation of the requisite heterocycle with the appropriate mesylate or bromide, followed by debenzylation (method B, Scheme II). Benzotriazole, indazole, and 1,2,3-triazole all gave both possible isomers, which were separated by conventional means; isomer assignment was made on the basis of spectral or physical characteristics (see Experimental Section). Interestingly, debenzylation of the benzotriazoles (**32k** and **32l**) by hydrogenation also gave some saturation of the benzotriazole moiety itself. Selective debenzylation was effected with HBr–acetic acid. The propylene-linked phenol (**40**) was prepared from the Mannich base (**37**)[7] by displacement with pyrazole, reduction, and double hydrogenolysis (method C, Scheme III). Reaction of 1-(chloromethyl)pyrazole (**41**) and 1-[2-(tosyloxy)ethyl]pyrazole (**42**) with 4-merceptophenol afforded the sulfur-linked phenols (**43**) (method D, Scheme IV). Treatment of 1,2,3-triazole with formalin gave the 2-hydroxymethyl derivative (**44**) recently reported[8] by Vereshchagin et al. However, conversion to the chloromethyl derivative (**45**) must have involved some rearrangement, because subsequent reaction with (benzyloxy)phenol gave both triazole isomers (**46**). Separation and hydrogenolysis afforded the desired (triazolylmethoxy)-

Scheme V. Method E



phenols (**47**) (method E, Scheme V).

The benzyl ether and phenol intermediates are listed in Tables II and III, respectively.

The two remaining analogues (**10** and **11**) were prepared directly from 1-(isopropylamino)-3-(4-hydroxyphenoxy)-2-propanol by alkylation with the appropriate (chloromethyl)pyrazole (**41** and **49**), respectively.

Pharmacology. Compounds were tested for β-adrenoceptor blocking and partial agonist activities in anesthetized rats as described previously.[2] The results, shown in Table I, are expressed as ED_{50} values (in micrograms per kilogram intravenously) for β_1- and β_2-blockade and ED_{30} values (in micrograms per kilogram intravenously) for partial agonist activity.

Discussion

In common with the 4-substituted phenoxypropanolamines described in the earlier papers, most of the analogues in Table I showed little or no β_2-blockade at doses as high as 2 mg kg^{-1} iv, clearly demonstrating the steric limitations of the β_2-receptor.

Potency at the β_1-receptor can be related primarily to the distance of the heteroatom from the phenoxy ring. Examination of the groups of compounds with different ring systems reveals that the most potent member in each group, i.e., **2**, **6**, **11**, **21**, incorporates a pyridinic nitrogen atom linked to the phenoxy ring by three or four atoms. This compares well with the three-atom link of the potent ether type of β_1-antagonist.[2] Further refinement of the position parameter is possible by comparison of the equipotent 2-substituted 1,2,3-triazoles (**21** and **22**). Computer modeling of these structures indicates that despite an extra methylene in the chain of **22**, different conformations of the connecting chains could allow the triazole 1-nitrogen atom in both molecules to occupy virtually the same position in space, 6 Å from the center of the phenoxy ring.

Other structure–activity relationships can be discerned. For example, there is some correlation between activity and heterocycle basicity. Comparison of analogues in which the phenoxy ring–heteroatom separation is kept constant but in which the type of heterocycle is varied reveals, in general, increasing activity with decreasing basicity (Table IV). Thus, the very weakly basic chloropyrazole **11** and triazoles **21** and **22** show the highest potencies at the β_1-receptor.

Another factor that is apparent from the biological activities is the positive effect of the oxygen link on potency. For example, the oxy-linked compounds **10** and **13** are considerably more potent than both carbon-linked compounds **9** and **19** and sulfur-linked analogues **12** and **18**. Although possibly due to differences in lipophilicity and in vivo distribution, an advantageous binding of the oxygen atom to the β_1-receptor is an alternative explanation.

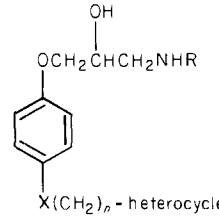
(5) A different approach has led to a series of cardioselective agents with somewhat related structural features. See: Baldwin, J. J.; Denny, G. H.; Hirschmann, R.; Freedman, M. B.; Ponticello, G. S.; Gross, D. M.; Sweet, C. S. *J. Med. Chem.* **1983**, *26*, 950, and references therein.

(6) Wakselman, M.; Robert, J.-C.; Decodts, G.; Vilkas, M. *Bull. Soc. Chim. Fr.* **1973**, *3*, 1179.

(7) Palekar, A. D.; Desai, P. D.; Kulkarni, R. A. *Indian J. Pharm.* **1973**, *35*, 135.

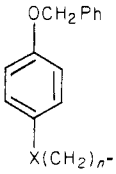
(8) Vereshchagin, L. I.; Maksikova, A. V.; Tikhonova, L. G.; Buzilova, S. R.; Sakovich, G. V. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1981**, *5*, 510.

Table I. 4-Substituted Phenoxypropanelamines and Biological Data



compd	R	X	n	heterocycle	mp, °C	salt	crystn solvent	yield, %	emp formula	anal.	β-antagonism: ED_{50}, μg/kg: inhibn of tachycardia	β-antagonism: ED_{50}, μg/kg: inhibn of depressor response	β-agonism: ED_{30}, μg/kg: increase in heart rate
1	*i*-Pr		1	1-imidazolyl	105-107	dioxalate	MeOH	11	$C_{20}H_{27}N_3O_{10}$	C, H, N	620	>1000	>1000
2	*i*-Pr		2	1-imidazolyl	104-106	dimaleate	*i*-PrOH	69	$C_{25}H_{33}N_3O_{10}$	C, H, N	186	>1000	>1000
3	*i*-Pr	O	2	1-imidazolyl	147-148	dioxalate	MeOH	51	$C_{21}H_{29}N_3O_{11}$	C, H, N	970	>2000	>1000
4	*i*-Pr	O	2	1-benzimidazolyl	170-173	dioxalate	EtOH	43	$C_{25}H_{31}N_3O_{11}$	C, H, N	687	>2000	>1000
5	*i*-Pr		2	1*H*-1,2,4-triazol-1-yl	173-175	2HCl	EtOH	24	$C_{16}H_{26}N_4O_2Cl_2$	C, H, N, Cl	233	>2000	>1000
6	*i*-Pr	O	2	1*H*-1,2,4-triazol-1-yl	155-158	2HCl	EtOH-*i*-PrOH	35	$C_{16}H_{26}N_4O_3Cl_2$	C, H, N	170	>2000	>1000
7	*i*-Pr	O	3	1*H*-1,2,4-triazol-1-yl	158-160	2HCl	EtOH	47	$C_{17}H_{28}N_4O_3Cl_2$	C, H, N, Cl	680	>2000	>1000
8	*i*-Pr		1	1-pyrazolyl	103-105	maleate	*i*-PrOH	54	$C_{20}H_{27}N_3O_6$	C, H, N	598	>2000	>1000
9	*i*-Pr		2	1-pyrazolyl	134-135	TsOH	*i*-PrOH	49	$C_{24}H_{33}N_3O_5S$	C, H, N, S	209	>2000	>1000
10	*i*-Pr	O	1	1-pyrazolyl	84-87	maleate	*i*-PrOH	56	$C_{20}H_{27}N_3O_7$	C, H, N	28	>2000	>1000
11	*i*-Pr	O	1	4-chloropyrazol-1-yl	71-75	oxalate	MeCN	61	$C_{18}H_{24}N_3O_7Cl$	C, H, N	4	2430	7
12	*i*-Pr	S	1	1-pyrazolyl	83-87	maleate	*i*-PrOH	65	$C_{20}H_{27}N_3O_6S$	C, H, N	327	>2000	>1000
13	*i*-Pr	O	2	1-pyrazolyl	103-105	maleate	*i*-PrOH	76	$C_{21}H_{29}N_3O_7$	C, H, N	50	>2000	>1000
14	*t*-Bu	O	2	1-pyrazolyl	145-148	maleate	EtOH	72	$C_{22}H_{31}N_3O_7$	C, H, N	67	1036	154
15	*i*-Pr	O	2	4-chloropyrazol-1-yl	120	TsOH	EtOH	56	$C_{24}H_{32}N_3O_6ClS$	C, H, N	24	523	194
16	*i*-Pr	O	2	4-phenylpyrazol-1-yl	141-143	maleate	*i*-PrOH	73	$C_{27}H_{33}N_3O_7$	C, H, N	160	>2000	>1000
17	*i*-Pr	O	2	1*H*-indazol-1-yl	121-123	HCl	EtOAc	49	$C_{21}H_{28}N_3O_3Cl$	C, H, N	263	>2000	>1000
18	*i*-Pr	S	2	1-pyrazolyl	84-86	maleate	*i*-PrOH	46	$C_{21}H_{29}N_3O_6S$	C, H, N	128	>2000	>1000
19	*i*-Pr		3	1-pyrazolyl	126-130	maleate	*i*-PrOH	60	$C_{22}H_{31}N_3O_6$	C, H, N	783	>2000	>1000
20	*i*-Pr	O	3	1-pyrazolyl	89-91	maleate	*i*-PrOH	41	$C_{22}H_{31}N_3O_7$	C, H, N	334	>2000	>1000
21	*i*-Pr	O	1	2*H*-1,2,3-triazol-2-yl	141-144	HCl	*i*-PrOH	59	$C_{15}H_{23}N_4O_3Cl$	C, H, N	11	>2000	19
22	*i*-Pr	O	2	2*H*-1,2,3-triazol-2-yl	119-122	HCl	EtOAc	51	$C_{16}H_{25}N_4O_3Cl$	C, H, N	14	>2000	14
23	*i*-Pr	O	2	2*H*-benzotriazol-2-yl	175-176	HCl	EtOH	62	$C_{20}H_{27}N_4O_3Cl$	C, H, N, Cl	50	988	>1000
24	*i*-Pr	O	2	4,5,6,7-tetrahydro-2*H*-benzotriazol-2-yl	157-158	HCl	MeCN	71	$C_{20}H_{31}N_4O_3Cl$	C, H, N, Cl	57	>2000	>1000
25	*i*-Pr	O	1	1*H*-1,2,3-triazol-1-yl	98-101	maleate	EtOH-*i*-PrOH	27	$C_{19}H_{26}N_4O_7$	C, H, N	40	>2000	50
26	*i*-Pr	O	2	1*H*-benzotriazol-1-yl	121-126	2TsOH	MeCN	64	$C_{34}H_{42}N_4O_9S_2$	C, H, N, S	1271	>2000	>1000
atenolol											91	2130	>1000
metoprolol											250	>2000	>1000

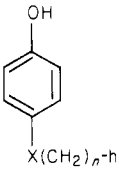
Table II. Benzyl Ether Intermediates



no.	X	n	heterocycle	mp, °C	crystn solvent	meth-od	yield, %	emp formula	anal.
31a		2	1-imidazolyl	104-106	MeCN	B	44	$C_{15}H_{15}N_2O$	C, H, N
31b		2	1*H*-1,2,4-triazol-1-yl	103-104	*i*-PrOH	B	65	$C_{17}H_{17}N_3O$	C, H, N
31c		2	1-pyrazolyl	94-95	*i*-PrOH	B	72	$C_{15}H_{15}N_2O$	C, H, N
32a	O	2	1-imidazolyl	137-138	EtOH	B	71	$C_{15}H_{15}N_2O_2$	C, H, N
32b	O	2	1-benzimidazolyl	115-117	*i*-PrOH	B	78	$C_{22}H_{20}N_2O_2$	C, H, N
32c	O	2	1*H*-1,2,4-triazol-1-yl	104-105	*i*-PrOH	B	62	$C_{17}H_{17}N_3O_2$	C, H, N
32d	O	2	1-pyrazol l	84-85	EtOH	B	70	$C_{15}H_{15}N_2O_2$	C, H, N
32e	O	2	4-chloropyrazol-1-yl	92-93	EtOH	B	72	$C_{15}H_{17}N_2O_2Cl$	C, H, N
32f	O	2	4-phenylpyrazol-1-yl	111-112	EtOH	B	77	$C_{24}H_{22}N_2O_2$	C, H, N
32g	O	2	1*H*-indazol-1-yl	81-83	hexane	B	52	$C_{22}H_{20}N_2O_2$	C, H, N
32h	O	2	2*H*-indazol-2-yl	110	EtOH	B	21	$C_{22}H_{20}N_2O_2$	C, H, N
32i	O	2	1*H*-1,2,3-triazol-1-yl	127-129	EtOH	B	32	$C_{17}H_{17}N_3O_2$	C, H, N
32j	O	2	2*H*-1,2,3-triazol-2-yl	107-108	EtOH	B	45	$C_{17}H_{17}N_3O_2$	C, H, N
32k	O	2	1*H*-benzotriazol-1-yl	108-110	MeOH	B	53	$C_{21}H_{19}N_3O_2$	C, H, N
32l	O	2	2*H*-benzotriazol-2-yl	105-107	EtOH	B	36	$C_{21}H_{19}N_3O_2$	C, H, N
33a	O	3	1*H*-1,2,4-triazol-1-yl	83-84	acetone-hexane	B	51	$C_{18}H_{19}N_3O_2$	C, H, N
33b	O	3	1-pyrazolyl	81-82	acetone-hexane	B	35	$C_{19}H_{18}N_2O_2$	C, H, N
38	C=O	2	1-pyrazolyl	111-114	EtOAc	C	70	$C_{19}H_{18}N_2O_2$	C, H, N
39	CHOH	2	1-pyrazolyl	84-86	EtOAc-hexane	C	98	$C_{19}H_{20}N_2O_2$	C, H, N
46a	O	1	1*H*-1,2,3-triazol-1-yl	78-80	*i*-PrOH	E	35	$C_{16}H_{15}N_3O_2$	C, H, N
46b	O	1	2*H*-1,2,3-triazol-2-yl	*a*		E	25	$C_{16}H_{15}N_3O_2$	C, H, N

[a] oil; purified by chromatography with chloroform-hexane.

Table III. Phenol Intermediates



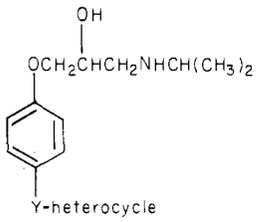
no.	X	n	heterocycle	mp, °C	crystn solvent	meth-od	yield, %	emp formula	anal.
27a		1	1-imidazolyl	206-208[a]	EtOH	A	75		
27b		1	1-pyrazolyl	113-115	EtOAc	A	47	$C_{10}H_{10}N_2O$	C, H, N
34a		2	1-imidazolyl	158-161	EtOH	B	75	$C_{11}H_{12}N_2O$	C, H, N
34b		2	1*H*-1,2,4-triazol-1-yl	165-167	*i*-PrOH	B	85	$C_{10}H_{11}N_3O$	C, H, N
34c		2	1-pyrazolyl	94-95	toluene	B	68	$C_{11}H_{12}N_2O$	C, H, N
35a	O	2	1-imidazolyl	131-133	EtOH	B	96	$C_{11}H_{12}N_2O_2$	C, H, N
35b	O	2	1-benzimidazolyl	191-192	EtOH	B	80	$C_{15}H_{14}N_2O_2$	C, H, N
35c	O	2	1*H*-1,2,4-triazol-1-yl	148-149	*i*-PrOH	B	85	$C_{10}H_{11}N_3O_2$	C, H, N
35d	O	2	1-pyrazolyl	103-105	toluene	B	55	$C_{11}H_{12}N_2O_2$	C, H, N
35e	O	2	4-chloropyrazol-1-yl	105	CCl_4	B	53	$C_{11}H_{11}N_2O_2Cl$	C, H, N
35f	O	2	4-phenylpyrazol-1-yl	155-157	toluene	B	83	$C_{17}H_{16}N_2O_2$	C, H, N
35g	O	2	1*H*-indazol-1-yl	124-125	toluene	B	58	$C_{15}H_{14}N_2O_2$	C, H, N
35h	O	2	2*H*-1,2,3-triazol-2-yl	63-66	Et_2O	B	81	$C_{10}H_{11}N_3O_2$	C, H, N
35i	O	2	1*H*-benzotriazol-1-yl	110-111	MeCN	B	50	$C_{14}H_{13}N_3O_2$	C, H, N
35j	O	2	2*H*-benzotriazol-2-yl	98	*i*-PrOH	B	55	$C_{14}H_{13}N_3O_2$	C, H, N
35k	O	2	4,5,6,7-tetrahydro-2*H*-benzotriazol-2-yl	93	toluene	B	69	$C_{14}H_{17}N_3O_2$	C, H, N
36a	O	3	1*H*-1,2,4-triazol-1-yl	145-146	EtOAc	B	61	$C_{11}H_{13}N_3O_2$	C, H, N
36b	O	3	1-pyrazolyl	108-110	EtOAc	B	60	$C_{12}H_{14}N_2O_2$	C, H, N
40		3	1-pyrazolyl[b]	177-180	EtOH	C	70	$C_{12}H_{14}N_2OCl$	C, H, N
43a	S	1	1-pyrazolyl	119-122	toluene	D	81	$C_{10}H_{10}N_2OS$	C, H, N
43b	S	2	1-pyrazolyl	87-91	toluene	D	47	$C_{11}H_{12}N_2OS$	C, H, N
47a	O	1	1*H*-1,2,3-triazol-1-yl	168-171	*i*-PrOH	E	91	$C_9H_9N_3O_2$	C, H, N
47b	O	1	2*H*-1,2,3-triazol-2-yl	68-70	CCl_4	E	60	$C_9H_9N_3O_2$	C, H, N

[a] Literature[5] mp 211 °C. [b] Characterized as the hydrochloride.

Increasing the size of the heterocycle either with benzo derivatives or bulky substituents, in general, reduces activity. With regard to partial agonist activity, no clear relationships are evident. An oxygen link is mandatory, as was found previously,[2] but not all compounds with the oxygen link show agonist activity, e.g., **10** and **23**.

In summary, a number of 4-substituted phenoxypropanolamines have been prepared in which the oxygen functionality of the 4-substituent, usually required to endow potent cardioselectivity on the β-blocking activity, has

Table IV. Comparison of Biological Activity with pK_a Values



no.	Y	heterocycle	β_1 ED_{50}, $\mu g\ kg^{-1}$ iv	pK_a[a]
1	CH_2	1-imidazolyl	620	7.2
5	CH_2CH_2	1*H*-1,2,4-triazol-1-yl	233	3.2
9	CH_2CH_2	1-pyrazolyl	209	2.0
6	OCH_2CH_2	1*H*-1,2,4-triazol-1-yl	170	3.2
13	OCH_2CH_2	1-pyrazolyl	50	2.0
22	OCH_2CH_2	2*H*-1,2,3-triazol 2-yl	14	<1.0
15	OCH_2CH_2	4-chloropyrazol-1-yl	24	<0.6
10	OCH_2	1-pyrazolyl	28	2.0
25	OCH_2	1*H*-1,2,3-triazol-1-yl	40	1.25
21	OCH_2	2*H*-1,2,3-triazol-2-yl	11	<1.0
11	OCH_2	4-chloropyrazol-1-yl	4	<0.6

[a] Values for *N*-alkyl-substituted azoles were obtained from ref 17.

been successfully replaced by nitrogen-containing heterocycles. Specifically, pyrazole 11 and 1,2,3-triazoles 21 and 22 have shown a very high level of β_1-antagonism in the rat with a selectivity ratio in excess of 100:1.

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were obtained on a Pye-Unicam SP 1000 spectrophotometer. NMR spectra were obtained on a Varian T-60 or XL-100 spectrometer using 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 filtration prior to evaporation. Chromatography was carried out with Merck silica gel 60. The azoles not commercially available (4-chloropyrazole,[9] 4-phenylpyrazole,[10] and 1,2,3-triazole[11]) were made by the published methods.

Preparation of 4-Substituted Phenoxy-3-(isopropylamino)- and Phenoxy-3-(*tert*-butylamino)-2-propanols (Table I; 1–26). The general conditions given below were followed for compounds **1–9** and **12–26**. A solution of the appropriate phenol (15 mmol) in 75 mL of DMF was treated with 0.72 g (15 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 100 mL of ethanol containing 15 mL of either isopropylamine or *tert*-butylamine, as required, 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 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)propylamine salt.

1-(Isopropylamino)-3-[4-(1-pyrazolylmethoxy)phenoxy]-2-propanol Hydrogen Maleate (10). A solution of 0.68 g (3 mmol) of 1-(isopropylamino)-3-(4-hydroxyphenoxy)-2-propanol in 6 mL of DMF was treated with 0.29 g (6 mmol) of sodium hydride, and the mixture was stirred for 5 min. After the addition of 0.46 g (3 mmol) of 1-(chloromethyl)pyrazole hydrochloride (**41**)[12] 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 gave the free base, which was converted to the hydrogen maleate salt as described above and recrystallized from 2-propanol to give 0.70 g (56%) of **10**, mp 84-87 °C. Anal. ($C_{20}H_{27}N_3O_7$) C, H, N.

1-(Isopropylamino)-3-[4-[(4-chloropyrazol-1-yl)methoxy]phenoxy]-2-propanol Hydrogen Oxalate (11). The title compound was prepared in a similar manner to **10** by using 1-(chloromethyl)-4-chloropyrazole (**49**) and only 1 equiv of sodium hydride: 61% yield; mp 82–85 °C (acetonitrile). Anal. ($C_{18}H_{24}N_3O_3Cl$) C, H, N.

General Methods for the Preparation of 4-Substituted Phenols (Table III). Method A. Preparation of 4-(Azolylmethyl)phenols (27). An intimate mixture of 4.96 g (40 mmol) of 4-hydroxybenzyl alcohol and the appropriate heterocycle (40 mmol) was heated at 160 °C for 30 min. The resulting solid product (**27**) was cooled and recrystallized.

Method B. Preparation of 4-(2-Azolylethyl)phenols (34), 4-(2-Azolylethoxy)phenols (35), and 4-(3-Azolylpropoxy)-phenols (36). (a) Alkylation Reactions. A solution of the requisite heterocycle (20 mmol) in 50 mL of DMF was treated with 0.96 g (20 mmol) of sodium hydride, and the mixture was stirred for 5 min. To this anion was added 20 mmol of the appropriate alkylating agent **28**,[13] **29**,[14] or **30**,[15] and the mixture was stirred at 60 °C for 30 min. The solvent was evaporated under reduced pressure, and the residue was partitioned between ethyl acetate and water. Workup gave the crude product, which, if a single isomer, was recrystallized from the appropriate solvent to give pure benzyl ether **31**, **32**, or **33**, respectively (Table II). Mixtures of isomers were separated and identified as follows.

1-[2-[4-(Benzyloxy)phenoxy]ethyl]-1*H*-indazole (32g) and Its 2-Isomer (32h). The crude mixture of isomers was separated by chromatogrphy with ethyl acetate–hexane (1:9) to give, after recrystallization from hexane, 3.6 g (52%) of the 1-isomer (**32g**): mp 81–83 °C; UV (EtOH)max 255 nm (ε 9600), 263 (9200), 291 (15400), 303 (9300). Anal. ($C_{22}H_{20}N_2O_2$) C, H, N. Further elution of the column with ethyl acetate–hexane (1:1) afforded, after recrystallization from ethanol, 1.44 g (21%) of the 2-isomer (**32h**): mp 110 °C; UV (EtOH) max 277 nm (ε 16600), 291 (17000). Anal. ($C_{22}H_{20}N_2O_2$) C, H, N. Isomer assignment was based on the characteristic[16] UV absorptions of 1- and 2-substituted indazoles.

1-[2-[4-(Benzyloxy)phenoxy]ethyl]-1*H*-1,2,3-trizole (32i) and Its 2-Isomer (32j). The crude mixture of isomers was extracted with boiling hexane until all the higher running component on TLC ($CHCl_3$) had been removed from the solids. The solids were filtered off, dried, and recrystallized from ethanol to give 1.9 g (32%) of the 1-isomer (**32i**): mp 127–129 °C; NMR ($CDCl_3$) δ 7.78 (1 H, d, J = 1 Hz), 7.73 (1 H, d, J = 1 Hz), 7.4 (5 H, m), 6.86 (4 H, m), 5.03 (2 H, s), 4.79 (2 H, t, J = 5 Hz), 4.32 (2 H, t, J = 5 Hz). Anal. ($C_{17}H_{17}N_3O_2$) C, H, N. The hexane filtrates were evaported, and the residue was recrystallized from ethanol to give 2.6 g (45%) of the 2-isomer (**32j**): mp 107–108 °C; NMR ($CDCl_3$) δ 7.58 (2 H, s), 7.33 (5 H, s), 6.82 (4 H, s), 4.97 (2 H, s), 4.75 (2 H, t, J = 5 Hz), 4.38 (2 H, t, J = 5 Hz). Anal. ($C_{17}H_{17}N_3O_2$) C, H, N. Isomer assignment was based on the NMR resonances of the triazole protons. The protons in the higher melting isomer resonate as a pair of doublets; i.e., they are non-

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equivalent and, therefore, correspond to the 1-isomer. The protons in the lower melting compound resonate as a singlet as required for the symmetrical 2-isomer.

1-[2-[4-(Benzyloxy)phenoxy]ethyl]-1*H*-benzotriazole (32k) and Its 2-Isomer (32l). The crude mixture of isomers was partitioned between toluene and 4 N HCl. The toluene layer was worked up, and the residue was recrystallized from ethanol to give 2.5 g (36%) of the 2-isomer (**32l**), mp 105–107 °C. Anal. ($C_{21}H_{19}N_3O_2$) C, H, N. The acid layer was neutralized with 2 N NaOH solution and extracted with toluene. Workup and recrystallization from methanol gave 3.6 g (53%) of the 1-isomer (**32k**), mp 108–110 °C. Anal. ($C_{21}H_{19}N_3O_2$) C, H, N. Separation and isomer assignment were based on the characteristic[17] acid solubility of 1-substituted benzotriazoles and the acid insolubility of 2-substituted benzotriazoles.

(b) Debenzylation by Hydrogenation To Give Phenols 34, 35a–d,h,i,k, and 36. The appropriate benzyl ether **31**, **32a–d,i–l**, or **33** (20 mmol) was dissolved in 250 mL of ethanol and hydrogenated over 200 mg of 10% Pd/C catalyst at room temperature and pressure. The catalyst was filtered off, the filtrates were evaporated, and the residue was recrystallized to give pure phenol. In the case of the benzotriazole compounds, the 1-isomer **32k** was deprotected with only a minor amount of heterocycle saturation, easily removed by recrystallization, affording the phenol **35i**. However, the 2-isomer **32l** was concomitantly deprotected and saturated to give only the tetrahydrobenzotriazole **35k**.

(c) Debenzylation by HBr–Acetic Acid To Give Phenols 35e–g,j. The appropriate benzyl ether **32e–g,l** (15 mmol) was stirred in 20 mL of 48% HBr–acetic acid at 25 °C 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 to pH 6 with concentrated HCl and extracted with ethyl acetate. Workup and recrystallization gave the pure phenol.

Method C. Preparation of 4-[3-(1-Pyrazolyl)propyl]phenol (40). A solution of 6.8 g (100 mmol) of pyrazole and 20 g (71 mmol) of 1-(dimethylamino)-3-[4-(benzyloxy)phenyl]propan-3-one[7] in 250 mL of 1-butanol was refluxed for 15 h. Evaporation, partition between ethyl acetate and water, and workup gave a crude product, which was recrystallized from ethyl acetate to give 15.1 g (70%) of 4′-(benzyloxy)-3-(1-pyrazolyl)propiophenone (**38**), mp 111–114 °C. Anal. ($C_{19}H_{18}N_2O_2$) C, H, N. The ketone (15 g, 49 mmol) was dissolved in 500 mL of ethanol and stirred with 2 g of sodium borohydride for 2 h. The solvent was evaporated, and the residue was partitioned between dichloromethane and water. Workup gave 14.9 g (98%) of 4-(benzyloxy)-α-[2-(1-pyrazolyl)-ethyl]benzyl alcohol (**39**). A small sample that recrystallized from ethyl acetate–hexane had mp 84–86 °C. Anal. ($C_{19}H_{20}N_2O_2$) C, H, N. The crude alcohol was dissolved in 600 mL of ethanol containing 8 mL of concentrated HCl and hydrogenated over 0.4 g of 10% Pd/C catalyst at room temperature and pressure. The catalyst was filtered off, the solvents were evaporated, and the residue was recrystallized from ethanol to give 8.2 g (70%) of **40**·HCl, mp 177–180 °C. Anal. ($C_{12}H_{15}N_2OCl$) C, H, N. The free base, an oil, was liberated from the salt by partition between ethyl acetate and sodium bicarbonate solution.

Method D. Preparation of 4-[(1-Pyrazolylalkyl)thio]-phenols (43). A solution of 3.15 g (25 mmol) of 4-mercaptophenol in 75 mL of DMF was stirred with 7.0 g of potassium carbonate and 25 mmol of either **41** or **42**, as appropriate, for 3 h at room temperature. The solvent was evaporated, and the residue was partitioned between ethyl acetate and water. Workup and recrystallization afforded the pure phenol **43**.

Method E. Preparation of 4-(1,2,3-Triazolylmethoxy)-phenols (47). A solution of 2.0 g (10 mmol) of 4-(benzyloxy)-phenol in 20 mL of DMF was treated with 0.96 g (20 mmol) of sodium hydride, and the mixture was stirred for 5 min. To this anion was added a solution of 1.54 g (10 mmol) of the (chloromethyl)-1,2,3-triazole hydrochloride (**45**) dissolved in 5 mL of DMF, and the mixture was stirred at 60 °C for 30 min. After evaporation of the solvent, the residue was partitioned between ethyl acetate and 2 N NaOH solution. Workup gave a crude mixture of isomers, which was extracted with cold hexane until all the higher running component on TLC ($CHCl_3$–MeOH, 19:1) had been removed from the solids. The solids were filtered off, dried, and recrystallized from 2-propanol to give 0.95 g (35%) of 1-[[(4-(benzyloxy)phenoxy]methyl]-1*H*-1,2,3-triazole (**46a**): mp 78–80 °C; NMR (Me_2SO-d_6) δ 8.31 (1 H, d, J = 1 Hz), 7.79 (1 H, d, J = 1 Hz), 7.4 (5 H, m), 7.0 (4 H, m), 6.33 (2 H, s), 5.07 (2 H, s). Anal. ($C_{16}H_{15}N_3O_2$) C, H, N. The hexane filtrates were evaporated, and the residue was purified by chromatography with chloroform–hexane (1:1) to give 0.70 g (25%) of the corresponding 2*H*-1,2,3-triazole (**46b**), as an oil: NMR (Me_2SO-d_6) δ 7.90 (2 H, s), 7.4 (5 H, m), 7.0 (4 H, m), 6.26 (2 H, s), 5.05 (2 H, s). Anal. ($C_{16}H_{15}N_3O_2$) C, H. N. Isomer assignment was based on the NMR resonances of the triazole protons. The benzyl ethers were then hydrogenolyzed as described in method B to afford phenols **47**.

2-[4-(Benzyloxy)phenyl]-1-(mesyloxy)ethane (28) was prepared by the published method.[13]

2-[4-(Benzyloxy)phenoxy]-1-bromoethane (29) was prepared by the published method.[14]

3-[4-(Benzyloxy)phenoxy]-1-bromopropane (30) was prepared by the published method.[15]

1-(Chloromethyl)pyrazole hydrochloride (41) was prepared by the published method[12] and used immediately without purification.

1-[2-(Tosyloxy)ethyl]pyrazole (42). A solution of 5 g (45 mmol) of 1-(2-hydroxyethyl)pyrazole[12] in 50 mL of pyridine was treated with 8.5 g (45 mmol) of tosyl chloride, and the solution was stirred for 2 h. The pyridine was evaporated, and the residue was acidified with concentrated HCl and washed with ether. After basification of the aqueous phase with solid sodium hydrogen carbonate, the product was extracted into ethyl acetate, washed with 1 N HCl, and worked up. Recrystallization from ether gave 4.6 g (38%) of **42**, mp 37–39 °C. Anal. ($C_{12}H_{14}N_2O_3S$) C, H, N.

2*H*-1,2,3-Triazole-2-methanol (44).[8] A solution of 4.0 g (58 mmol) of 1,2,3-triazole[11] in 15 mL of 40% formalin was left at 25 °C for 2 h. The solution was extracted with 8 × 50 mL of dichloromethane and worked up without a water wash. Recrystallization of the residue from ether gave 1.55 g (27%) of (**44**), mp 63–67 °C. Anal. ($C_3H_5N_3O$) C, H, N.

(Chloromethyl)-1,2,3-triazole Hydrochloride (45). A solution of 0.99 g (10 mmol) of **44** in 5 mL of thionyl chloride was left for 5 min and then evaporated to dryness under reduced pressure and at a temperature below 25 °C. The resulting crude solid hydrochloride **45** (1.54 g, 100%) was used immediately and without purification. The product was assumed to be a mixture of the 1- and 2-substituted triazoles.

4-Chloro-1-pyrazolemethanol (48). A solution of 7.0 g (68 mmol) of 4-chloropyrazole[9] in 10 mL of 40% formalin and 70 mL of THF was left at 25 °C for 2 h. The solution was evaporated to dryness, and the residue was partitioned between water and dichloromethane. Workup and recrystallization from toluene–hexane (1:1) gave 6.8 g (75%) of **48**, mp 72–73 °C. Anal. ($C_4H_5N_2OCl$) C, H, N.

1-(Chloromethyl)-4-chloropyrazole (49). A solution of 2.7 g (20 mmol) of **48** in 20 mL of dichloromethane was added dropwise to 3 mL of thionyl chloride in 10 mL of dichloromethane at 0 °C. After 2 h at 25 °C the solution was evaporated to dryness. The residue was dissolved in ether, filtered to remove a small amount of solid, and evaporated to give 2.8 g (93%) of crude **49** as an oily free base. The compound was used immediately and without further purification.

Pharmacological Methods. β-Adrenoceptor antagonism was measured in rats anesthetized with pentobarbitone sodium (75 mg/kg ip). The rats were bilaterally vagotamized, and the trachea was cannulated. Isoprenaline was 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 the injection of isoprenaline, the test compound was injected, and the heart rate and blood pressure were recorded. The procedure was repeated with cumulative doses of test compound up to 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 level was calculated. The ED_{50} values (defined as the

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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.[19] Statistical analysis of the results showed that the 95% confidence limits for the ED_{50} values averaged 30% (standard deviation 14%).

β-Adrenoceptor agonism was measured by the method of Barrett and Carter,[20] in rats anesthetized with pentobarbitone sodium (75 mg/kg ip) and 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 the activity. Blood pressure and heart rate were recorded as above. A dose–response relationship was established, and ED_{30} 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_{30} values averaged 60% (standard deviation 37%).

Acknowledgment. We thank the Physical Methods Department for the elemental analyses and IR and NMR spectra and Dr. A. Krohn for the computer modeling studies.

Registry No. 1, 80200-45-9; 2, 80200-39-1; 3, 80200-61-9; 4, 80200-65-3; 5, 80200-42-6; 5 (free base), 88670-84-2; 6, 80200-66-4; 6 (free base), 88670-85-3; 7, 80200-33-5; 7 (free base), 88670-86-4; 8, 88670-67-1; 9, 80200-41-5; 10, 80200-58-4; 11, 80200-26-6; 12, 80200-68-6; 13, 80200-24-4; 14, 80200-30-2; 15, 80200-37-9; 16, 80200-35-7; 17, 80200-54-0; 17 (free base), 88670-87-5; 18, 80200-53-9; 19, 80200-49-3; 20, 80200-32-4; 21, 80200-27-7; 21 (free base), 88670-88-6; 22, 80200-28-8; 22 (free base), 88670-89-7; 23, 80200-46-0; 23 (free base), 88670-90-0; 24, 80200-47-1; 24 (free base), 88670-91-1; 25, 80200-56-2; 26, 88670-69-3; 27a, 41833-17-4; 27b, 80200-09-5; 28, 61439-60-9; 29, 3351-59-5; 30, 80199-92-4; 31a, 80199-93-5; 31b, 88670-73-9; 31c, 88670-74-0; 32a, 88670-75-1; 32b, 88670-76-2; 32c, 88670-77-3; 32d, 80199-91-3; 32e, 88670-78-4; 32f, 80200-69-7; 32g, 80200-21-1; 32h, 88670-79-5; 32i, 88670-80-8; 32j, 80200-22-2; 32k, 88670-81-9; 32l, 80199-94-6; 33a, 88670-82-0; 33b, 88670-83-1; 34a, 80200-06-2; 34b, 80200-08-4; 34c, 80200-07-3; 35a, 80199-99-1; 35b, 80200-00-6; 35c, 80200-01-7; 35d, 80199-98-0; 35e, 80200-05-1; 35f, 80200-04-0; 35g, 80200-15-3; 35h, 80200-16-4; 35i, 88670-72-8; 35j, 80200-10-8; 35k, 80200-11-9; 36a, 80200-03-9; 36b, 80200-02-8; 40·HCl, 88070-70-6; 41·HCl, 73901-67-4; 42, 80200-20-0; 43a, 80200-19-7; 43b, 80200-14-2; 44, 78910-04-0; 45·HCl, 88670-71-7; 46a, 80199-96-8; 46b, 80199-97-9; 47a, 80200-18-6; 47b, 80200-17-5; 48, 80199-86-6; 49, 80199-87-7; 4-mercaptophenol, 637-89-8; 2-(isopropylamino)-3-(4-hydroxyphenoxy)-2-propanol, 16656-05-6; 1*H*-1,2,4-triazole, 288-88-0; 4-chloro-1*H*-pyrazole, 15878-00-9; 4-phenyl-1*H*-pyrazole, 10199-68-5; 2*H*-1,2,3-triazole, 288-35-7; 1*H*-benzotriazole, 95-14-7; formalin, 50-00-0; 1-(2-hydroxyethyl)pyrazole, 6314-23-4; 4-hydroxybenzyl alcohol, 623-05-2; imidazole, 288-32-4; 1*H*-pyrazole, 288-13-1; 1*H*-benzimidazole, 51-17-2; 1*H*-indazole, 271-44-3; 2*H*-benzotriazole, 273-02-9; 4-(benzyloxy)phenol, 103-16-2; 1-(dimethylamino)-3-[4-(benzyloxy)phenyl]propan-3-one, 51345-76-7.

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Synthesis, Receptor Binding, and Target-Tissue Uptake of Carbon-11 Labeled Carbamate Derivatives of Estradiol and Hexestrol

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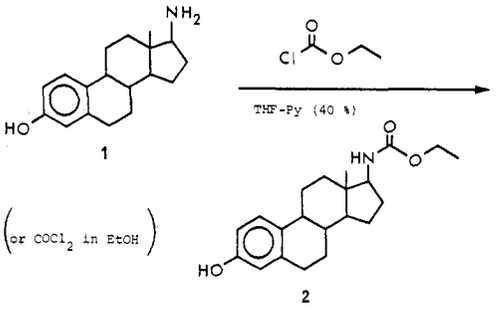
The reaction of ethyl chloroformate with amino compounds has been evaluated as a simple route to carbon-11 labeling of steroid hormone–receptor-based imaging agents. Both a 17β-amino analogue of estradiol and an aminoethyl derivative of the nonsteroidal estrogen hexestrol with potential affinity for the estrogen receptor were studied. The unlabeled carbamate derivatives of the amino estrogens were prepared by standard methods, and the ^{11}C-labeled analogues were synthesized from [^{11}C]ethyl chloroformate, generated by purging ethanol with [^{11}C]phosgene. Both carbamates showed weak in vitro binding affinity for the estrogen receptor, and only the ^{11}C-labeled hexestrol exhibited a small but significant estrogen-responsive uterus uptake in immature rats.

With the aim to develop radiopharmaceuticals for imaging estrogen receptor positive human breast tumors, a variety of steroidal and nonsteroidal estrogens labeled with γ-emitting radioisotopes have been prepared over the past few years.[1-11] Most of these analogues were labeled with radioisotopes of iodine. Although various vinyl and aryl iodides possess reasonable metabolic stability,[10] aliphatic iodides exhibit poor in vivo stability with the attendant risk for high radioactivity uptake in the thyroid.[11] Accordingly, bromine-77 has recently been favored as the radiohalogen of choice.[8,9,11] In addition to radiohalogens and mercury-203,[12] the positron-emitting carbon-11 radionuclide has also been used for the labeling of steroid analogues.[13,14] The short 20-min half-life of carbon-11 requires that ^{11}C-labeled estrogens have rapid in vivo target localization with rapid clearance from nontarget tissues.

Scheme I



In addition, fast, convenient synthetic methods are required for the preparation of ^{11}C-labeled estrogens.

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