β-Adrenergic Blocking Agents. 19. 1-Phenyl-2-[[(substituted-amido)alkyl]amino]ethanols

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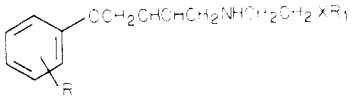
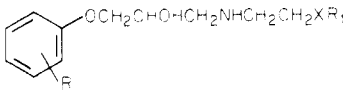
The synthesis of a series of derivatives of 1-phenyl-2-[[(substituted amido)alkyl]amino]ethanols is described. The compounds were investigated for β-adrenoceptor blocking properties, and many showed a surprising degree of potency and β_1-cardioselectivity when tested in vivo in anesthetized cats. The structure–activity relationships shown by this series of compounds are discussed and related to known β-adrenergic blocking agents.

Our previously described work[1,2] shows that aryloxypropanolamines with an ether, **1**, or thioether, **2**, link in the side chain are potent cardioselective β_1-adrenoceptor blocking agents.



1, X = O
2, X = S

This led us to postulate that the oxygen or sulfur atom present in these molecules makes an important contribution to their cardioselectivity. In an extension of this work, we have replaced the ether and thioether links with a variety of amidic moieties in both the arylethanolamine[3] and aryloxypropanolamine[4,5] series of β-adrenergic blocking agents to give compounds of structures **3** and **4**.



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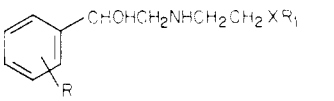


4, X = NHCO, CONH, NHCONH, $NHSO_2$

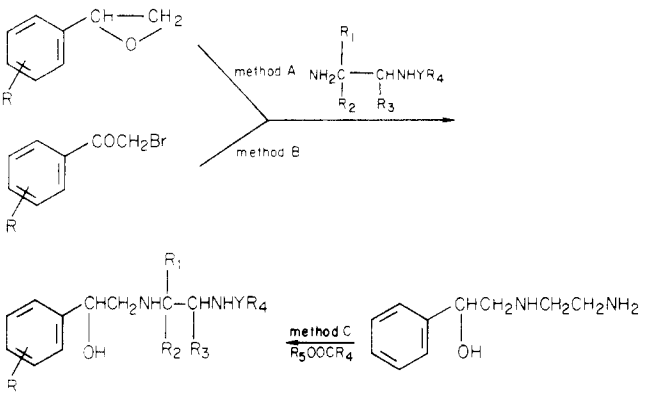
In this paper we describe the structure–activity relationships of a series of arylethanolamines **4** (where X = NHCO, NHCONH, and $NHSO_2$), and subsequent papers will describe the aryloxypropanolamine analogues.

Chemistry. The majority of the compounds listed in Tables I–IV were synthesized via methods A, B, and C illustrated in Scheme I.

Method A was the most frequently used, although method C was more convenient for the synthesis of compounds where $R^1 = R^2 = R^3 = H$.

Method B was used for varying the substituent R on the aryl ring. The designation D used in the tables signifies a separately described method of preparation. The amidoalkylamine precursors used in methods A and B were made by acylating an alkylenediamine with the appropriate ester, sulfonyl chloride,[7] or isocyanate.[8] Where the alkylenediamine was unsymmetrical, the position of acylation was determined by NMR spectroscopy. The Experimental Section describes a typical acylation procedure, and Table V lists those amidic alkylamines which have been characterized and are novel. For method C, only the diamine precursor with an unsubstituted phenyl ring was synthesized.

Scheme I[a]



[a] R, R_1, R_2, R_3, R_4, and Y relate to the substituents described in Tables I–IV, and R_5 is a suitable ester substituent.

Pharmacology. β-Adrenoceptor blocking potency was estimated in vivo using a rat preparation and the previously described cat preparation.[6] In the procedure for the rat preparation, a control group of four rats (Alderley Park strain) was anesthetized with 60 mg/kg of pentobarbitone, intraperitoneally, and the heart rate was recorded as described in the above cat preparation. Isoproterenol (0.1 μg/kg) was then injected into the femoral vein and the increase in heart rate recorded. The compound under investigation was then injected subcutaneously at four different doses, 10, 1.0, 0.1, and 0.01 mg, four rats being used at each level. The rats were then anesthetized in a similar manner to the control group and 30 min later were challenged with 0.1 μg/kg of isoproterenol and the heart rate recorded. The percentage blockade of the isoproterenol response for each dose level was calculated as follows:

$$\% \text{ blockade} = \frac{\text{control tachycardia} - \text{compound tachycardia}}{\text{control tachycardia}} \times 100$$

From these results a dose–response curve was constructed, and from this the ED_{50} values quoted in the tables were estimated. Statistical analysis of the results showed that the ED_{50} transformed to a $\log_{10}$ scale has a standard error of approximately ±0.14 log unit (i.e., a mean error of approximately 25–30% for each experiment). The cat results given in the tables are expressed as the total dose, infused over a period of 30 min, causing a 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 μg/kg dosed iv). The degree (%) of blockade of the vasodepressor response at that dose level is also

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(5) L. H. Smith, U.K. Patents 1 455 116 and 1 457 876.
(6) J. D. Fitzgerald and S. R. O'Donnell, *Br. J. Pharmacol.*, **43**, 222 (1971).
(7) A. V. Kirsanov and N. A. Kirsanova, *Zh. Obshch. Khim.*, **32**, 887 (1962).
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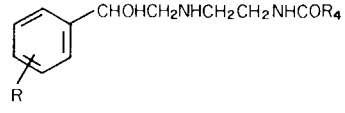
Table I

$C_6H_5CHOHCH_2NHCH_2CH_2NHCOR_4$

no.	R_4	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, mg/kg, giving 50% inhibn of tachycardia in rat	dose, μg/kg, giving 50% inhibn of tachycardia in cat	% inhibn of depressor response
5	CH_3	106-108	EtOAc	31.5	$C_{12}H_{18}N_2O_2$	C, H, N	A	0.08	238	50
6	C_2H_5	91-92	EtOAc	13	$C_{13}H_{20}N_2O_2$	C, H, N	A	0.07	86	46
7	n-C_3H_7	90-91	EtOAc	11	$C_{14}H_{22}N_2O_2$	C, H, N	D	0.45	92	0
8	i-C_3H_7	101	EtOAc	28	$C_{14}H_{22}N_2O_2$	C, H, N	A	0.7	93	27
9	i-C_4H_9	163-165	MeCN	29	$C_{15}H_{24}N_2O_2 \cdot 0.5(COOH)_2$	C, H, N	D	0.72	311	25
10	n-C_5H_{11}	87-88	EtOAc	18	$C_{16}H_{26}N_2O_2$	C, H, N	A	1.4	167	8
11	CH_2OH	160-161	EtOH	25	$C_{12}H_{18}N_2O_3 \cdot (COOH)_2$	C, H, N	C	0.3		
12	CH_2OCH_3	94-96	EtOAc	18	$C_{13}H_{20}N_2O_3$	C, H, N	A	0.4	227	44
13	CF_3	186-187	i-PrOH	43	$C_{12}H_{15}F_3N_2O_2 \cdot (COOH)_2$	C, H, N	C	0.1		
14	c-C_5H_9	106-108	EtOAc	22	$C_{16}H_{24}N_2O_2$	C,[a] H, N	A	0.42	12	8
15	c-C_6H_{11}	217-218	i-PrOH	12	$C_{17}H_{26}N_2O_2 \cdot HCl$	H,[b] C, N	A	0.16	240	0
16	C_6H_5	122-124	EtOAc	28	$C_{17}H_{20}N_2O_2 \cdot 0.25H_2O$	C, H, N	A	10.0		
17	4-OH-C_6H_4	186	EtOH	79	$C_{17}H_{20}N_2O_3 \cdot (COOH)_2$	C, H, N	D	9.0	1061	10
18	-CH_2-C_6H_5	113-114	EtOAc	18	$C_{18}H_{22}N_2O_2$	C, H, N	A	0.38	31	6
19	-CH_2-4-OCH_3-C_6H_4	114-115	EtOAc	24	$C_{19}H_{24}N_2O_3$	C, H, N	A	0.32	37	24
20	-CH_2-4-Cl-C_6H_4	117-120	EtOAc	12	$C_{18}H_{21}ClN_2O_2 \cdot 0.25H_2O$	C, H, N	A	0.7	294	3
21	-CH_2-4-NH_2-C_6H_4	132-133	EtOH	37	$C_{18}H_{23}N_3O_2$	C, H, N	C	2.5		
22	-CH_2-4-$NHCOCH_3$-C_6H_4	148-149	H_2O	56	$C_{20}H_{25}N_3O_3$	C, H, N	C	1.2		
23	-CH_2-3,4-$(OCH_3)_2$-C_6H_4	111-112	EtOAc	45	$C_{20}H_{26}N_2O_4$	C, H, N	C	7.0		
24	-$CH_2OC_6H_4$	97-98	i-PrOH	37	$C_{18}H_{22}N_2O_3 \cdot 0.5H_2O$	C, H, N	C	1.0		
25	-CH_2O-4-Cl-C_6H_4	104-106	EtOAc	8	$C_{18}H_{21}ClN_2O_3 \cdot 0.5H_2O$	C, H, N	A	2.5	487	36
26	-CH_2O-4-CN-C_6H_4	62-63	EtOH-H_2O	78	$C_{19}H_{21}N_3O_3 \cdot H_2O$	C, H, N	C	0.7		
27	-CH_2O-4-$COCH_3$-C_6H_4	124-125	MeCN	46	$C_{20}H_{24}N_2O_4 \cdot H_2O$	C, H, N	C	0.6		
28	-CH_2O-4-$CHOHCH_3$-C_6H_4	90-91	H_2O	71	$C_{20}H_{26}N_2O_4 \cdot H_2O$	C, H, N	D	1.6		
29	-CH_2O-2-$CONH_2$-C_6H_4	143-145	MeCN	12	$C_{19}H_{23}N_3O_4$	C, H, N	C	5.2		
30	-CH_2O-2-$OCH_2CH{=}CH_2$-C_6H_4	137-139	MeCN	10	$C_{21}H_{26}N_2O_4 \cdot (COOH)_2$	C, H, N	A	5.8		

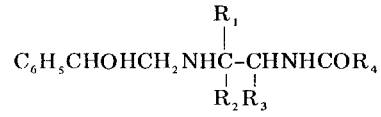
[a] C: calcd, 69.6; found, 69.0. [b] H: calcd, 8.3; found, 8.9.

Table II



no.	R	R_4	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, mg/kg, giving 50% inhibn of tachycardia in rat	dose, μg/kg, giving 50% inhibn of tachycardia in cat	% inhibn of depressor response
31	4-Br	i-C_3H_7	138-140	EtOAc	17	$C_{19}H_{21}BrN_2O_2$	C, H, N	B	1.6		
32	4-NO_2	i-C_3H_7	129-131	EtOAc	11.5	$C_{14}H_{21}N_3O_4$	C, H, N	B	10.0	1372	0
33	4-OMe	i-C_3H_7	112-113	EtOAc	21	$C_{15}H_{24}N_2O_3$	C, H, N	B	0.3	20	0
34	4-NH_2	i-C_3H_7	141-142	MeCN	77	$C_{14}H_{23}N_3O_2$	C, H, N	D	0.6	79	69
35	4-$NHSO_2CH_3$	i-C_3H_7	183-184	EtOH	60	$C_{15}H_{25}N_3O_4S \cdot HCl$	C, H, N	D	5.2		
36	2,4-Cl_2	i-C_3H_7	194-196	MeCN	2	$C_{14}H_{20}Cl_2N_2O_2 \cdot HCl$	C, H, N	D	0.75		
37	4-CH_3	C_2H_5	106-107	EtOAc	19	$C_{14}H_{22}N_2O_2$	C, H, N	B	0.5		
38	2-Cl	-$CH_2C_6H_5$	160-162	i-PrOH	3	$C_{18}H_{21}ClN_2O_2 \cdot 0.5$fumarate	C, H, N	D	0.6	182	45

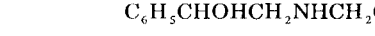
Table III



no.	R_1	R_2	R_3	R_4	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, mg/kg, giving 50% inhibn of tachycardia in rat	dose, μg/kg, giving 50% inhibn of tachycardia in cat	% inhibn of depressor response
39	CH_3	H	H	$CH_2C_6H_5$	160–161	EtOH	22	$C_{19}H_{24}N_2O_2 \cdot 0.5(COOH)_2$	C, H, N	A	0.1	7	36
40	CH_3	H	H	CH_2-2-Cl-C_6H_4	130–131	EtOAc	12	$C_{19}H_{23}ClN_2O_2$	C, H, N	A	0.03	17	19
41	CH_3	H	H	c-C_6H_{11}	174–175	*i*-PrOH/EtOAc	4	$C_{18}H_{28}N_2O_2 \cdot (COOH)_2 \cdot 0.5H_2O$	N,[a] C, H	A	0.11	312	19
42	CH_3	CH_3	H	$CH_2C_6H_5$	159–160	EtOH	34	$C_{20}H_{26}N_2O_2 \cdot 0.5$fumarate	C, H, N	A	0.1	80	28
43	CH_3	CH_3	H	*i*-C_3H_7	197–198	EtOH	14	$C_{16}H_{26}N_2O_2 \cdot 0.5(COOH)_2 \cdot 0.25H_2O$	C, H, N	A	0.27	77	9
44	H	H	CH_3	$CH_2C_6H_5$	136–137	EtOAc	21	$C_{19}H_{24}N_2O_2$	C, H, N	D	8.0		

[a] N: calcd, 6.95; found, 7.6.

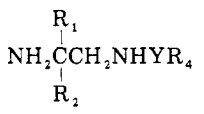
Table IV



no.	Y	R_4	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, mg/kg, giving 50% inhibn of tachycardia in rat	dose, μg/kg, giving 50% inhibn of tachycardia in cat	inhibn of depressor response
45	COO	C_2H_5	90–91	EtOAc-pet. ether	12	$C_{13}H_{20}N_2O_3$	C, H, N	D	2.8		
46	CONH	*n*-C_4H_9	102–104	EtOAc	18	$C_{15}H_{25}N_3O_2$	C, H, N	A	0.5	259	54
47	CONH	$CH_2CH{=}CH_2$	102–104	Et_2O	5	$C_{14}H_{21}N_3O_2 \cdot 0.25H_2O$	C, H, N	A	0.26	138	0
48	CONH	C_6H_5	125–126	EtOAc	17	$C_{17}H_{21}N_3O_2$	C, H, N	A	2.9	378	0
49	SO_2	*n*-C_3H_7	180–182[a]	EtOH	18	$C_{13}H_{22}N_2O_3S \cdot (COOH)_2 \cdot 0.25H_2O$	C, H, N	A	0.5	63	0
50	SO_2	C_6H_5	228–230[a]	EtOH	16	$C_{16}H_{20}N_2O_3S \cdot 0.5(COOH)_2$	C, H, N	A	1.0	115	27
51	SO_2	2-NO_2-C_6H_4	208–209	EtOH-H_2O	6	$C_{16}H_{19}N_3O_5S \cdot 0.5(COOH)_2$	C, H, N	A	2.5	373	23
52	SO_2	$CH_2C_6H_5$	100–102	EtOAc	8	$C_{17}H_{22}N_2O_3S$	C, H, N	A	2.0	729	0
53 (sotalol)										546	85
54 (butidrine)										1217	47
55 (pronethalol)										1500	
56 (practolol)										167	8

[a] Melts with decomposition.

Table V



no.	R_1	R_2	Y	R_4	mp, °C	crystn solvent	yield, %	emp formula	anal.
57	H	H	CO	CH_2OCH_3	137-138	EtOH	58	$C_5H_{12}N_2O_2\cdot(COOH)_2$	C, H, N
58	H	H	CO	c-C_5H_9	164-165	EtOH	49	$C_8H_{16}N_2O\cdot(COOH)_2$	C, H, N
59	H	H	CO	c-C_6H_{11}	154-155	EtOH	35	$C_9H_{18}N_2O\cdot(COOH)_2$	C, H, N
60	H	H	CO	CH_2-4-Cl-C_6H_4	194-196	EtOH	58	$C_{10}H_{13}ClN_2O\cdot HCl\cdot 0.25H_2O$	C, H, N
61[b]	CH_3	H	CO	$CH_2C_6H_5$	220-221	EtOH-H_2O	11	$C_{11}H_{16}N_2O\cdot 0.5(COOH)_2$	C, H, N
62[b]	CH_3	H	CO	CH_2-4-Cl-C_6H_4	174-176	EtOH-MeCN	33	$C_{11}H_{15}ClN_2O\cdot HCl$	C, H, N
63	CH_3	CH_3	CO	i-C_3H_7	269-270	EtOH	39	$C_8H_{18}N_2O\cdot HCl$	C, H, N
64	CH_3	CH_3	CO	$CH_2C_6H_5$	268-270	EtOH	62	$C_{12}H_{18}N_2O\cdot HCl$	H,[c] C, N
65	H	H	CONH	n-C_4H_9	138-139	EtOH	33	$C_7H_{17}N_3O\cdot(COOH)_2$	C, H, N
66	H	H	CONH	$CH_2CH{=}CH_2$	128-130	i-PrOH	19	$C_6H_{13}N_3O\cdot HCl\cdot 0.25H_2O$	N,[a] C, H
67	H	H	SO_2	n-C_3H_7	145-147	EtOH	19	$C_5H_{14}N_2O_2S\cdot(COOH)_2\cdot 0.5H_2O$	C, H, N

[a] N: calcd, 22.8; found, 22.3. [b] NMR spectra of these compounds indicate the presence of 5-10% of the isomer $NH_2CH_2CH(CH_3)NHCOR_4$. [c] H: calcd, 7.8; found, 7.3.

given. The relative potencies in these two systems give an indication of selectivity for β_1 (cardiac) as opposed to β_2 (vascular) receptors. Statistical analysis of the results shows that the mean ED_{50} on the log scale for compounds with an average of two to three tests per compound is ±0.12 log unit (i.e., a mean error of approximately 30%).

Discussion of Results

The object of this study was to observe the effect, on both β-blocking potency and cardioselectivity, of replacing the alkylamino moiety of an arylethanolamine with an amidoalkylamino moiety. The test results in Tables I–IV give the ED_{50} values (mg/kg) in the rat and the ED_{50} values (μg/kg) and percentage inhibition of the depressor response in the cat. In general, the compounds show a similar order of potency in the two screens. Only those compounds with significant activity in the rat were examined in the cat, and the cat results have been used to define the structure–activity relationships.

For comparison purposes, the arylethanolamines sotalol, butidrine, pronethalol, and the β_1 cardioselective aryloxypropanolamine practolol have been included at the end of Table IV.

The biological data in Tables I–IV show that, in general, the pharmacological profile of compounds in this series differs markedly from the ethanolamines **53–55**, used for comparison, and appears to be more like the aryloxypropanolamine practolol **56**.

Thus, compounds **7**, **10**, **14**, **18**, **20**, **33**, **43**, and **49** can be seen to be very potent inhibitors of the isoprenaline tachycardia response while having minimal effects on the depressor response. This was a surprising finding because it is exceptional for β_1 selectivity to be so widely exhibited by a series of arylethanolamines.[9] Indeed, apart from the work by Williams et al.[10] on a series of o-methoxyarylethanolamines, of which one example was β_1 selective on isolated guinea pig tissues, this appears to be the only report of a series containing several potent and cardioselective arylethanolamines. Approximately half the compounds in Tables I–III and all but one of the amidic variations in Table IV show cardioselectivity, which is apparently not limited by ring or side-chain substitution as in compounds **32**, **33** and **41**, **43**. This would appear to indicate that the amidoalkylamino moiety is playing a major role in the cardioselectivity observed in this series. This finding is in accordance with our earlier work,[1,2] where we demonstrated that an oxygen or sulfur atom, in an analogous position on the amine side chain, also appeared to be responsible for the β_1 selectivity found in a series of aryloxypropanolamines.

The potency of the compounds in this series was also surprising. Apart from compounds **16**, **17**, **32**, **44**, and **52**, the majority of the compounds tested were more potent than sotalol, which is the most potent of the clinically available arylethanolamines, and were, in fact, more like aryloxypropanolamines in potency. We could, however, find little correlation between the substituents on the amide group in Table I and potency, apart from the conclusion that an aryl ring, next to the carbonyl moiety of an amide group, lowers potency (cf. **16** and **17**).

Although potency is influenced by the aryl substituent R, no correlation was found in the small number of compounds examined.

The results in Table III show that branching of the side chain also affects potency.

Thus, a methyl group on the carbon atom adjacent to the amino group can increase potency (cf. **18** and **39**), the effects of *gem*-dimethyl groups are ambiguous (cf. **18**, **42** and **8**, **43**) and a methyl group adjacent to the amide moiety decreased potency (cf. **44**).

The effect on potency of varying the amidic group is shown in Table IV. The benzamido compound **16** was of low activity, but the phenylureido and phenylsulfonamido compounds **48** and **50** both showed good activity and selectivity in the cat. Similarly, the n-propylsulfonamido analogue **49** was more active than the n-propionamido analogue **7**. However the benzylsulfonamido analogue **52** was less active than the phenylacetamido analogue **18**.

In summary, our study shows that the introduction of an amidic moiety into the alkylamine side chain of an arylethanolamine gives potent cardioselective β-adrenoceptor blocking agents, and we shall duly report our findings with the aryloxypropanolamines.

Experimental Section

Chemistry. All melting points were obtained using 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 A60 using tetramethylsilane as the internal standard and were consistent with the assigned structures.

(9) J. H. Biel and B. K. B. Lum, *Prog. Drug Res.*, **10**, 57, (1966).
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2-[(2-Acetamidoethyl)amino]-1-phenylethanol (5). Method A. A solution of styrene oxide (1.2 g, 0.01 mol), *N*-(2-aminoethyl)acetamide (1.02 g, 0.01 mol), and *i*-PrOH (50 mL) was heated under reflux for 5 h. The solution was then evaporated to dryness and the residue was crystallized from EtOAc: yield 0.7 g (31.5%); mp 106–108 °C.

2-[(2-Isobutyramidoethyl)amino]-1-(4-bromophenyl)-ethanol (31). Method B. 4-Bromophenacyl bromide (2.8 g, 0.01 mol) was added to a stirred solution of *N*-(2-aminoethyl)isobutyramide (3.9 g, 0.03 mol) in MeOH (50 mL) at 10 °C, and the mixture was stirred for 0.3 h and then treated with 48% HBr (1.88 mL).

The mixture was again cooled to 10 °C, $NaBH_4$ (0.48 g, 0.02 mol) was added, and the mixture was stirred for 1.5 h, then acidified with concentrated HCl, and evaporated to low bulk under reduced pressure. Water (150 mL) was added, and the mixture was washed with EtOAc, basified with 10 N NaOH, and extracted with EtOAc (3 × 75 mL). The combined extracts were dried ($MgSO_4$) and evaporated to dryness under reduced pressure, and the residue was crystallized from EtOAc: yield 0.55 g (17%); mp 138–140 °C.

2-[[2-[(4-Cyanophenoxy)acetamido]ethyl]amino]-1-phenylethanol (26). Method C. An intimate mixture of ethyl 4-cyanophenoxyacetate (2.05 g, 0.01 mol) and 2-[(2-aminoethyl)amino]-1-phenylethanol (1.8 g, 0.01 mol) was heated at 120 °C for 1 h, cooled, and crystallized from EtOH–H_2O: yield 2.8 g (78%); mp 62–63 °C.

2-[*N*-(2-Aminoethyl)-*N*-benzylamino]-1-phenylethanol Bis(hydrogen oxalate). A mixture of *N*-[2-(benzylamino)-ethyl]isobutyramide hydrochloride (12.8 g, 0.05 mol), $NaHCO_3$ (4.2 g, 0.05 mol), styrene oxide (6 g, 0.05 mol), and *i*-PrOH (50 mL) was refluxed for 18 h and then evaporated to dryness.

A solution of the residue in 5 N HCl (200 mL) was refluxed for 4 h, then cooled, and washed with Et_2O (100 mL). The aqueous phase was basified with NaOH (18 N) and extracted with chloroform (3 × 150 mL), and the combined chloroform extracts were dried and evaporated to an oil: yield 11.5 g (85%); characterized as the bis(hydrogen oxalate), mp 178–180 °C (EtOH). Anal. [$C_{17}H_{22}ON_2 \cdot 2(COOH)_2$] C, H, N.

2-[(2-Isovaleramidoethyl)amino]-1-phenylethanol Oxalate (9). A mixture of 2-[*N*-(2-aminoethyl)-*N*-benzylamino]-1-phenylethanol (2.7 g, 0.01 mol), Et_3N (1.5 mL), isovaleric anhydride (1.86 g, 0.01 mol), and toluene (30 mL) was stirred at room temperature for 2 h and then evaporated to dryness. A solution of the residue in HOAc (30 mL) was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure until 230 mL of hydrogen had been absorbed. The mixture was filtered, the filtrate was evaporated to dryness, and the residue was stirred with 1 N NaOH and EtOAc. The EtOAc phase was dried ($MgSO_4$) and added to a solution of oxalic acid in EtOAc, and the precipitated oxalate was collected and crystallized from MeCN: yield 0.9 g (29%); mp 163–165 °C.

2-[(2-Butyramidoethyl)amino]-1-phenylethanol (7) was prepared in a similar manner and crystallized from EtOAc: yield 11%; mp 90–91 °C.

2-[[2-[4-(Benzyloxy)benzamido]ethyl]amino]-1-phenylethanol. A solution of *N*-(2-aminoethyl)-4-(benzoyloxy)benzamide (2.7 g, 0.01 mol) and styrene oxide (1.2 g, 0.01 mol) in *i*-PrOH (50 mL) was heated under reflux for 18 h. The solution was evaporated to dryness, and the residue was crystallized from EtOAc: yield 1.2 g (31%); mp 152–153 °C. Anal. ($C_{24}H_{26}N_2O_3$) C, H, N.

2-[[2-(4-Hydroxybenzamido)ethyl]amino]-1-phenylethanol Hydrogen Oxalate (17). A solution of 2-[[2-[4-(benzyloxy)-benzamido]ethyl]amino]-1-phenylethanol (1.65 g, 0.0042 mol) in HOAc (50 mL) was hydrogenated over 5% Pd/C at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate evaporated to dryness. A solution of the residue in EtOH was added to a solution of oxalic acid in EtOAc, and the precipitated oxalate was collected and crystallized from EtOH: yield 1.3 g (79%); mp 186 °C.

2-[[2-[[4-(α-Hydroxyethyl)phenoxy]acetamido]ethyl]-amino]-1-phenylethanol Monohydrate (28). $NaBH_4$ (0.38 g, 0.01 mol) was added in portions to a stirred solution of 2-[[2-[(4-acetylphenoxy)acetamido]ethyl]amino]-1-phenylethanol (**23**; 1.1 g, 0.003 mol) in MeOH (30 mL), and the mixture was stirred at room temperature for 1 h and then acidified to pH 4 with HOAc and evaporated to dryness. A solution of the residue in water (50 mL) was basified with 2 N NaOH, and the precipitated solid was collected and crystallized from H_2O: yield 0.8 g (71%); mp 90–91 °C.

2-[*N*-Benzyl-*N*-(2-isobutyramidoethyl)amino]-1-[4-(methanesulfonylamido)phenyl]ethanol. A mixture of 4-(methanesulfonylamino)phenacyl bromide (2.92 g, 0.01 mol), *N*-[2-(*N*-benzylamino)ethyl]isobutyramide (4.4 g, 0.02 mol), and dioxane (50 mL) was stirred at room temperature for 1 h and filtered, and the filtrate was evaporated to dryness. Water (50 mL) was added to the residue, the mixture was extracted with EtOAc (2 × 50 mL), and the combined EtOAc extracts were dried (Na_2SO_4) and evaporated to dryness.

$NaBH_4$ (1.14 g, 0.03 mol) was added in portions over 0.5 h to a stirred solution of the residue in EtOH (30 mL), and then the mixture was diluted with H_2O (300 mL), neutralized with 10% $NaHCO_3$ solution, and extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were dried (Na_2SO_4) and evaporated to dryness, and the residue was crystallized from EtOAc: yield 3.3 g (76%); mp 112–113 °C. Anal. ($C_{22}H_{31}N_3O_4S$) C, H, N.

2-[(2-Isobutyramidoethyl)amino]-1-[4-(methanesulfonylamido)phenyl]ethanol Hydrochloride (35). A solution of 2-[*N*-benzyl-*N*-(2-isobutyramidoethyl)amino]-1-[4-(methanesulfonylamido)phenyl]ethanol (1.73 g, 0.04 mol) in HOAc (30 mL) was hydrogenated at room temperature and atmospheric pressure over 30% Pd/C until uptake ceased. The mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in EtOAc, the solution was acidified with etheral HCl, and the precipitated hydrochloride was collected and recrystallized from ethanol: yield 0.9 g (60%); mp 183–184 °C.

2-[*N*-Benzyl-*N*-(2-isobutyramidoethyl)amino]-1-(4-nitrophenyl)ethanol. This compound was prepared in a similar manner to that used for the 4-(methanesulfonylamido) analogue used in the preparation of compound **35** and was crystallized from a mixture of EtOAc and cyclohexane: yield 45%; mp 117–118 °C. Anal. ($C_{21}H_{27}N_3O_4$) C, H, N.

1-(4-Aminophenyl)-2-[(2-isobutyramidoethyl)amino]-ethanol (34). A solution of hydrazine hydrate (2.7 g, 0.054 mol) in ethanol (20 mL) was added dropwise over 0.5 h to a stirred, refluxing mixture of 2-[*N*-benzyl-*N*-(2-isobutyramidoethyl)-amino]-1-(4-nitrophenyl)ethanol (7.0 g, 0.018 mol), Raney nickel (2 g), and ethanol (100 mL), then the mixture was filtered, and the filtrate was evaporated to dryness: yield 6.8 g.

A solution containing 0.8 g of the above residue in ethanol (30 mL) was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure until uptake ceased. The mixture was filtered, the filtrate was evaporated to dryness and the residue was crystallized from MeCN: yield 0.43 g (77%); mp 141–142 °C.

1-(2-Chlorophenyl)-2-[[2-(phenylacetamido)ethyl]-amino]ethanol Fumarate (38). A solution of 2-bromo-1-(2-chlorophenyl)ethanol (4.6 g, 0.02 mol) and *N*-(2-aminoethyl)-phenylacetamide (3.68 g, 0.02 mol) in ethanol (50 mL) was kept at 40 °C for 3 days and then evaporated to dryness. HBr, 4 N (200 mL), was added to the residue, and the mixture was washed with EtOAc (3 × 50 mL). The aqueous phase was basified to pH 12 with 10 N NaOH and extracted with EtOAc (3 × 50 mL), and the combined EtOAc extracts were dried ($MgSO_4$) and evaporated to dryness. A solution of the residue in MeOH (50 mL) was added to a solution of fumaric acid (2.3 g, 0.02 mol) in MeOH (50 mL), the mixture was evaporated to dryness, and the residue was triturated with MeCN and filtered. The residue was crystallized from *i*-PrOH: yield 0.2 g (3%); mp 160–162 °C.

1-(2,4-Dichlorophenyl)-2-[(2-isobutyramidoethyl)-amino]ethanol Hydrochloride (36) was prepared in a similar manner: yield 2%; mp 194–196 °C (MeCN).

2-[[2-(Ethoxycarbonamido)ethyl]amino]-1-phenylethanol (45). A stirred mixture of 2-[(2-aminoethyl)amino]-1-phenylethanol (1.8 g, 0.01 mol), K_2CO_3 (1.38 g, 0.01 mol), and EtOH (40 mL) was treated with ethyl chloroformate (1.09 g, 0.01 mol) and then stirred and refluxed for 30 min and evaporated to dryness. HCl, 1 N (30 mL), was added to the residue, the mixture was washed with EtOAc (20 mL), and the aqueous phase was neutralized with $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were evaporated to dryness, and

the residue was crystallized from EtOAc/petroleum ether (bp 60–80 °C): yield 0.3 g (12%); mp 90–91 °C.

2-[*N*-(2-Aminopropyl)-*N*-benzylamino]-1-phenylethanol Hydrochloride. A mixture of 2-(benzylamino)-1-phenylethanol (11.35 g, 0.05 mol), MeCN (100 mL), KI (0.1 g), and chloroacetone (2.32 g, 0.025 mol) was heated under reflux for 1.5 h, then cooled, and filtered, and the filtrate was evaporated to dryness.

A mixture of the residue, hydroxylamine hydrochloride (3.0 g, 0.05 mol), K_2CO_3 (7.9 g, 0.05 mol), H_2O (10 mL), and EtOH (50 mL) was refluxed for 2 h and then evaporated to near dryness. Water (100 mL) was added, the mixture was extracted with EtOAc (3 × 50 mL), and the combined EtOAc extracts were dried (Na_2SO_4) and evaporated to dryness. A 70%, w/v, solution of sodium bis(2-methoxyethoxy)aluminum hydride ("Red-Al"; 29.8 mL, 0.1 mol) in benzene was added over 0.5 h to a stirred solution of the residue in toluene (100 mL), and the solution was stirred at room temperature for 18 h.

The stirred mixture was acidified with 2 N HCl, the aqueous phase was separated, and the toluene phase was extracted again with 2 N HCl (100 mL). The combined aqueous acid extracts were basified with 10 N NaOH and extracted with $CHCl_3$ (3 × 100 mL), and the combined chloroform extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in Et_2O, ethereal HCl was added, the Et_2O was decanted, and the residual gum was crystallized from 5% MeOH/acetonitrile: yield 0.44 g (5%); mp 197–198 °C. Anal. ($C_{18}H_{24}ON_2$) C, H, N.

The mother liquors were evaporated to dryness, and the residue was stirred with water (50 mL) and filtered. The filtrate was basified with 10 N NaOH and extracted with Et_2O, and the extracts were dried (Na_2SO_4) and evaporated to give crude base (1.7 g, 24%), which was used without further purification to prepare compound **44**.

2-[[2-(Phenylacetamido)propyl]amino]-1-phenylethanol (44). Phenylacetyl chloride (0.98 g, 0.0063 mol) was added to a stirred solution of 2-[*N*-(2-aminopropyl)-*N*-benzylamino]-1-phenylethanol (1.7 g, 0.006 mol) and triethylamine (1 mL) in toluene (50 mL), and the mixture was stirred for 0.5 h and then washed successively with 1 N NaOH (20 mL) and water (20 mL). The toluene phase was dried (Na_2SO_4) and evaporated to dryness.

A solution of the residue in EtOH was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure and then filtered, and the filtrate was evaporated to dryness. The residue was crystallized from EtOAc: yield 0.4 g (21%); mp 136–137 °C.

***N*-(2-Aminoethyl)cyclopentanecarboxamide (58).** A mixture of methyl cyclopentanecarboxylate and (12.8 g, 0.1 mol) ethylenediamine (24 g, 0.4 mol) was heated at 100 °C for 18 h, cooled, and then poured into water (100 mL). The resulting suspension was filtered, and the filtrate was evaporated to dryness. A solution of the residue in EtOAc was added to a solution of oxalic acid in EtOAc, and the precipitated oxalate was collected and crystallized from EtOH: yield 12 g (49%); mp 164–165 °C.

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Cerebrovasodilatation through Selective Inhibition of the Enzyme Carbonic Anhydrase. 2. Imidazo[2,1-*b*]thiadiazole and Imidazo[2,1-*b*]thiazolesulfonamides

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A series of imidazo[2,1-*b*]thiadiazole and imidazo[2,1-*b*]thiazolesulfonamide carbonic anhydrase inhibitors is described and their anticonvulsant activities are listed. Many of the compounds have the same degree of ionization as acetazolamide and methazolamide, but their higher lipophilicity means that they are more able to penetrate into the central nervous system. One compound, 6-*tert*-butyl-2-sulfamoylimidazo[2,1-*b*]-1,3,4-thiadiazole (**8**, UK-15 454) had an anticonvulsant ED_{50} of 2.6 mg/kg when administered orally to mice. **8** selectively increased cerebral blood flow in animals without producing a high level of metabolic acidosis.

Because of the increase in the number of elderly people, cerebrovascular disease is now becoming a major medical and social problem; there is, therefore, an urgent need to discover an effective therapy that will improve the function of the aging brain. It is known that the degree and extent of the neurological deficit correlate with decreases in both cerebral blood flow and oxygen utilization,[1-3] but it is not known whether either of these constitutes the primary defect. Current therapy is mainly confined to vasodilator drugs,[4] even though these are usually unselective in their vasodilator action and frequently lower blood pressure.

In the previous publication,[5] we described how 4-[(4-methoxypiperidino)sulfonyl]-2-chlorobenzenesulfonamide (UK-12 130) caused a selective increase in cerebral blood flow in man and animals by raising CO_2 levels locally through inhibition of brain and/or erythrocyte carbonic anhydrase. By this means, autoregulation[6,7] was surmounted and, since blood pressure was not decreased,[8] CO_2 achieved a dilation limited only by the responsiveness of the cerebral vasculature.

The carbonic anhydrase inhibitor acetazolamide is also known to increase cerebral blood flow in patients with cerebrovascular disease.[8-10] However, acetazolamide is a potent inhibitor of carbonic anhydrase in the kidney, and the increase in cerebral blood flow is always accompanied by a marked diuresis[11] which eventually leads to a metabolic acidosis.

The related carbonic anhydrase inhibitor methazolamide is able to penetrate erythrocytes very readily and to enter

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