title compound was prepared from **21**[9] by a procedure similar to that used for its cis isomer (**24**·HCl), except in this case the N_2O_4/HOAc solution was added to the reaction mixture in small portions over a period of 48 h at ≤−50 °C with occasional mixing. After complete addition, the mixture was kept at −50 to −30 °C for an additional 24 h and then worked up as described for **24**·HCl to afford 34% of crude **25**·HCl, which was used without purification: mp 235–237 °C dec; R_f 0.28 (EtOAc/MeOH/NH_4OH, 5:3:0.5); mass spectrum, m/e 291 ($M^+ + 1$).

α-Amino-*N*-(2-phenylethyl)acetamide (26). To a stirred, ice-cooled solution of *N*-Z-Gly-ONp (0.73 g, 2.2 mmol) in dry MeCN (10 mL) was added a solution of phenethylamine (0.72 g, 2.2 mmol) in MeCN (5 mL) and the mixture was stirred at 25 °C for 2 h. The solvent was removed in vacuo and the solid residue was washed repeatedly with 10% $NaHCO_3$ and then with H_2O. The EtOAc solution was evaporated to give 0.53 g (76%, based on *N*-Z-Gly-ONp) of *N*-Z-Gly-$NHCH_2CH_2Ph$ as a solid, mp 104–107 °C. This product (0.4 g, 1.28 mmol) was dissolved in MeOH (15 mL), 10% ethereal HCl (0.2 mL) was added and the mixture was hydrogenated over 10% Pd/C (40 mg, 10% w/w) at room temperature and atmospheric pressure for 6 h. The mixture was filtered and MeOH was evaporated. The residue was washed with cold ether and dried in vacuo to give 0.24 g (89%) of **26**·HCl as a solid, mp 85–86 °C. This was dissolved in H_2O and the solution was basified with $NaHCO_3$ and extracted with EtOAc. Removal of EtOAc gave **26** as an oil which solidified at −15 °C.

1-Methyl-*N*-substituted-4-(*N*-phenylpropanamido)-piperidine-2-carboxamides (14–19). To a stirred solution of **24**·HCl or **25**·HCl (1 equiv) in dry MeCN at −20 °C was added triethylamine (2 equiv), followed by isobutyl chloroformate[11] (1 equiv). After stirring for 15 min at −20 °C, a solution of the appropriate amine [$(Ph(CH_2)_{1-4}NH_2$] or **26** (1 equiv) in dry MeCN was added, and the mixture was stirred for 15 min at −10 °C and 24 h at 25–27 °C. The solvent was removed in vacuo, and the residue was mixed with H_2O, acidified (pH 3) with 10% HCl, and extracted with EtOAc. In the case of **17** and **18**, the organic layer was dried (Na_2SO_4) and EtOAc was removed to give the crude product, which was purified as its HCl salt as indicated in Table II. In the case of **14–16** and **19**, the aqueous layer was cooled (ice bath), basified (pH 12) with Na_2CO_3, and extracted with EtOAc. Drying and then removing the EtOAc gave the crude product, which was purified by crystallization of the base (**14**, **16**, and **19**) or the HCl salt (**15**) as shown in Table II. The HBr salts of **14** (mp 170–173 °C), **16** (mp 105–108 °C), and **19** (mp 98–101 °C) were prepared with an ethereal solution of HBr.

Guinea Pig Ileum Myenteric Plexus and Mouse Vas Deferens Preparations. This was performed according to modifications[7,8] of the published procedures of Kosterlitz et al.[12,13] The IC_{50} of fentanyl was determined in the GPI or MVD from the log dose–response curves. The preparations were then incubated with 2×10^{-7} β-FNA for 60 min. The agonist effect of β-FNA was washed until the tissue recovered its normal response. The IC_{50} ratio of fentanyl was then evaluated on the β-FNA-treated preparation. The IC_{50} ratio, which represents the IC_{50} of fentanyl after treatment with β-FNA divided by the control IC_{50}, was determined.

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β-Adrenergic Blocking Agents. 23. 1-[(Substituted-amido)phenoxy]-3-[[(substituted-amido)alkyl]amino]propan-2-ols

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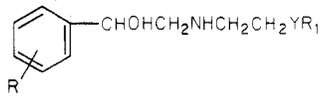
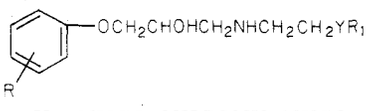
The synthesis of a series of 1-phenoxy-3-[(amidoalkyl)amino]propan-2-ols, in which the phenoxy ring is variously substituted with ortho and para amidic moieties, is described. Several of the compounds have β-blocking potency comparable to that of propranolol and cardioselectivity similar to that of practolol, when given intravenously to anesthetized cats. In contrast to previous findings with cardioselective β blockers, both ortho and para substitution give variable degrees of cardioselectivity. Potency, however, is favored by ortho substitution.

In two previous papers[1,2] we have shown that an amidic moiety in the side chain of an arylethanolamine, **1**, or an



1, Y = NHCO, NHCONH, $NHSO_2$



2, Y = NHCO, NHCONH, $NHSO_2$

(aryloxy)propanolamine, **2**, confers a high degree of cardioselectivity and β-adrenergic blocking potency. Furthermore, in earlier studies on (aryloxy)propanolamines, which were variously substituted in the aryloxy ring, we found that a para amidic substituent gave optimum cardioselectivity.[3] Other workers have reported similar findings[4-7] and cardioselectivity has also been achieved by replacing the isopropyl or *tert*-butyl substituent, conventionally used in β blockers with an (aryloxy)alkyl group in which the aryl ring has a para-amidic substituent.[8] We therefore considered it of interest to combine the above features by synthesizing a series of 1-[(substituted-amido)phenoxy]-3-[[(substituted-amido)alkyl]amino]-propanol-2-ols.

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(2) M. S. Large and L. H. Smith, *J. Med. Chem.*, **25**, 1417 (1982).
(3) L. H. Smith, *J. Appl. Chem. Biotechnol.*, **28**, 201 (1978).
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(7) G. Shtacher, M. Erez, and S. Cohen, *J. Med. Chem.*, **16**, 516 (1973).
(8) J. Augstein, D. A. Cox, A. L. Ham, P. R. Leeming, and M. Snarey, *J. Med. Chem.*, **16**, 1245 (1973).

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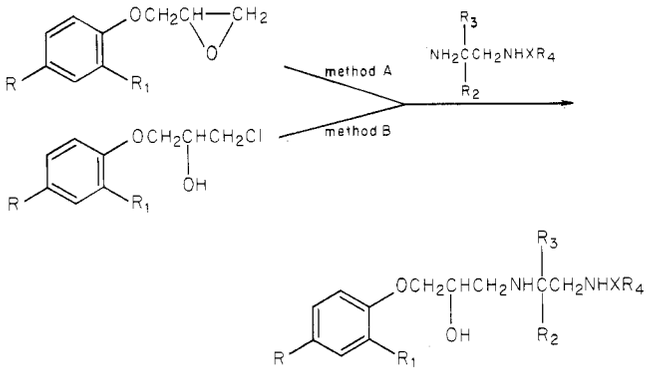
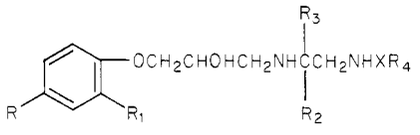
Scheme I[a]



[a] R, R_1, R_2, R_3, R_4, and X relate to the substituents described in Tables I–V.

This paper discusses the structure–activity relationships of a series of compounds described by structure **3**, in which



3

either R or R_1 is an amidic substituent or R and R_1 are nonamidic, but R_4 is an aryl ring bearing a para-amidic substituent and X has the values shown in Tables IV and V.

Chemistry. The majority of compounds listed in Tables I–V were synthesized by methods A and B illustrated in Scheme I. The designation C used in the tables signifies a separately described method of preparation. The (amidoalkyl)amine precursors used in methods A and B were made by acylating an alkylenediamine by literature methods.

Results and Discussion

The compounds presented in this work have been divided into five classes (Tables I–V) according to the nature of the amidic substituent, in order to facilitate structure–activity relationship discussion. Table I lists those compounds that have an acylamino substituent in the aryl nucleus. The *p*- and *o*-acetamido compounds **4** and **5**, while not directly comparable, have similar potencies, but cardioselectivity appears to be favored by para substitution. The combination of a variety of ortho substituents with a *p*-acylamino substituent does not affect cardioselectivity, as shown by the ortho-substituted *p*-propionamidophenoxy compounds **6–11**, all of which are very cardioselective. Furthermore, potency appears to be greatly enhanced by an *o*-ethyl substituent, as shown by compounds **9** and **11**. Variations in R_4 were very limited in this class, the only direct comparison being compound **9** vs. **11**, where there is very little difference in the effect of potency and cardioselectivity between a phenylacetamido and a phenylureido moiety.

The para-substituted carbamoyl analogues **18** and **19** in Table II were weakly active, and compound **18** was not very cardioselective. By comparison, the ortho-substituted compounds **12–17** were potent, with compounds **14** and **17** displaying both high potency and cardioselectivity. Both of these latter compounds are substituted at R_4 by a phenyl ring that is separated from the side-chain amidic moiety by a methylene and imino group, respectively. In the one example examined, potency is enhanced but cardioselectivity is reduced by branching the alkylene chain at R_2 (**14** vs. **15**). Overall, cardioselectivity in this class was variable

Table I

no.	R	R_1	R_4	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose,[a] mg/kg, giving 50% inhibn of tachycardia	% inhibn of depressor response
4	$NHCOCH_3$	H	4-$COCH_3$-$C_6H_4OCH_2$	128–130	EtOAc	8	$C_{23}H_{29}N_3O_6 \cdot 0.5H_2O$	C, H, N	A	756	0
5	H	$NHCOCH_3$	*i*-C_3H_7	199–200	EtOH	26	$C_{17}H_{27}N_3O_4 \cdot C_2H_2O_4$	C, H, N	C	683	22
6	$NHCOC_2H_5$	Cl	*i*-C_3H_7	167–168	EtOH	6	$C_{18}H_{28}ClN_3O_4$	C, H, N	B	1365	2
7	$NHCOC_2H_5$	NO_2	*i*-C_3H_7	147–148	CH_3CN	5	$C_{18}H_{28}N_4O_6$	C, H, N	B	99	0
8	$NHCOC_2H_5$	Br	$C_6H_5CH_2$	169–170	EtOH	16	$C_{22}H_{28}BrN_3O_4$	C, H, N	A	1343	0
9	$NHCOC_2H_5$	C_2H_5	$C_6H_5CH_2$	135–137	CH_3CN	26	$C_{24}H_{33}N_3O_4 \cdot 0.25H_2O$	C, H, N	A	15	0
10	$NHCOC_2H_5$	c-C_6H_{11}	$C_6H_5CH_2$	169–171	EtOH	21	$C_{28}H_{39}N_3O_4 \cdot C_4H_4O_4$	C, H, N	B	630	
11	$NHCOC_2H_5$	C_2H_5	C_6H_5NH	168–170	CH_3CN	6	$C_{23}H_{32}N_4O_4 \cdot 0.25H_2O$	C, H, N	A	26	0

[a] In anesthetized cats.

Table II

no.	R	R_1	R_2	X	R_4	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose,[a] mg/kg, giving 50% inhibn of tachycardia	% inhibn of depressor response
12	H	$CONH_2$	H	CO	*i*-C_3H_7	136–138	CH_3CN	25	$C_{16}H_{25}N_3O_4$	C, H, N	B	131	0
13	H	$CONH_2$	H	CO	CH_2= $CHCH_2NH$	140–141	EtOH	13	$C_{16}H_{24}N_4O_4 \cdot 0.25H_2O$	C, H, N	B	229	13
14	H	$CONH_2$	H	CO	$C_6H_5CH_2$	131–133	EtOH	16	$C_{20}H_{25}N_3O_4 \cdot 0.25H_2O$	C, H, N	B	11	0
15[c]	H	$CONH_2$	CH_3	CO	$C_6H_5CH_2$	gum	*b*	12	$C_{21}H_{27}N_3O_4 \cdot H_2O$	C, H, N	B	5	30
16	H	$CONH_2$	H	CO	NH_2	167–169	EtOH	6	$C_{13}H_{20}N_4O_4 \cdot C_2H_2O_4$	C, H, N	B	180	33
17	H	$CONH_2$	H	CO	C_6H_5NH	156–157	EtOH	20	$C_{19}H_{24}N_4O_4$	C, H, N	B	6	0
18	$CONHCH_3$	H	H	CO	*i*-C_3H_7	161–162	CH_3CN	41	$C_{17}H_{27}N_3O_4$	C, H, N	B	1325	26
19	CONH-C_6H_{13}	Cl	H	CO	C_6H_5NH	186–188	EtOH	4	$C_{25}H_{35}ClN_4O_4 \cdot 0.5C_2H_2O_4$	C, H, N	A	1500	

[a] In anesthetized cats. [b] Isolated by chromatography on silica gel with $CHCl_3$/MeOH (7:3, v/v) as eluant. [c] Presumed to be a mixture of diastereoisomers.

and less consistent than the selectivity shown by the acylamino compounds in Table I. There is a marked increase in potency on replacing an unsubstituted *o*-carbamoyl moiety with an N-substituted oxyacetamido moiety. Thus, the oxyacetamido analogues of compound **12**, i.e., compounds **21** and **35** in Table III, are far more potent while having a similar degree of cardioselectivity. Replacement of the isobutyramido substituent (R_4) with other substituents had little effect on potency (cf. **21** with **20** and **23–25**), but the *tert*-butyl and benzyl substituents **24** and **25** do lead to reduced cardioselectivity. Interestingly, when R_4 is a benzyl moiety with a substituent on the phenyl ring, the substituent appears to influence the degree of cardioselectivity. Thus, compounds **26** and **27**, bearing ortho substituents, are very selective, while compound **28** with a para substituent is less selective; potency, however, was not affected by this variation. When R_4 is a phenoxymethyl moiety, variously substituted in the phenyl ring, the ortho-substituted analogues **29–31** have variable effects on potency and cardioselectivity. Replacement of the methyl substituent on the amide group of the *o*-oxyacetamido moiety by hydroxyethyl had little effect on potency or cardioselectivity (cf. **21** with **35**, and **25** with **36**).

The miscellaneous amide groups listed in Table IV are too diverse and small in number to allow for SAR interpretations. There are, however, some points of interest to be gleaned from the data. Thus, the *o*-methylsulfonamido compound **42** showed good potency and moderate cardioselectivity. The *p*-*n*-butylureido (**38**) and *p*-acetylaminomethylene (**39**) substituents lead to high cardioselectivity, while the *p*-carbamoylmethylene substituent (**40**) appears to confer poor potency and selectivity; this may be a consequence of the phenylsulfonamido substituent at R_4.

A limited number of analogues were synthesized in which the amidic substituent was introduced into the phenyl ring of a benzamido, phenylacetamido, or phenoxyacetamido moiety on the alkylamine side chain. In all the examples shown in Table V, the phenyl ring was substituted in the para position, R_6. As in Table IV, the amidic groups exemplified are too small in number and too diverse for any detailed SAR interpretation. It is of interest, however, to note that all the compounds are potent and cardioselective and that the *p*-acylaminobenzenesulfonamide **47** is more potent than the analogous benzamide **43**. Two analogous compounds, **46** and **45**, show that an acetylaminomethylene substituent is preferable to a carbamoylmethylene substituent for both potency and cardioselectivity.

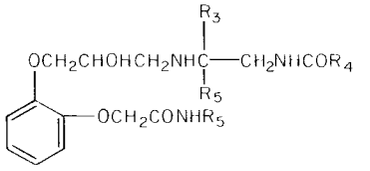
In summary, this study shows that the introduction of ortho- and para-amidic functions into the phenoxy ring of 1-phenoxy-3-[[(substituted-amido)alkyl]amino]propan-2-ols results in variable degrees of cardioselectivity. Potency, however, is favored by ortho substitution. This is in contrast to the findings in other series,[3-6] where para substituents gave both higher potency and cardioselectivity.

Experimental Section

Chemistry. All melting points were obtained with an Electrothermal capillary melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. ^1H NMR spectra for all the compounds described were recorded either on a Varian HA100D or a Varian A60 with tetramethylsilane as the internal standard and were consistent with the assigned structures.

3-[[2-(Phenylacetamido)ethyl]amino]-1-[2-bromo-4-propionamidophenoxy]propan-2-ol (8). Method A. A mixture of 1-[2-bromo-4-propionamidophenoxy]-2,3-epoxypropane (1.5

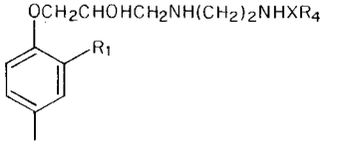
Table III



no.	R_5	R_2	R_3	R_4	mp, °C	crystn solvent	yield, %	emp formula[a]	anal.	method of prepn	dose,[b] mg/kg, giving 50% inhibn of tachycardia	% inhibn of depressor response
20	CH_3	H	H	CH_3	127-129	EtOH/Et_2O	42	$C_{16}H_{25}N_3O_5$	C, H, N	A	8	14
21	CH_3	H	H	i-C_3H_7	157-159	CH_3CN	33	$C_{18}H_{29}N_3O_5$	C, H, N	A	12	0
22	CH_3	CH_3	CH_3	i-C_3H_7	gum	*c*	20	$C_{20}H_{33}N_3O_5 \cdot 0.5H_2O$	C, H, N	A	5	39
23	CH_3	H	H	c-C_3H_7	151-153	CH_3CN	18	$C_{18}H_{27}N_3O_5$	C, H, N	A	22	4
24	CH_3	H	H	t-C_4H_9	145-146	EtOH	13	$C_{19}H_{31}N_3O_5 \cdot C_2H_2O_4$	C, H, N	A	10	40
25	CH_3	H	H	$C_6H_5CH_2$	162-164	CH_3CN	36	$C_{22}H_{29}N_3O_5$	C, H, N	A	3	41
26	CH_3	H	H	2-$ClC_6H_4CH_2$	169-171	CH_3CN	18	$C_{22}H_{28}ClN_3O_5$	C, H, N	A	9	0
27	CH_3	H	H	2-$NH_2C_6H_4CH_2$	133-135	EtOAc	58	$C_{22}H_{30}N_4O_5$	C, H, N	C	5	0
28	CH_3	H	H	4-$OHC_6H_4CH_2$	168-170	MeOH	18	$C_{22}H_{29}N_3O_6 \cdot 0.5Fu \cdot 0.25H_2O$	C, H, N	C	6	33
29	CH_3	H	H	2-CH_2=$CHCH_2OC_6H_4OCH_2$	122-124	EtOAc	6	$C_{25}H_{33}N_3O_7$	C, H, N	A	25	0
30	CH_3	H	H	2-CH_2=$CHCH_2C_6H_4OCH_2$	110-111	EtOAc	5	$C_{25}H_{33}N_3O_6$	C, H, N	A	9	25
31	CH_3	H	H	2-$CNC_6H_4OCH_2$	134-135	EtOH	24	$C_{23}H_{28}N_4O_6$	C, H, N	A	8	41
32	CH_3	H	H	2,3-$CH_3OC_6H_3CH_2$	131-133	CH_3CN	8	$C_{24}H_{33}N_3O_7$	C, H, N	C	7	36
33	CH_3	H	H	n-C_4H_9NH	131-133	EtOAc	4	$C_{19}H_{32}N_4O_5$	C, H, N	A	33	39
34	CH_3	H	H	CH_2=$CHCH_2NH$	149-150	CH_3CN	4	$C_{18}H_{28}N_4O_5$	C, H, N	A	9	18
35	C_2H_4OH	H	H	i-C_3H_7	125-126	CH_3CN	10	$C_{19}H_{31}N_3O_6$	C, H, N	A	4	11
36	C_2H_4OH	H	H	$C_6H_5CH_2$	136-138	CH_3CN	15	$C_{23}H_{31}N_3O_6 \cdot 0.25H_2O$	C, H, N	A	4	18
37[d]	C_2H_4OH	CH_3	H	$C_6H_5CH_2$	151-153	EtOH	6	$C_{24}H_{33}N_3O_6 \cdot 0.5Fu \cdot 0.5H_2O$	C, H, N	A	5	33

[a] Fu = fumarate. [b] In anesthetized cats. [c] Isolated by chromatography on silica gel with $CHCl_3$/MeOH (7:3, v/v) as eluant. [d] Presumed to be a mixture of diastereoisomers.

Table IV



no.	R	R_1	X	R_4	mp, °C	solvent	yield, %	emp formula	anal.	method of prepn	dose,[a] mg/kg, giving 50% inhibn of tachy-cardia	% inhibn of depressor response
38	NHCONH-n-C_4H_9	H	CO	i-C_3H_7	166-168	CH_3CN	15	$C_{20}H_{34}N_4O_4 \cdot 0.5H_2O$	C, H, N	A	231	0
39	$CH_2NHCOCH_3$	H	CO	i-C_3H_7	144-145	CH_3CN	20	$C_{18}H_{29}N_3O_4$	C, H, N	B	224	0
40	CH_2CONH_2	H	SO_2	C_6H_5	112-115	*b*	3	$C_{19}H_{25}N_3O_5S \cdot H_2O$	C, H, N	A	793	37
41	$CH_2NHCONH_2$	OCH_3	CO	i-C_3H_7	151-152	EtOH	3	$C_{18}H_{30}N_4O_5$	C, H, N	A	240	
42	H	$NHSO_2CH_3$	CO	i-C_3H_7	169-171	EtOH	30	$C_{16}H_{27}N_3O_5S \cdot C_2H_2O_4$	C, H, N	C	24	17

[a] In anesthetized cats. [b] Isolated by chromatography on silica gel with $CHCl_3$/MeOH (9:1, v/v) as eluant.

Table V

no.	R_1	X	R_6	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, mg/kg,[a] giving 50% inhibn of tachycardia	% inhibn of depressor response
43	H	CO	$NHCOCH_3$	157–159	EtOH	35	$C_{20}H_{25}N_3O_4 \cdot 0.25H_2O$	C, H, N	A	95	0
44	CN	$COCH_2$	$NHSO_2CH_3$	180–181	*i*-PrOH	12	$C_{21}H_{26}N_4O_5S \cdot 0.5C_2H_2O_4 \cdot H_2O$	C, H, N	C	8	0
45	CN	$COCH_2O$	CH_2CONH_2	108–109	*i*-PrOH	28	$C_{22}H_{26}N_4O_5 \cdot H_2O$	C, H, N	A	47	18
46	CN	$COCH_2O$	$CH_2NHCOCH_3$	98–100	*i*-PrOH	19	$C_{23}H_{28}N_4O_5 \cdot H_2O$	C, H, N	C	13	0
47	H	SO_2	$NHCOCH_3$	231–233	$EtOH/H_2O$	41	$C_{19}H_{25}N_3O_5S \cdot HCl \cdot 0.25H_2O$	C, H, N	C	17	2
48	(practolol)									168	8
49	(propranolol)									62	85

[a] In anesthetized cats.

g, 0.005 mol), *N*-(2-aminoethyl)phenylacetamide[9] (0.9 g, 0.005 mol), and *i*-PrOH (50 mL) was refluxed for 18 h and then evaporated to dryness. The residue was crystallized from MeCN and then from EtOH: yield 0.38 g (16%); mp 169–170 °C.

3-[(2-Isobutyramidoethyl)amino]-1-(2-carbamoylphenoxy)propan-2-ol (12). Method B. A mixture of 3-chloro-1-(2-carbamoylphenoxy)propan-2-ol (2.3 g, 0.01 mol), *N*-(2-aminoethyl)isobutyramide[10] (1.3 g, 0.01 mol), $NaHCO_3$ (0.84 g, 0.01 mol), H_2O (5 mL), and *i*-PrOH (40 mL) was refluxed for 18 h, cooled to room temperature, and then filtered. The filtrate was evaporated to dryness, and the residue was crystallized from MeCN: yield 0.8 g (25%); mp 136–138 °C.

3-[(2-Isobutyramidoethyl)amino]-1-[2-(methylsulfonamido)phenoxy]propan-2-ol Hydrogen Oxalate (42). Methanesulfonyl chloride (1.15 g, 0.01 mol) was added dropwise over 0.1 h to a stirred solution of 1-(2-aminophenoxy)-3-[*N*-benzyl-*N*-(2-isobutyramidoethyl)amino]propan-2-ol (3.8 g, 0.01 mol) in pyridine (20 mL) and the mixture was stirred for 1 h and then added to H_2O (200 mL). The mixture was extracted with EtOAc, and the ethyl acetate extract was washed with H_2O and then dried (Na_2SO_4) and evaporated to dryness.

A solution of the residue in EtOH (40 mL) was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure until uptake of hydrogen ceased. The mixture was filtered, and the filtrate was evaporated to dryness. A solution of the residue in ethyl acetate was added to a solution of oxalic acid in ethyl acetate, and the precipitated hydrogen oxalate was collected and crystallized from EtOH: yield 1.4 g (30%); mp 169–171 °C.

Compound **5** was prepared in a similar manner but with acetic anhydride instead of methanesulfonyl chloride.

1-(2-Aminophenoxy)-3-[*N*-benzyl-*N*-(2-isobutyramidoethyl)amino]propan-2-ol (Used as Starting Material for Compounds 42 and 5). A mixture of *N*-[2-(benzylamino)-ethyl]isobutyramide hydrochloride[10] (25.6 g, 0.1 mol), 5 N NaOH (20 mL), 1-(2-nitrophenoxy)-2,3-epoxypropane[11] (19.5 g, 0.1 mol), and *n*-PrOH (200 mL) was refluxed for 5 h and then evaporated to dryness. The residue was partitioned between H_2O and Et_2O, and the Et_2O phase was dried (Na_2SO_4) and evaporated to dryness to give 1-(2-nitrophenoxy)-3-[*N*-(2-isobutyramidoethyl)amino]-propan-2-ol as a yellow oil (41 g).

A mixture of 1-(2-nitrophenoxy)-3-[*N*-benzyl-*N*-(2-isobutyramidoethyl)amino]propan-2-ol (4.15 g, 0.01 mol), EtOH (50 mL), and Raney nickel (0.5 g) was stirred at reflux while adding a solution of hydrazine hydrate (1.5 g, 0.03 mol) in EtOH (10 mL) dropwise over 0.3 h, and the mixture was refluxed for an additional further 1 h. The mixture was filtered, the filtrate was evaporated to dryness, and the residue was crystallized from a mixture of EtOAc and c-C_6H_{12}: yield 1.9 g (50%); mp 94–96 °C.

1-[[2-[2-(2-Aminophenyl)acetamido]ethyl]amino]-3-[2-[(*N*-methylcarbamoyl)methoxy]phenoxy]propan-2-ol (27). A solution of 1-[[2-[2-(2-nitrophenyl)acetamido]ethyl]amino]-3-[2-[(*N*-methylcarbamoyl)methoxy]phenoxy]propan-2-ol (prepared by method A) (0.46 g, 0.001 mol) in EtOH (30 mL) was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was crystallized from EtOAc: yield 0.25 g (58%); mp 133–135 °C.

3-[2-[2-(4-Acetamidophenoxy)acetamido]ethyl]amino]-1-(2-cyanophenoxy)-propan-2-ol Hydrate (46). A mixture of 3-[(2-aminoethyl)amino]-1-(2-cyanophenoxy)propan-2-ol[2] (0.84 g, 0.0035 mol) and ethyl 4-acetamidophenoxyacetate[12] (0.89 g, 0.0035 mol) was heated at 100 °C for 1.5 h. The mixture was cooled and crystallized from MeCN and then from *i*-PrOH: yield 0.85 g (19%); mp 198–100 °C.

Compounds **32** and **44** were prepared in a similar manner by using the appropriate diamine and ester as starting materials.

3-[[2-[2-(4-Hydroxyphenyl)acetamido]ethyl]amino]-1-[2-[(*N*-methylcarbamoyl)methoxy]phenoxy]propan-2-ol

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Fumarate (28). A solution of 3-[[2-[2-[4-(benzyloxy)phenyl]-acetamido]ethyl]amino]-1-[2-[(*N*-methylcarbamoyl)methoxy]-phenoxy]propan-2-ol (prepared by method A: mp 162–164 °C; Anal. C, H, N) (1.04 g, 0.002 mol) in EtOH (25 mL) was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure. The mixture was filtered, and the filtrate was evaporated to dryness. A solution of the residue in MeOH was added to a solution of fumaric acid in MeOH, and the precipitate was collected and recrystallized from MeOH: yield 0.2 g (18%); mp 168–170 °C.

3-[[2-(4-Acetamidobenzenesulfonamido)ethyl]amino]-1-phenoxypropan-2-ol Hydrochloride (47). A mixture of 4-acetamidobenzenesulfonyl chloride[13] (2.34 g, 0.01 mol) and $CHCl_3$ (25 ml) was added over 0.2 h to a stirred solution of 3-[*N*-(2-aminoethyl)-*N*-benzylamino]-1-phenoxypropan-2-ol[10] (3.02 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in $CHCl_3$ (50 mL). The mixture was washed successively with 10% $NaHCO_3$ solution and H_2O and then dried (Na_2SO_4) and evaporated to dryness.

A solution of the residue in a mixture of ethanol (50 mL) and HOAc (1 mL) was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure. The mixture was filtered, and filtrate was evaporated to dryness. The residue was dissolved in water (20 mL), and the solution was neutralized with $NaHCO_3$ and then extracted with EtOAc (3 × 20 mL). The combined extracts were dried and then acidified with ethereal HCl. The precipitated hydrochloride was collected and crystallized from $EtOH/H_2O$: yield 1.8 g (41%); mp 231–233 °C.

Pharmacology. β-Adrenoreceptor blocking potency was estimated in vivo by using the previously described cat preparation.[14] The results given in Tables I–V are the estimated dose, infused over a period of 30 min, that would cause a 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 μg/kg dosed iv). The estimated degree (percent) of blockade of the vasodepressor response at that dose level is also given. Three to five dose levels of each compound were used to calculate these estimates. The relative potencies in these two systems give an indication of selectivity for β_1 (cardiac) as opposed to β_2 (vascular) receptors. Mean log ED_{50}'s were calculated for each compound on the basis of two or three tests, and the standard errors of the means were computed. On average, these mean values had an error of 30%. Previous data[14] have shown that the error in the percent inhibition of the depressor response at the ED_{50} value for inhibition of isoproterenol-induced tachycardia is less than 5%.

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Registry No. **4**, 58027-28-4; **5**, 58027-75-1; **6**, 58027-66-0; **7**, 58027-62-6; **8**, 58027-90-0; **9**, 58027-89-7; **10**, 84051-23-0; **11**, 58027-88-6; **12**, 58027-39-7; **13**, 58027-41-1; **14**, 58027-40-0; **15**, 58027-60-7; **16**, 58027-72-8; **17**, 58027-38-6; **18**, 58027-44-4; **19**, 84051-24-1; **20**, 58027-21-7; **21**, 58027-22-8; **22**, 58027-56-8; **23**, 58027-30-8; **24**, 84051-25-2; **25**, 58027-27-3; **26**, 58027-33-1; **27**, 58027-87-5; **28**, 58027-86-4; **29**, 58027-31-9; **30**, 58027-32-0; **31**, 58027-36-4; **32**, 84051-26-3; **33**, 58027-23-9; **34**, 58027-29-5; **35**, 58027-25-1; **36**, 58027-24-0; **37**, 58027-53-5; **38**, 58027-11-5; **39**, 58027-69-3; **40**, 58027-20-6; **41**, 58027-94-4; **42**, 58027-80-8; **43**, 58827-22-8; **44**, 58827-85-3; **45**, 81253-57-8; **46**, 58827-83-1; **47**, 58827-21-7; **47** (free base), 84051-27-4; 1-(2-bromo-4-propionamidophenoxy)-2,3-epoxypropane, 58027-49-9; *N*-(2-aminoethyl)phenylacetamide, 15070-17-4; 3-chloro-1-(2-carbamoylphenoxy)propan-2-ol, 58027-55-7; *N*-(2-aminoethyl)isobutyramide, 53673-16-8; methanesulfonyl chloride, 124-63-0; 1-(2-aminophenoxy)-3-[*N*-benzyl-*N*-(2-isobutyramidoethyl)amino]propan-2-ol, 58027-73-9; *N*-[2-(benzylamino)ethyl]isobutyramide hydrochloride, 58027-76-2; 1-(2-nitrophenoxy)-2,3-epoxypropane, 21407-49-8; 1-[[2-[2-(2-nitrophenyl)acetamido]ethyl]amino]-3-[2-[(*N*-methylcarbamoyl)methoxy]phenoxy]propan-2-ol, 58027-77-3; 1-[[2-[2-(2-nitrophenyl)acetamido]ethyl]amino]-3-[2-[(*N*-methylcarbamoyl)methoxy]phenoxy]propan-2-ol, 58027-35-3; 3-[(2-aminoethyl)amino]-1-(2-cyanophenoxy)propan-2-ol, 58827-72-8; ethyl 4-acetamidomethylphenoxyacetate, 55458-50-9; 3-[[2-[2-[4-(benzyloxy)phenyl]acetamido]ethyl]amino]-1-[2-[(*N*-methylcarbamoyl)methoxy]phenoxy]propan-2-ol, 58027-46-6; 4-acetamidobenzenesulfonyl chloride, 121-60-8; 3-[*N*-(2-aminoethyl)-*N*-benzylamino]-1-phenoxy-2-propan-2-ol, 84051-28-5.

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Piperazinylimidazo[1,2-*a*]pyrazines with Selective Affinity for in Vitro α-Adrenergic Receptor Subtypes

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Regioselective syntheses of alkyl- and halogen-substituted piperazinylimidazo[1,2-*a*]pyrazines by novel oxidation–dehydration of [(β-hydroxyalkyl)amino]pyrazines are described. Lanthanide shift reagent studies allowed correction of literature assignments of NMR chemical shifts and coupling constants for the imidazo[1,2-*a*]pyrazine ring system (e.g., $J_{5,8} > J_{6,8}$). Equilibrium constants for displacement of specifically bound [^{3}H]clonidine and [^{3}H]prazosin from calf cerebral cortex homogenates in vitro are tabulated for reference and title compounds, and structure–affinity relationships for α_2- vs. α_1-adrenergic receptors are considered. Compound **2a**, 8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine, is equipotent with mianserin on the clonidine receptor (α_2) but ca. 70 times as selective as mianserin for this α_2-adrenergic receptor. Reduction of the imidazo ring (2,3-dihydro) lowers affinity for the α_2 receptor without affecting α_1-receptor affinity. Computer-assisted molecular modeling techniques are applied to the estimation of conformational energies of **2a** and its 5-position isomer in relation to the semirigid molecule mianserin.

Piperazinylpyrazines[1,2] and piperazinylquinoxalines[3,4] with selective actions on central nervous system neurons were the subjects of previous publications from these laboratories. From these studies, 6-chloro-2-(1-piperazinyl)pyrazine (MK0212, **1**) was selected for clinical study because of its serotoninmimetic properties. During in vitro receptor-binding studies of **1**, significant affinity

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