g (0.14 mol) of 2,6-diethoxybenzoic acid and 7 mL (0.14 mol) of Br_2. The product was recrystallized from isopropyl ether–light petroleum: yield 28.7 g.

3-Chloro-2,6-diethoxybenzoic Acid (27). A solution of 4.05 mL (0.05 mol) of SO_2Cl_2 in 25 mL of $CHCl_3$ was added dropwise, while stirring, to a solution of 10.5 g (0.05 mol) of 2,6-diethoxybenzoic acid in 75 mL of $CHCl_3$. The mixture was heated at 50 °C for 30 min. The solvent was then evaporated, and the residue was recrystallized from isopropyl ether–light petroleum: yield 10.1 g.

(*S*)-(−)-1-Trityl-2-pyrrolidinecarboxamide (29). Trityl chloride (88.0 g, 0.31 mol) was added in portions to a mixture of 47.6 g (0.31 mol) of (*S*)-(−)-prolinamide hydrochloride and 88 mL (0.63 mol) of triethylamine in 350 mL of $CHCl_3$ while stirring and cooling in ice. The mixture was stirred overnight at room temperature and was then extracted with H_2O. The organic layer was separated and dried with anhydrous $MgSO_4$, and the chloroform was evaporated. The residue was recrystallized twice from EtOH–(*i*-Pr)$_2$O: yield 59.0 g (53%); mp 198–199 °C; $[\alpha]^{20}_D$ −34.3° (*c* 1.0, $CHCl_3$). Anal. ($C_{24}H_{24}N_2O$) C, H, N.

(*S*)-(−)-2-[(3-Bromo-2,6-dimethoxybenzamido)methyl]-pyrrolidine Hydrochloride (19). A solution of 35.6 g (0.1 mol) of **29** in 200 mL of dry THF was added dropwise, while stirring and cooling in ice, to a stirred mixture of 8.0 g (0.2 mol) of $LiAlH_4$ in 150 mL of dry Et_2O. The mixture was stirred and heated under reflux for 27 h. After dropwise addition of 50 mL of a saturated Na_2SO_4 solution while stirring and cooling in ice, the mixture was filtered. The filtrate was dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue (41.0 g of oil) was dissolved in a mixture of 400 mL of $CHCl_3$ and 15 mL of triethylamine. To the solution was added dropwise, while stirring a solution prepared as follows: A mixture of 50 mL of $SOCl_2$ and 26.1 g (0.1 mol) of 2,6-dimethoxy-3-bromobenzoic acid was heated on a steam bath for 0.5 h. Toluene was added, and the solvent and excess $SOCl_2$ were evaporated at reduced pressure. The residual acid chloride was dissolved in 200 mL of $CHCl_3$.

After the addition of the chloroform solution, the mixture was left overnight at room temperature. The solvent was then evaporated, and to the residue was added 15 mL of 12 N HCl in 300 mL of EtOH. The solution was left at room temperature for 1 h. The ethanol was then evaporated, and the residue was triturated with Et_2O, stirred with 700 mL of H_2O, and extracted with Et_2O. The water layer was made alkaline with NaOH and extracted with $CHCl_3$. The extract was dried with $MgSO_4$, and the solvent was evaporated. The residue, an oil which crystallized on scratching, was washed with peteroleum ether and dried: yield 18.6 g; mp 85–90 °C.

The crude free base was converted to the hydrochloride salt by adding a solution of 3 N HCl gas in Et_2O to a solution of the base in 100 mL of EtOH. The salt was precipitated by the addition of Et_2O. The product was filtered off and recrystallized from EtOH–(*i*-Pr)$_2$O, yielding 18.0 g of the pure compound. Three grams of the hydrochloride dissolved in 200 mL of H_2O was converted into the free base by the addition of NaOH. After the solution was extracted with $CHCl_3$, the extract was dried, and the solvent was evaporated, 2.1 g of the pure base was obtained, mp 106–107 °C.

Pharmacology. Apomorphine-Induced Behavior. Blockade of apomorphine-induced hyperactivity and sterotypies was performed as described previously.[4,10] Male Sprague–Dawley rats, weighing 250–300 g, were used. the behavior was scored 5, 20, 40, and 60 min after injection of apomorphine (1 mg/kg), given subcutaneously into the neck. The test compounds were dissolved in saline or water and injected ip 60 min prior to apomorphine. The ED_{50}'s for stereotypies are the doses that reduce the strength of apomorphine-induced stereotypies by 50% over the total observation period of 60 min. The ED_{50}'s for hyperactivity are the doses that reduce the number of animals showing hyperactivity by 50% over the observation period of 60 min. Each ED_{50} was calculated by Theil's method and corrected for ties according to Sen's procedure based on Kendell's τ.[29,30] The 90% confidence interval was calculated according to a slightly modified version of Sen's procedure.

Measurement of Catalepsy in Rats. Eight rats at each dose level were tested in open perspex cages [40 (l) × 25 (w) ×15 (h) cm] fitted with a 7-cm-high horizontal bar. Catalepsy was measured 1, 2, 4, 8, and 24 h after injection of the test compound. The fore limbs of each animal were placed on the horizontal bar. A cataleptic state was scored if the rat failed to remove itself from the bar within 60 s. Maximal catalepsy tended to occur between 2 and 8 h following the treatment. The dosage at which 50% of the animals were cataleptic (ED_{50} and the 95% confidence interval) was calculated by probit analysis on the peak cataleptic effect observed for each compound.

Acute Toxicity. The acute toxicity was assessed in rats observed for 24 h after ip injection. The LD_{50} values and the 95% confidence intervals were determined by probit analysis based on four doses, with five animals per dose level. If data were not suitable for regression analysis, the approximate LD_{50} values were determined from log dose–response curves.

Acknowledgment. The excellent technical work of B. A. Kristina Ängeby is gratefully acknowledged. We also thank Dr. L. Agnati, Bologna, and B. A. O. Stockman, Astra Läkemedel AB, for invaluable help and suggestions in the statistical analysis.

(29) P. K. Sen, *J. Am. Stat. Assoc.*, **63**, 1379 (1968).
(30) H. Theil, *Ned. Akod. Wetemsch. Proc., Ser A*, **53**, 386 (1950).

β-Adrenergic Blocking Agents. 22. 1-Phenoxy-3-[[(substituted-amido)alkyl]amino]-2-propanols

M. S. Large and L. H. Smith*

Imperial Chemical Industries PLC, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England.
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The synthesis of a series of 1-phenoxy-3-[[(substituted-amido)alkyl]amino]-2-propanols is described. Many of the compounds are more potent than propanolol as β blockers, while having cardioselectivity comparable to that of practolol, when given intravenously to anesthetized cats. The structure–activity relationships shown by this series of compounds provide further evidence that the addition of substituents to the alkylamino moeity of a β blocker can confer cardioselectivity and that amidic substituents are remarkably effective.

Cardioselectivity has been shown to be associated with a variety of para substituents in the aryl moiety of an (aryloxy)propranolamine.[1-3] More recent work shows that the property can also be obtained by replacing the conventional isopropyl or *tert*-butyl substituent of a β-blocker

(1) L. H. Smith, *J. Appl. Chem. Biotechnol.*, **28**, 201 (1978).
(2) B. Ablad, E. Carlsson, and L. Ek, *Life Sci.*, **12**, 107 (1973).
(3) B. Basil, J. R. Clark, E. C. J. Coffee, R. Jordan, A. H. Loveless, D. L. Pain, and K. R. H. Wooldridge, *J. Med. Chem.*, **19**, 399 (1976).

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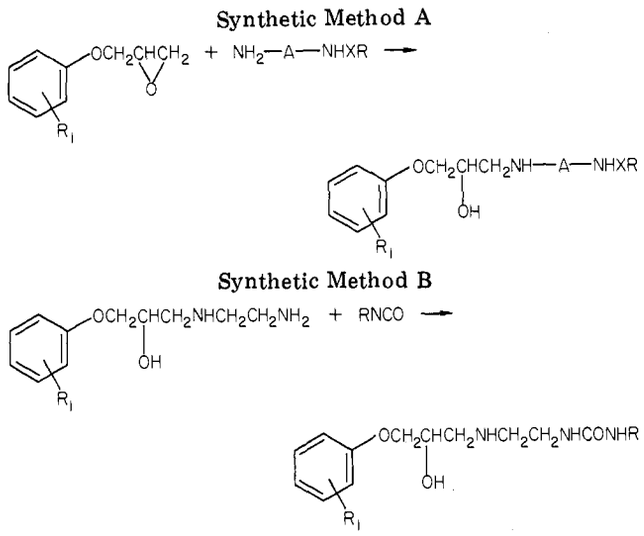
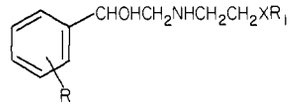
Scheme I[a]



[a] Where X = CO, COY, CONH, SO_2, and R, R_1, A and Y relate to the substituents described in the tables.

by either a 3,4-dimethoxyphenethyl substituent[4-6] or by a suitably substituted phenoxyalkylamine moiety.[7,8]

In our previous paper[9] we described a series of 1-phenyl-2-[[(substituted-amido)alkyl]amino]ethanols **1**,

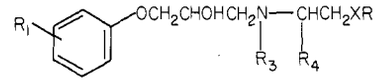


1

2, X = NHCO, NHCONH, $NHSO_2$

which are cardioselective β-adrenoceptor blocking agents. We attributed the cardioselectivity of these compounds to the amidic moiety **2**, which linked the ethanolamine side chain to a variety of aryl, alkyl, aralkyl, and aryloxyalkyl substituents (R_1).

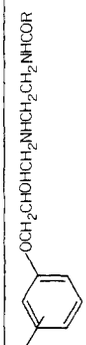
We now report on an analogous series of 1-phenoxy-3-[[(substituted-amido)alkyl]amino]-2-propanols **3**, which are an order of magnitude more potent than the previous series and which also show more widespread cardioselectivity.



3

Chemistry. The majority of compounds listed in Tables I–V were synthesized by methods A and B illustrated in Scheme I. Most of the compounds were prepared by method A, while method B was used to prepare some of the ureido analogues. The designation C used in the tables signifies a separately described method of preparation. The amidoalkylamine precursors used in method A were synthesized by acylating an alkylenediamine as described in our previous publications.[9,10]

Table I. Physical and Pharmacological Properties of the Alkyl and Aryl Amides

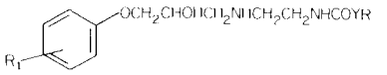


no.	R	R_1	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, μg/kg, giving 50% inhibn of tachycardia	inhibn, %, of depressor response
4	H	H	107–109	EtOAc	15	$C_{12}H_{18}N_2O_3$	C, H, N	C	9	8
5	CH_3	H	103–105	EtOAc	13	$C_{13}H_{20}N_2O_3$	C, H, N	A	15	7
6	CF_3	H	106–108	EtOAc/PE[a]	49	$C_{13}H_{17}F_3N_2O_3$	C, H, N	C	4	0
7	C_2H_5	H	126–127	MeCN	26	$C_{14}H_{22}N_2O_3$	C, H, N	A	6	33
8	C_2H_5	2-CN	96–97	EtOAc	12	$C_{15}H_{21}N_3O_3$	C, H, N	A	7	0
9	n-C_3H_7	H	86–87	EtOAc	36	$C_{15}H_{24}N_2O_3$	C, H, N	A	12	12
10	i-C_3H_7	H	125–126	EtOAc	30	$C_{15}H_{24}N_2O_3$	C, H, N	A	14	0
11	i-C_3H_7	2-CH_3	120–122	EtOAc	27	$C_{16}H_{26}N_2O_3$	C, H, N	A	27	11
12	i-C_3H_7	2-Cl	129–130	EtOAc	30	$C_{15}H_{23}ClN_2O_3$	C, H, N	A	16	23
13	i-C_3H_7	2-NO_2	108–110	EtOAc	25	$C_{15}H_{23}N_3O_5$	C, H, N	A	6	5
14	t-C_4H_9	2-NO_2	165–166	MeCN	22	$C_{16}H_{25}N_3O_5 \cdot C_2H_2O_4$	C, H, N	A	11	25
15	t-C_4H_9	2-CN	152–154	MeCN	17	$C_{17}H_{25}N_3O_3 \cdot C_4H_4O_4 \cdot 0.5H_2O$	C, H, N	A	19	0
16	n-C_5H_{11}	H	101–102	EtOAc	33	$C_{17}H_{28}N_2O_3$	C, H, N	A	159	0
17	n-C_6H_{17}	H	95–96	EtOAc	37	$C_{20}H_{34}N_2O_3$	C, H, N	A	840	3
18	c-C_3H_5	H	125–126	EtOAc	36	$C_{15}H_{22}N_2O_3$	C, H, N	A	22	0
19	c-C_6H_{11}	H	138–139	MeCN	7	$C_{18}H_{28}N_2O_3$	C, H, N	A	20	0
20	C_6H_5	H	198–199	EtOH	21	$C_{18}H_{22}N_2O_3 \cdot HCl$	C, H, N	A	77	0
21	2-Cl-C_6H_4	H	182–183	MeCN	23	$C_{18}H_{21}ClN_2O_3 \cdot HCl$	C, H, N	A	161	0
22	2-$(CH_3)_2N$-C_6H_4	H	82–84	TLC[b]	33	$C_{20}H_{27}N_3O_3 \cdot 0.25H_2O$	C, H, N	A	465	0
23	3,4-$(OH)_2$-C_6H_4	H	178–180	EtOH	46	$C_{18}H_{22}N_2O_5 \cdot C_2H_2O_4 \cdot 0.5H_2O$	C, H, N	C	14	0
24	2,5-$(OH)_2$-C_6H_4	H	195–197	EtOH/H_2O	42	$C_{18}H_{22}N_2O_5 \cdot 0.5C_2H_2O_4$	C, H, N	C	616	0

[a] PE = petroleum ether, bp 60–80 °C. [b] Purified by silica gel chromatography using $CHCl_3$/MeOH (4:1 v/v) as developing solvent.

(4) S. G. Hastings, R. D. Smith, R. M. Corey, A. D. Essenburg, C. E. Pettway, and D. K. Tessman, *Arch. Int. Pharmacodyn. Ther.*, **226**, 81 (1977).
(5) K. Sugawara, N. Takami, ane M. Dzaki, *Arch. Int. Pharmacodyn. Ther.*, **240**, 294 (1979).
(6) W. J. Rzeszota, R. E. Gibson, D. A. Simms, and J. N. Vaugen, *J. Am. Chem. Soc.*, **102**, 34 (1980).
(7) J. Augstein, D. A. Cox, A. L. Ham, P. R. Leeming, and M. Snarey, *J. Med. Chem.*, **16**, 1245 (1973).
(8) L. H. Smith and H. Tucker, *J. Med. Chem.*, **20**, 1653 (1977).
(9) M. S. Large and L. H. Smith, *J. Med. Chem.*, **23**, 112 (1980).

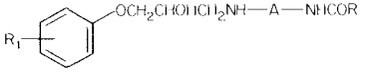
Table II. Physical and Pharmacological Properties of Aralkyl and Aryloxyalkyl Amides



no.	R	R_1	Y	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, μg/kg, giving 50% inhibn of tachycardia	inhibn, %, of depressor response
25	C_6H_5	H	CH_2	124–125	EtOAc	27	$C_{19}H_{24}N_2O_3$	C, H, N	A	29	0
26	2-Cl-C_6H_4	H	CH_2	137–138	EtOAc	33	$C_{19}H_{23}ClN_2O_3$	C, H, N	A	9	12
27	4-Cl-C_6H_4	H	CH_2	119–120	MeCN	41	$C_{19}H_{23}ClN_2O_3$	C, H, N	A	17	8
28	2-NO_2-C_6H_4	H	CH_2	130–131	EtOAc	16	$C_{19}H_{23}N_3O_5$	C, H, N	A	20	0
29	4-NO_2-C_6H_4	H	CH_2	135–136	EtOAc	8	$C_{19}H_{23}N_3O_5$	C, H, N	A	33	5
30	4-CH_3O-C_6H_4	H	CH_2	122–123	EtOAc	25	$C_{20}H_{26}N_2O_4$	C, H, N	A	14	2
31	2-Cl-C_6H_4	2-Cl	CH_2	144–146	EtOAc	55	$C_{19}H_{22}Cl_2N_2O_3$	C, H, N	A	10	30
32	C_6H_5	H	$(CH_2)_2$	112–113	EtOAc/PE[a]	32	$C_{20}H_{24}N_2O_3$	C, H, N	A	31	0
33	H	H	CH_2O	128–129	EtOH	9	$C_{13}H_{20}N_2O_3 \cdot C_2H_2O_4$	C, H, N	A	7	18
34	CH_3	H	CH_2O	135–137	EtOH	19	$C_{14}H_{22}N_2O_4 \cdot C_2H_2O_4$	C, H, N	A	16	0
35	C_6H_5	H	CH_2O	131–133	MeCN	25	$C_{19}H_{24}N_2O_4 \cdot C_2H_2O_4 \cdot 0.5H_2O$	C, H, N	A	38	0
36	2-CH_3O-C_6H_4	H	CH_2O	156–158	MeCN	5	$C_{20}H_{26}N_2O_5 \cdot C_2H_2O_4 \cdot 0.5H_2O$	C, H, N	A	70	3
37	C_6H_5	2-CN	CH_2O	130–132	MeCN	8	$C_{20}H_{23}N_3O_4 \cdot C_2H_2O_4$	C, H, N	C	21	35
38	4-Cl-C_6H_4	H	$(CH_2)_2CO$	172–174	EtOH	42	$C_{21}H_{27}ClN_2O_4 \cdot C_2H_2O_4 \cdot 0.25H_2O$	C, H, N	A	78	25

[a] PE = petroleum ether, bp 60–80 °C.

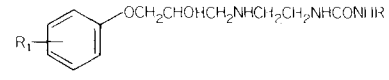
Table III. Physical and Pharmacological Properties of Compounds with Alternative Links between Amino and Amide Functions



no.	R	R_1	A	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, μg/kg, giving 50% inhibn of tachycardia	inhibn, %, of depressor response
39	i-C_3H_7	H	$(CH_2)_3$	94–95	EtOAc	26	$C_{16}H_{26}N_2O_3$	C, H, N	A	210	0
40	CH_3	H	$(CH_2)_6$	111–113	MeCN	20	$C_{17}H_{28}N_2O_3 \cdot C_2H_2O_4$	C, H, N	A	44	16
41[d]	i-C_3H_7	H	$CH(CH_3)CH_2$	124–126	EtOAc	20	$C_{16}H_{26}N_2O_3$	C, H, N	A	5	37
42[d]	n-C_5H_{11}	H	$CH(CH_3)CH_2$	102–103	EtOAc	11	$C_{18}H_{30}N_2O_3$	C, H, N	A	5	0
43[d]	$CH_2C_6H_5$	H	$CH(CH_3)CH_2$	124–126	EtOAc	22	$C_{20}H_{26}N_2O_3$	C, H, N	A	3	0
44[d]	$CH_2C_6H_5$	2-$OCH_2CH{=}CH_2$	$CH(CH_3)CH_2$	102–105	EtOAc	28	$C_{23}H_{30}N_2O_4$	C, H, N	A	19	30
45[d]	$CH_2C_6H_5$	2-CN	$CH(CH_3)CH_2$	124–128	EtOAc	33	$C_{21}H_{25}N_3O_3$	C, H, N	A	4	10
46[d]	2-Cl-$C_6H_4CH_2$	2-NO_2	$CH(CH_3)CH_2$	98–101	TLC[a]	4	$C_{20}H_{24}ClN_3O_5 \cdot 0.5H_2O$	C, H, N	A	7	34
47	i-C_3H_7	H	$C[(CH_3)_2]CH_2$	oil	TLC[a]	16	$C_{17}H_{28}N_2O_3 \cdot 0.25H_2O$	C, H; N[b]	A	3	0
48	$C_6H_5CH_2$	H	$C[(CH_3)_2]CH_2$	oil	TLC[a]	25	$C_{23}H_{28}N_2O_3 \cdot 0.5H_2O$	C, H; N[c]	A	11	0

[a] Purified by silica gel chromatography using $CHCl_3$/MeOH (4:1, v/v) as developing solvent. [b] N: calcd, 8.9; found, 8.3. [c] N: calcd, 7.9; found, 7.0. [d] The proton noise decoupled ^{13}C NMR spectrum of 46 (Me_2SO-d_6 solution at 60 °C recorded on a JEOL FX 900) indicates that 46 is a 1:1 mixture of diastereoisomers: two pairs of signals of similar intensity were assigned to the CH_3 (18.17 and 18.07 ppm) and the CHOH (68.29 and 68.12 ppm) carbon atoms of the diastereoisomers. Compounds 41–45 are presumed to be mixtures of diastereoisomers.

Table IV. Physical and Pharmacological Properties of the Ureas



no.	R	R_1	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, μg/kg, giving 50% inhibn of tachycardia	inhibn, %, of depressor response
49	H	H	108–110	MeCN	10	$C_{12}H_{19}N_3O_3$	C, H, N	A	12	0
50	H	2-CN	156–157	EtOH	24	$C_{13}H_{18}N_4O_3$	C, H, N	A	60	21
51	CH_3	2-CN	139–140	MeCN	40	$C_{14}H_{20}N_4O_3$	C, H, N	B	44	18
52	C_2H_5	H	118–120	EtOAc	16	$C_{14}H_{23}N_3O_3$	C, H, N	A	24	0
53	i-C_3H_7	H	145–147	MeCN	25	$C_{15}H_{25}N_3O_3$	C, H, N	A	99	0
54	i-C_3H_7	2-CN	147–149	MeCN	14	$C_{16}H_{24}N_4O_3$	C, H, N	B	168	0
55	$CH_2CH{=}CH_2$	H	131–132	EtOAc	22	$C_{15}H_{23}N_3O_3$	C, H, N	A	24	5
56	n-C_4H_9	H	116–117	EtOAc	26	$C_{16}H_{27}N_3O_3$	C, H, N	A	22	8
57	n-C_4H_9	2-CN	145–147	MeCN	21	$C_{17}H_{26}N_4O_3$	C, H, N	A	304	0
58	c-C_6H_{11}	H	156–158	MeCN	13	$C_{18}H_{29}N_3O_3$	C, H, N	A	282	6
59	C_6H_5	H	144–145	EtOAc	18	$C_{18}H_{23}N_3O_3 \cdot 0.25H_2O$	C, H; N[a]	A	53	0
60	C_6H_5	2-CH=CH_2	179–181	EtOH–H_2O	7	$C_{20}H_{25}N_3O_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$	C, H, N	A	85	0
61	C_6H_5	2-OCH_3	160–161	MeCN	49	$C_{19}H_{25}N_3O_4$	C, H, N	A	60	0
62	C_6H_5	2-$OCH_2CH{=}CH_2$	126–128	i-PrOH	4	$C_{21}H_{27}N_3O_4$	C, H, N	A	37	24
63	C_6H_5	2-$COCH_3$	165–167	EtOH–H_2O	8	$C_{20}H_{25}N_3O_4 \cdot C_2H_2O_4$	C, H, N	A	89	25
64	C_6H_5	2-$COOCH_3$	126–127	MeCN	36	$C_{20}H_{25}N_3O_5$	C, H, N	C	133	10
65	C_6H_5	2-Cl	157–158	MeCN	34	$C_{18}H_{22}ClN_3O_3$	C, H, N	A	37	4
66	C_6H_5	2-CN	155–156	MeCN	11	$C_{19}H_{22}N_4O_3 \cdot 0.25H_2O$	C, H, N	A	9	0
67	C_6H_5	2-NO_2	159–161	MeCN	16	$C_{18}H_{22}N_4O_5$	C, H, N	A	52	14
68	4-CH_3-C_6H_4	H	147–149	EtOAc	16	$C_{19}H_{25}N_3O_3$	C, H, N	A	124	32
69	4-CH_3O-C_6H_4	H	126–128	EtOAc	9	$C_{19}H_{25}N_3O_4$	C, H, N	A	287	33
70	2-CH_3O-C_6H_4	2-CN	152–153	MeCN	52	$C_{20}H_{24}N_4O_4$	C, H, N	B	143	0
71	2-Cl-C_6H_4	2-CN	143–144	MeOH–MeCN	28	$C_{19}H_{21}ClN_4O_3$	C, H, N	B	366	0
72	4-Cl-C_6H_4	2-CN	159–160	MeCN	13	$C_{19}H_{21}ClN_4O_3 \cdot 0.25H_2O$	C, H, N	A	25	1
73	2-NO_2-C_6H_4	2-CN	125–126	MeCN	18	$C_{19}H_{21}N_5O_5$	C, H, N	B	97	11

[a] N: calcd, 12.6; found, 13.6.

Table V. Physical and Pharmacological Properties of the Sulfonamides

no.	R	R_1	R_3	R_4	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, μg/kg, giving 50% inhibn of tachycardia	inhibn, %, of depressor response
74	CH_3	H	H	H	155–156	MeOH	11	$C_{13}H_{20}N_2O_4S \cdot C_2H_2O_4$	C, H, N	A	39	0
75	*n*-C_3H_7	H	H	H	87–88	EtOAc/PE[a]	35	$C_{14}H_{22}N_2O_4S$	C, H, N	A	15	0
76	*i*-C_3H_7	H	H	H	181–183	EtOH	14	$C_{14}H_{22}N_2O_4S \cdot 0.5C_2H_2O_4$	C, H, N	A	8	9
77	C_6H_5	H	H	H	85–87	EtOAc	29	$C_{17}H_{22}N_2O_4S$	C, H, N	A	18	12
78	C_6H_5	2-CN	H	H	136–138	EtOH	35	$C_{18}H_{21}N_3O_4S \cdot C_2H_2O_4 \cdot H_2O$	C, H, N	A	67	28
79	4-CH_3-C_6H_4	H	H	H	145–148	EtOH	35	$C_{18}H_{24}N_2O_4S \cdot C_2H_2O_4 \cdot 0.5H_2O$	C, H, N	A	51	29
80	4-Cl-C_6H_4	H	H	H	166–169	EtOH	15	$C_{17}H_{21}ClN_2O_4S \cdot C_2H_2O_4$	C, H, N	A	63	21
81	2-NO_2-C_6H_4	H	H	H	186–188	MeCN	9	$C_{16}H_{21}N_3O_6S \cdot 0.5C_2H_2O_4$	C, H, N	A	7	12
82	3-NH_2-4-CH_3-5-NO_2-C_6H_2	H	H	H	223–225	EtOAc	5	$C_{16}H_{24}N_4O_6S \cdot 0.5C_2H_2O_4$	C, H, N	A	217	34
83[c]	2-NO_2-C_6H_4	H	H	CH_3	oil	TLC[b]	24	$C_{16}H_{23}N_3O_6S$	C, H, N	A	3	0
84	C_6H_5	H	CH_3	H	114–117	EtOAc	14	$C_{18}H_{24}N_2O_4S \cdot C_2H_2O_4$	C, H, N	C	904	16
85	(practolol)										167	8
86	(propranolol)										62	85

[a] PE = petroleum ether, bp 60–80 °C. [b] Purified by silica gel chromatography using $CHCl_3$/MeOH (9:1 v/v) as developing solvent. [c] Presumed to be a mixture of diastereoisomers; cf. 46.

Discussion

The object of this study was to discover the effect, on both β-blocking potency and β_1-cardioselectivity, of replacing the branched chain alkylamino moiety of an (aryloxy)propanolamine, such as propranolol, with an amidoalkylamino moiety. Tables I–V give the ED_{50} values (micrograms per kilogram) and the percentage inhibition of the depressor response in the cat at that dose level. For comparison purposes, the β_1 β_2 blocker propranolol (**86**) and the β_1-cardioselective blocker practolol (**85**) have been included at the end of Table V.

The compounds described have been divided into five tables to facilitate discussion of the structure–activity relationships. Table I lists those amides derived from alkyl- and arylcarboxylic acids, Table II lists those amides derived from aralkyl- and aryloxyalkylcarboxylic acids, and Table III consists of analogues of Tables I and II where the link between the amino and amido groups is an alkylene chain other than ethylene. Table IV consists of ureido analogues. Table V consists of sulfonamido analogues. The tables show that the introduction of an amidoalkylamino moiety into the side chain of an (aryloxy)propanolamine confers a high degree of potency and cardioselectivity on the molecule. Sixty-eight percent of the compounds shown are more potent than propranolol (**86**; ED_{50} = 62 μg/kg), and 64% are as cardioselective as practolol (**85**)(i.e., a depressor response inhibition of 0–10%).

The biological data in Table I shows that most of the simple alkyl amides are very potent and many are cardioselective at the ED_{50}. Furthermore, the potency of these compounds is relatively insensitive to variation in chain length or side-chain branching, provided that the chain is short; cf. **5**, **7**, **9**, and **10**, (C_1–C_3, respectively). However, potency falls away markedly in the longer chain compounds **16** and **17** (C_5 and C_8, respectively). Cardioselectivity, on the other hand, appears to be unaffected by chain length, since both compounds **16** and **17** are highly cardioselective.

The cycloalkyl amides **18** and **19** have comparable potency and selectivity to the small-chain alkyl amides, but the aryl amides (**20**–**24**), with the exception of the 3,4-dihydroxybenzamide **23**, are significantly less potent. We investigated the effect of ortho substituents in the aryl ring of the (aryloxy)propanol moiety in a series of isobutyramides (**11**–**13**), a variation known to increase potency amongst conventional isopropyl and *tert*-butylamino-substituted β-blockers.[12] There were, however, only small and random variations in potency, but a significant finding was the overall but relatively small reduction in cardioselectivity, when compared with the unsubstituted compound, **10**. With this exception, the level of cardioselectivity was spread randomly among the compounds in Table I and could not be related to those factors affecting potency.

The arylalkyl amides and aryloxyalkyl amides listed in Table II are similar to the alkyl amides in that they are more potent than the analogous benzamides: thus, the phenylacetamides **25** and **26** were more potent than the benzamides **20** and **21**. Also, in contrast to the benzamides, 2 or 4 substitution of the phenylacetamido ring has minimal effect on potency; cf. **26**–**30**. Only one analogous comparison can be made between the phenoxyacetamides

(10) L. H. Smith, U.K. Patent 1 455 116 (1976); *Chem. Abstr.*, **81**, P104983*m*.
(11) J. D. Fitzgerald and S. R. O'Donnell, *Br. J. Pharmacol.*, **43**, 222 (1971).
(12) L. H. Smith, *J. Med. Chem.*, **19**, 1119 (1976).

and the benzamides; i.e., compound **35** was more potent than compound **20**, but the overall trend among the phenoxyacetamides in Table II showed them also to be more potent than the benzamides. It would therefore appear that a link separating the amide and aryl moieties favors potency.

Variation of the alkylene chain that separates the secondary amino group from the amide group (Table III) showed that a small branched alkylene chain gave optimal potency; thus, in a series of isobutyramides the compounds with *tert*-butylene and isopropylene links (**47** and **41**, respectively) were slightly more potent than the compound with an ethylene linkage, **10**, and all three were much more potent than the longer chain propylene analogue **39**. However, the effect on cardioselectivity was variable. Ortho substitution of the aryl ring, of the (aryloxy)propanol moeity, in those compounds with a branched alkylene link had little effect on potency: cf., **43**, **44**, and **45**, but did, however, diminish cardioselectivity.

Replacement of the amide moiety by a ureido moiety (Table IV) resulted in an observable increase in the number of highly cardioselective compounds: thus, the series of alkyl- and cycloalkylureas **49**, **52**, **53**, **55**, and **56** with no substituent in the aryloxy ring all had a depressor response below 10%. Potency was, however, very variable. In a small related series, increasing the bulk of the alkyl substituent on the ureido moiety decreased potency: cf., **51**, **54**, and **57**. The arylureas **59**, **68**, and **69** were less potent and cardioselective than the alkylureas, a similar finding to the comparison between benzamides and alkyl amides. Substitution in the aryloxy ring in a series of phenylureas, **60–67**, had only a marginal effect on cardioselectivity and potency (cf., **59**).

The replacement of the carboxamide moiety with a sulfonamide moiety (Table V) resulted in variable potency and cardioselectivity. The difference in activity between alkylsulfonamides and arylsulfonamides was less marked, and it appears that a large group adjacent to the sulfonamide moiety favors potency: thus, when compounds **74–77** were compared, the methyl-substituted sulfonamide was less potent than either the phenyl or propyl analogues; there was a less marked difference in cardioselectivity. Substitution of the phenylsulfonamide ring gave variable results, with the *o*-nitro analogue having potency and cardioselectivity similar to that of the unsubstituted compound: cf. **77** and **81**. Two para-substituted analogues, **79** and **80**, had lower potency and were less cardioselective. Branching the alkylene chain at R_4 increased potency with little effect on cardioselectivity; cf. **81** and **83**. Substitution of the secondary amino moiety to give a tertiary amino moiety dramatically reduced potency but had little effect on cardioselectivity; cf. **84** and **77**.

In summary, our study shows that the introduction of an amidic moiety into the alkylamine side chain of an (aryloxy)propanolamine gives potent cardioselective β-adrenoceptor blocking agents. The most potent group has a branched alkylene chain and is to be found in Table III, whereas the largest cardioselective group is the ureido analogues in Table IV.

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. NMR spectra for all the compounds described were recorded either on a Varian HA100D or a Varian A 60 with tetramethylsilane as the internal standard and were consistent with the assigned structures.

3-[(2-Isobutyramidoethyl)amino]-1-phenoxypropan-2-ol (10). Method A. A mixture of 1,2-epoxy-3-phenoxypropane (1.5 g, 0.01 mol), *N*-(2-aminoethyl)isobutyramide hydrogen oxalate[10] (2.2 g, 0.01 mol), 4 N NaOH (5 mL) and *n*-PrOH (40 mL) was refluxed for 18 h and then evaporated to dryness. The residue was partitioned between H_2O and EtOAc, and the EtOAc phase was dried and evaporated to dryness. The residue was crystallized from EtOAc: yield 0.85 g (30%); mp 125–126 °C.

3-[[2-(3-Methylureido)ethyl]amino]-1-(2-cyanophenoxy)-propan-2-ol (51). Method B. 1,2-Epoxy-3-(2-cyanophenoxy)-propane[13] (3.5 g, 0.2 mol) was added to 1,2-diaminoethane (60 g, 1 mol), and the mixture was stirred at room temperature for 18 h and then added to water (500 mL). The mixture was filtered, and the filtrate evaporated to dryness to give 3-(2-aminoethyl)-amino]-1-(2-cyanophenoxy)propan-2-ol as a light brown oil: yield 33 g (70%). A sample was characterized as the dihydrochloride, which was recrystallized from EtOH–H_2O: mp 235–236 °C. Anal. ($C_{12}H_{17}N_3O_2$·HCl) C, H, N.

A solution of methyl isocyanate (0.57 g, 0.01 mol) in MeCN (5 mL) was added over 0.1 h to a stirred solution of 3-(2-aminoethyl)amino]-1-(2-cyanophenoxy)propan-2-ol (2.35 g, 0.01 mol) in MeCN (40 mL) while the temperature was kept below −20 °C. The mixture was allowed to warm to room temperature, and the insoluble solid was collected and recrystallized from MeCN: yield 1.15 g (40%); mp 139–140 °C.

3-[[2-(Phenoxyacetamido)ethyl]amino]-1-(2-cyanophenoxy)propan-2-ol Hydrogen Oxalate (37). A mixture of 3-[(2-aminoethyl)amino]-1-(2-cyanophenoxy)propan-2-ol (2.35 g, 0.01 mol), and ethyl phenoxyacetate (1.7 g, 0.01 mol) was heated at 100 °C for 18 h. The mixture was cooled, and the residue was partitioned between 2 N HCl and EtOAc. The aqueous phase was basified with 10 N NaOH and extracted with EtOAc, and the EtOAc extract was dried (Na_2SO_4) and evaporated to dryness. The residue was crystallized as the hydrogen oxalate from MeCN: yield 0.35 g (8%); mp 130–132 °C.

3-[[2-(3-Phenylureido)ethyl]amino]-1-[2-(methoxycarbonyl)phenoxy]propan-2-ol (64). A solution of 1,2-epoxy-3-[2-(methoxycarbonyl)phenoxy]propane[14] (2.08 g, 0.01 mol) and 1-[2-(benzylamino)ethyl]-3-phenylurea[10] (2.69 g, 0.01 mol) in *i*-PrOH (40 mL) was refluxed for 18 h and then evaporated to dryness. The residue was dissolved in EtOH (50 mL), the solution was treated with 30% Pd/C, and the mixture was shaken under hydrogen at room temperature and atmospheric pressure for 5 h. The catalyst was filtered off, and the filtrate was evaporated to dryness. The residue was crystallized from MeCN: yield 1.4 g (36%); mp 126–127 °C.

3-[[2-(2,5-Dihydroxybenzamido)ethyl]amino]-1-phenoxypropan-2-ol Oxalate (24). A solution of 3-[[2-[2,5-bis(benzyloxy)benzamido]ethyl]amino]-1-phenoxypropan-2-ol (2.2 g, 0.0036 mol) (prepared by method A: hydrogen oxalate, mp 176–178 °C) in HOAc (50 mL) was hydrogenated over 5% Pd/C at room temperature and atmospheric pressure. The catalyst was filtered, and the filtrate was evaporated to dryness. The residue was crystallized from MeOH/EtOAc and then from EtOH/H_2O: yield 0.6 g (42%); mp 195–197 °C.

3-[[2-(3,4-Dihydroxybenzamido)ethyl]amino]-1-phenoxypropan-2-ol hydrogen oxalate (23) was prepared in a similar manner and crystallized from EtOH: yield 46%; mp 178–180 °C.

3-[[2-(Trifluoroacetamido)ethyl]amino]-1-phenoxypropan-2-ol (6). Trifluoroacetic anhydride (2.1 g, 0.01 mol) 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 toluene (30 mL), and the mixture was stirred an additional 0.5 h after the addition was complete. The solution was washed with H_2O and then dried (Na_2SO_4) and evaporated to dryness.

A solution of the residue in EtOH (50 mL) was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure. The mixture was filtered, and the was filtrate evaporated to dryness, and the residue was crystallized from EtOAc/petroleum ether (bp 60–80 °C): yield 1.5 g (49%); mp 106–108 °C.

(13) W. E. Kreighbaum, W. L. Matier, R. D. Dennis, L. Minielli, D. Deitchmann, J. L. Perhach, Jr., and W. T Comer, *J. Med. Chem.*, **23**, 285 (1980).
(14) S. N. Rastogi, N. Anand, P. P. Gupta, and J. N. Sharma, *J. Med. Chem.*, **16**, 797 (1973).

3-[(2-Formamidoethyl)amino]-1-phenoxypropan-2-ol (4) was similarly prepared by treatment of 3-[*N*-(2-aminoethyl)-*N*-benzylamino]-1-phenoxypropan-2-ol[10] with methyl formate in *i*-PrOH at a reflux, followed by hydrogenolysis, and was crystallized from EtOAc: yield 15%; mp 107–109 °C.

3-[*N*-(2-Benzenesulfonamidoethyl)-*N*-methylamino]-1-phenoxypropan-2-ol Hydrogen Oxalate (84). Iodomethane (0.28 g, 0.002 mol) was added dropwise to a stirred mixture of 3-[(2-benzenesulfonamidoethyl)amino]-1-phenoxypropan-2-ol (**77**; 0.7 g, 0.002 mol), THF (10 mL), and an 80% dispersion of sodium hydride in oil (0.06 g, 0.002 mol). The mixture was stirred at room temperature for 1 h and then diluted with water and extracted with ether. The ether extract was dried and evaporated to dryness, and the residue was chromatographed on Merck Kieselgel 60F254 preparative TLC plates with $CHCl_3$/MeOH (9:1 v/v) as developing solvent. The band having R_f 0.5 was removed and extracted with methanol, and the methanol evaporated to dryness. The residue was crystallized as the hydrogen oxalate from EtOAc: yield 0.1 g (14%); mp 114–117 °C.

Pharmacology. β-Adrenoreceptor blocking potency was estimated in vivo with the previously described cat preparation.[11] 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 B_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[11] 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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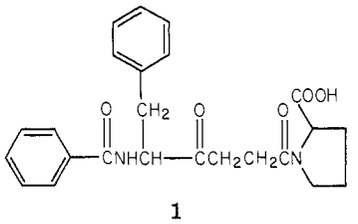
Derivatives of the Potent Angiotensin Converting Enzyme Inhibitor 5(*S*)-Benzamido-4-oxo-6-phenylhexanoyl-L-proline: Effect of Changes at Positions 2 and 5 of the Hexanoic Acid Portion

Ronald G. Almquist,*[†] Jac Crase,[†] Clive Jennings-White,[†] Robert F. Meyer,[‡] Milton L. Hoefle,[‡] Ronald D. Smith,[§,⊥] Arnold D. Essenburg,[§] and Harvey R. Kaplan[§]

Bio-Organic Chemistry Laboratory, SRI International, Menlo Park, California 94025, and Departments of Chemistry and Pharmacology, Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Warner Lambert Company, Ann Arbor, Michigan 48105. *Received February 1, 1982*

Several derivatives of the potent angiotensin converting enzyme inhibitor 5(*S*)-benzamido-4-oxo-6-phenylhexanoyl-L-proline (**1**) were synthesized and tested for converting enzyme inhibition activity and blood pressure lowering effects in rats. One compound, 5(*S*)-benzamido-2(*R*)-methyl-4-oxo-6-phenylhexanoyl-L-proline (**2a**), had an I_{50} against angiotensin converting enzyme of 1.0×10^{-9} M and is the most potent inhibitor prepared thus far in this class of compounds. Testing of **2a** orally at 30 mg/kg for inhibition of the angiotensin I induced blood pressure increase in conscious normotensive rats gave 100% inhibition that required 143 min before the angiotensin I blood pressure response returned to 70% of the pretreatment control response. In the conscious renal hypertensive rat, **2a** given orally at a dose of 3 mg/kg caused a lowering of blood pressure that reached its maximum of 40 mmHg 8 h following drug administration.

In a previous publication,[1] numerous derivatives of the potent angiotensin converting enzyme (ACE) inhibitor 5(*S*)-benzamido-4-oxo-6-phenylhexanoyl-L-proline[2] (**1**)



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were described. These compounds were tested as ACE inhibitors both in vivo and in vitro and as antihypertensive agents in renal hypertensive rats. Many of these compounds were potent ACE inhibitors in vitro but much less potent in vivo.

In order to increase the in vivo activity of this class of ACE inhibitors, we tried two approaches. First, structural changes in **1** were made with the hope of increasing its ACE inhibiting activity and thus decreasing the amount of compound that must be absorbed orally to inhibit ACE in vivo. Considering that the tripeptide Phe-Ala-Pro had over 10 times the ACE inhibitory activity of our model tripeptide Phe-Gly-Pro,[2] we thought that a 2-methyl substitution in the hexanoyl chain of **1** would greatly increast its ACE inhibition. Therefore, compounds **2a–d** were synthesized to investigate the 2-methyl substitution effect.

A second method of increasing oral absorption of compounds is to increase their lipophilicity. We have synthesized a series of derivatives of **1**, compounds **3a–4c**, with increased lipid character. These compounds were tested in vitro and in vivo as ACE inhibitors.

Chemistry. The synthetic pathway for the preparation of compounds **2a–4c** is shown in Scheme I. As described previously[1] using a modification of the Dakin–West reaction,[3] the oxazolone **5** was reacted with the desired acid

[†] SRI International.
[‡] Department of Chemistry, Warner Lambert Co.
[§] Department of Pharmacology.
[⊥] Present address: Revlon Health Care, Tuckahoe, NY.

(1) R. F. Meyer, E. D. Nicolaides, F. J. Tinney, E. A. Lunney, A. Holmes, M. L. Hoefle, R. D. Smith, A. D. Essenburg, H. R. Kaplan, and R. G. Almquist, *J. Med. Chem.*, **24**, 964 (1981).
(2) R. G. Almquist, W.-R. Chao, M. E. Ellis, and H. L. Johnson, *J. Med. Chem.*, **23**, 1392 (1980).

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