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β-Adrenergic Blocking Agents. 15. 1-Substituted Ureidophenoxy-3-amino-2-propanols

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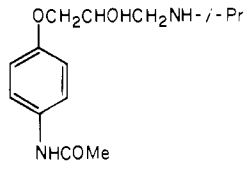
A series of 1-substituted ureidophenoxy-3-amino-2-propanols was synthesized and the compounds were screened as β-adrenergic receptor antagonists in cats. Many of the compounds are potent cardioselective β-blockers. Their structure–activity relationships and chemistry are discussed.

In paper 10, the syntheses and biological properties of the adrenergic β-receptor antagonist 4-(2-hydroxy-3-isopropylaminopropoxy)acetanilide (practolol, 1) and several homologues were reported.[1] The cardioselective β-



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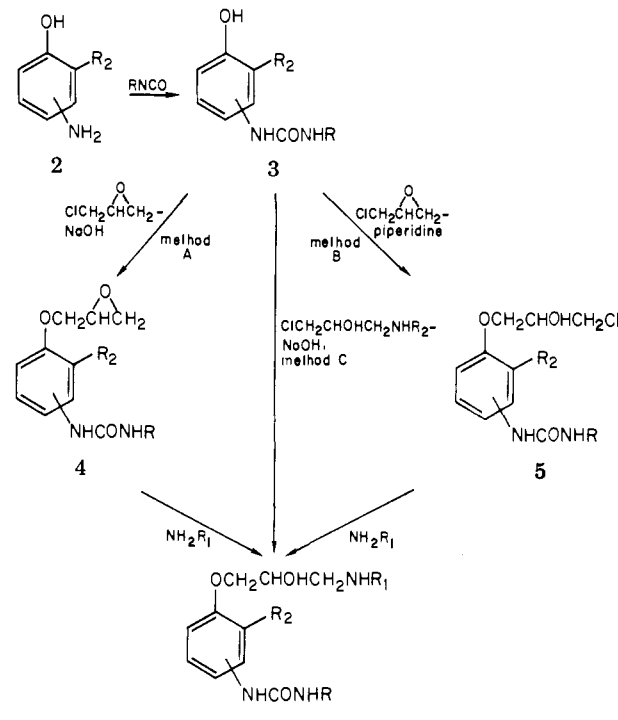
blocking property of practolol has since become established[2] and in the course of our synthetic program on cardioselective β-receptor antagonists we have now prepared a series of analogues of practolol in which the acylamino moiety in the aryl residue has been replaced by a ureido moiety.[3]

Many of the compounds described show a similar profile of activity to practolol in that they markedly inhibit the isoproterenol-induced tachycardia with only small effects on the isoproterenol depressor response. This finding is in accordance with other workers who have claimed selectivity of action for ureido-substituted aryloxypropanolamines.[4] This paper describes the synthesis and the structure–activity relationships within this series of homologues.

Chemistry. The compounds described in Tables I and II were prepared as shown in Scheme I. The above methods are analogous to those used for previously described 1-amino-3-aryloxy-2-propanols.[1,6] Of these, method A was preferred to methods B and C because of higher yield; therefore, the Experimental Section is limited to three brief descriptions of typical procedures. The epoxide intermediates (4) were used without further purification and their methods of synthesis are adequately described in previous papers. The synthesis of a typical ureidophenol is described and Table II lists those phenols that are novel and have been characterized. The aminophenols used as starting material are adequately described in the literature with the exception of 2-acetyl-4-aminophenol which is described in the Experimental Section.

Pharmacology. β-Adrenoceptor blocking potency was estimated in vivo using the previously described cat

Scheme I

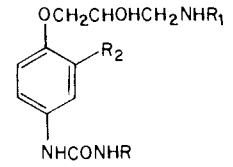


preparation.[5] The results given in Tables I and II are expressed as the total dose, infused over a period of 30 min, causing a 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 μg/kg dosed iv). The degree (%) of blockade of the vasodepressor response at that dose level is also given. The relative potencies of these two systems give some 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 was ±0.12 log unit (i.e., a mean error of approximately 30%).

Discussion of Results

Throughout the series many of the compounds have shown a selectivity of action similar to that found in

Table I



Compd	R	R_1	R_2	Mp, °C	Crystn solvent	Yield,[d] %	Emp formula	Analyses	Dose, μg/kg, giving 50% inhibn of tachycardia	Inhibn, %, of depressor response
1	H	*i*-Pr	H	143-145	EtOAc-EtOH	14	$C_{13}H_{21}N_3O_3$	C, H, N	631	20
2	H	*t*-Bu	H	98-100	EtOAc	10	$C_{14}H_{23}N_3O_3$	C, H, N	101	0
3	Me	*i*-Pr	H	150-152	EtOAc-EtOH	32	$C_{14}H_{23}N_3O_3$	C, H, N	70	29
4	Me	*t*-Bu	H	62-64	EtOAc	52	$C_{15}H_{25}N_3O_3 \cdot 0.5H_2O$	C, H, N	74	0
5	Me	*i*-Pr	Cl	162-164	EtOAc-*i*-PrOH	28	$C_{14}H_{22}ClN_3O_3$	C, H, N	104	26
6	Me	*t*-Bu	Cl	108-110	EtOAc	15	$C_{15}H_{24}ClN_2O_3$	C, H, N	25	52
7	Me	*i*-Pr	Br	161-163	EtOAc	4	$C_{14}H_{22}BrN_3O_3$	C, H, N	33	63
8	Me	*i*-Pr	I	176-178	EtOAc	2	$C_{14}H_{22}IN_3O_3 \cdot 0.5H_2O$	C, H, N	100	33
9	Me	*i*-Pr	Me	156-158	EtOAc-*i*-PrOH	22	$C_{15}H_{25}N_3O_3$	C, H, N	170	32
10	Me	*t*-Bu	*n*-Pr	124-126	EtOAc	21	$C_{18}H_{31}N_3O_3$	C, H, N	93	7
11	Me	*i*-Pr	COMe	150-152	MeCN	8	$C_{16}H_{25}N_3O_4$	C, H, N	395	43
12	Me	*t*-Bu	$CH_2CH{=}CH_2$	134	EtOAc	18	$C_{18}H_{29}N_3O_3$	C, H, N	56	74
13	Et	*i*-Pr	H	162-164	EtOAc	37	$C_{15}H_{25}N_3O_3$	C, H, N	427	0
14	Et	*t*-Bu	H	242	Aq EtOH	23	$C_{16}H_{27}N_3O_3 \cdot 0.5(COOH)_2$	C, H, N	201	34
15	Et	*i*-Pr	Cl	150-152	EtOAc	27	$C_{15}H_{24}ClN_3O_3$	C, H, N	188	0
16	Et	*i*-Pr	Br	151-152	EtOAc-*i*-PrOH	7	$C_{15}H_{24}BrN_3O_3 \cdot 0.5H_2O$	C, H, N	69	19
17	Et	*t*-Bu	I	106-108	EtOAc	18	$C_{16}H_{26}IN_3O_3$	C, H, N	23	6
18	Et	*i*-Pr	Me	135-137	EtOAc	45	$C_{16}H_{27}N_3O_3$	C, H, N	234	27
19	Et	*t*-Bu	Me	120-122	EtOAc	44	$C_{17}H_{29}N_3O_3$	C, H, N	57	58
20	Et	$CH(Me)CH_2OPH$	Me	118-120	EtOAc	20	$C_{22}H_{31}N_3O_4$	C, H, N	885	18
21	Et	*i*-Pr	Et	114-117	EtOAc	7	$C_{17}H_{29}N_3O_3 \cdot 0.5H_2O$	C, H, N	118	33
22	Et	*t*-Bu	Et	126-128	EtOAc	28	$C_{18}H_{31}N_3O_3$	C, H, N	80	2
23	Et	*i*-Pr	$CH_2CH{=}CH_2$	116	EtOAc	39	$C_{18}H_{29}N_3O_3$	C, H, N	180	68
24	Et	*t*-Bu	$CH_2CH{=}CH_2$	128	EtOAc	33	$C_{19}H_{31}N_3O_3 \cdot 0.25H_2O$	C, H, N	38	30
25	Et	$C(CH_2OH)(CH_3)_2$	$CH_2CH{=}CH_2$	139-141	EtOAc	13	$C_{19}H_{31}N_3O_4 \cdot 0.5H_2O$	C, H, N	224	50
26	Et	c-C_3H_5	$CH_2CH{=}CH_2$	118-120	EtOAc	21	$C_{18}H_{27}N_3O_3$	C, H, N	1140	37
27	Et	*i*-Pr	OEt	146-147	EtOAc-*i*-PrOH	13	$C_{17}H_{29}N_3O_4$	C, H, N	295	41
28	Et	*i*-Pr	OH	164-166	EtOAc-MeOH	2	$C_{15}H_{25}N_3O_4 \cdot 0.5H_2O$	C, H, N	521	15
29	Et	*i*-Pr	SMe	158-160	EtOAc-*i*-PrOH	3	$C_{16}H_{27}N_3O_3S$	C, H, N	198	32
30	*n*-Pr	*i*-Pr	H	150	EtOAc-EtOH	42	$C_{16}H_{27}N_3O_3$	C, H, N	147	0
31	*n*-Pr	*t*-Bu	H	144	EtOAc-EtOH	38	$C_{17}H_{29}N_3O_3$	C, H, N	33	0
32	*n*-Pr	*i*-Pr	I	130	EtOAc	2	$C_{16}H_{26}IN_3O_3$	C, H, N	77	100
33	*n*-Pr	*i*-Pr	Me	126-128	EtOAc	43	$C_{17}H_{29}N_3O_3$	C, H, N	61	59
34	*n*-Pr	*t*-Bu	Me	128-131	EtOAc	39	$C_{18}H_{31}N_3O_3$	C, H, N	44	0
35	*n*-Pr	*i*-Pr	$CH_2CH{=}CH_2$	128-130	EtOAc	5	$C_{19}H_{31}N_3O_3 \cdot 0.5H_2O$	H; C,[a] N[b]	213	15
36	*n*-Bu	*i*-Pr	H	138	EtOAc-EtOH	16	$C_{17}H_{29}N_3O_3$	C, H, N	416	0
37	*n*-Bu	*t*-Bu	H	107-109	EtOAc	15	$C_{18}H_{31}N_3O_3$	C, H, N	48	0
38	*n*-Bu	*t*-Bu	Cl	132-133	EtOAc	12	$C_{18}H_{30}ClN_3O_3$	C, H, N	8	0
39	*n*-Bu	*i*-Pr	Me	109-111	EtOAc	26	$C_{18}H_{31}N_3O_3$	C, H, N	46	0
40	*n*-Bu	*t*-Bu	Me	131-132	EtOAc	32	$C_{19}H_{33}N_3O_3$	C, H, N	12	11
41	*n*-C_6H_{13}	*i*-Pr	H	142	EtOAc	18	$C_{19}H_{33}N_3O_3$	C, H, N	274	0
42	*n*-C_6H_{13}	*t*-Bu	H	114	EtOAc	7	$C_{20}H_{35}N_3O_3$	C, H, N	94	30
43	*n*-C_6H_{13}	*i*-Pr	Me	110	EtOAc	11	$C_{20}H_{35}N_3O_3$	C, H; N[c]	189	19
44	*n*-C_6H_{13}	*t*-Bu	Me	108-110	EtOAc	9	$C_{21}H_{37}N_3O_3 \cdot 0.25H_2O$	C, H, N	30	50

45	n-C_6H_{13}	*i*-Pr	COMe	124–125	EtOAc	1	$C_{21}H_{35}N_3O_4$	C, H, N	182	0
46	n-C_8H_{17}	*i*-Pr	Me	114–116	EtOAc	6	$C_{22}H_{29}N_3O_3$	C, H, N	169	28
47	n-C_8H_{17}	*t*-Bu	Me	106	EtOAc	12	$C_{23}H_{41}N_3O_3$	C, H, N	80	11
48	*i*-Pr	*t*-Bu	H	124–126	EtOAc	16	$C_{17}H_{29}N_3O_3$	C, H, N	95	24
49	*i*-Pr	*i*-Pr	Me	130–131	EtOAc	20	$C_{17}H_{29}N_3O_3$	C, H, N	438	57
50	*i*-Pr	*t*-Bu	Me	90–92	EtOAc	12	$C_{18}H_{31}N_3O_3 \cdot 0.5H_2O$	C, H, N	49	5
51	$CH_2CH{=}CH_2$	*i*-Pr	H	144	EtOAc–EtOH	18	$C_{16}H_{25}N_3O_3$	C, H, N	262	70
52	$CH_2CH{=}CH_2$	*t*-Bu	H	68	EtOAc	17	$C_{17}H_{27}N_3O_3 \cdot 0.25H_2O$	C, H, N	89	6
53	$CH_2CH{=}CH_2$	*i*-Pr	Cl	141–142	EtOAc	29	$C_{16}H_{24}ClN_3O_3$	C, H, N	131	43
54	$CH_2CH{=}CH_2$	*t*-Bu	Cl	118–120	EtOAc	17	$C_{17}H_{26}ClN_3O_3$	C, H, N	22	19
55	$CH_2CH{=}CH_2$	*i*-Pr	Me	126–129	EtOAc–*i*-PrOH	40	$C_{17}H_{27}N_3O_3$	C, H, N	107	12
56	$CH_2CH{=}CH_2$	*t*-Bu	Me	129–132	EtOAc	30	$C_{18}H_{29}N_3O_3$	C, H, N	45	32
57	C_6H_4-*p*-Cl	*t*-Bu	H	180–182	EtOAc	1	$C_{20}H_{26}ClN_3O_3 \cdot 0.5H_2O$	C, H, N	403	39
58	c-C_6H_{11}	*i*-Pr	Cl	140–142	EtOAc	2	$C_{19}H_{30}ClN_3O_3 \cdot 0.25H_2O$	C, H, N	252	14
59				166–167	EtOAc–*i*-PrOH	12	$C_{15}H_{25}N_3O_3 \cdot HCl$	C, H, N	3240	103
60				148–150	H_2O	2	$C_{14}H_{23}N_3O_3 \cdot 0.5H_2O$	C, H, N	28.0	58
61	Practolol								167	8
62	Propranolol								62	85

[a] C: calcd, 63.8; found, 64.3. [b] N: calcd, 11.7; found, 11.1. [c] N: calcd, 11.5; found, 10.9. [d] Overall yield, based on ureidophenol.

practolol, that is, a marked inhibition of the isoproterenol-induced tachycardia with only small effects on the isoproterenol depressor response. The ortho and meta analogues **59** and **60** (Table I) showed no such selectivity, a finding that had previously been observed with the *o*-acylamino analogues.[1]

Inspection of the biological data shows that it is difficult to correlate this selectivity of action with the substituents R, R_1, and R_2 as this property is randomly distributed throughout the series. Variation of these substituents does, however, play an important role in the potency of the compounds.

The amino substituent (R_1) was in the main confined to *i*-Pr and *t*-Bu groups which gave optimum potency in our previous series of acylamino[1] and carbamoyl[7] analogues.

Three variations are, however, exemplified by compounds **20**, **25**, and **26** which were less potent than the corresponding *i*-Pr and *t*-Bu analogues. A comparison of the 18 pairs of *i*-Pr and *t*-Bu analogues shown in Table I shows that the *t*-Bu analogues, without exception, are the more potent.[10]

An ortho substituent (R_2) in the aromatic ring invariably increases potency and appears to be free of steric limitations. Thus, in an analogous series (Table III) potency can be seen to be independent of the steric bulk (M.R.) of R_2, and the various substituents are all more potent than the unsubstituted analogue **13**.

The influence of the π value of R_2 shows a trend toward potency residing in the more lipophilic groups, while the electronic contribution of R_2 appears to have little effect on potency.

The steric influence of the ureido substituent R does, however, appear to play a part in the potency of the compounds. This is suggested by the "step-jumps" in potency that can be observed in the analogous series listed in Table IV, where there is an incremental increase in the π value of *R*.

In general, potency throughout the series appears to increase with lipophilicity if allowance is made for steric hinderance. Thus, compounds **38** and **40**, the most potent in the series, are substituted at R and R_1 with the lipophilic *n*-butyl and *tert*-butyl groups, respectively. Selectivity of action is, however, not apparently related to any single physical parameter and no general conclusion can be drawn for this property.

Experimental Section

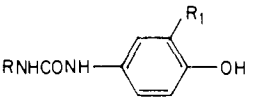
All melting points were taken using open capillaries and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

1-[2-Allyl-4-(3-ethylureido)phenoxy]-3-isopropylamino-2-propanol (23). Method A. A mixture of 1-[2-allyl-4-(3-ethylureido)phenoxy]-2,3-epoxypropane (3.2 g, 0.01 mol) and *i*-$PrNH_2$ (25 mL, 0.3 mol) was heated under reflux for 2 h. The mixture was evaporated to dryness under reduced pressure and extracted with a mixture of 2 N HCl and Et_2O. The acid phase was separated and basified with 11 N NaOH. The mixture was filtered and the solid residue was crystallized from EtOAc: yield 1.5 g (39%); mp 116 °C.

1-[4-(3-*n*-Butylureido)-2-methylphenoxy]-3-isopropylamino-2-propanol (39). Method B. A mixture of 1-[4-(3-*n*-butylureido)-2-methylphenoxy]-3-chloro-2-propanol (3.0 g, 0.009 mol), *i*-$PrNH_2$ (25 mL, 0.3 mol), and *n*-PrOH (25 mL) was heated under reflux for 6 h. The mixture was evaporated to dryness and the product was isolated as described in method A and crystallized from EtOAc: yield 1.0 g (26%); mp 112–114 °C.

Compound 39. Method C. A mixture of 4-(3-*n*-butylureido)-2-methylphenol (2.2 g, 0.01 mol), NaOH (0.8 g, 0.02 mol), H_2O (4 mL), 1-chloro-3-isopropylamino-2-propanol hydrochloride

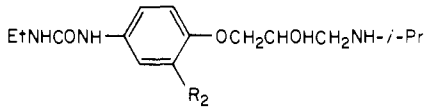
Table II



Compd	R	R_1	Mp, °C	Crystn solvent	Yield,[a] %	Emp formula	Analyses
1	Me	H	167	MeCN	64	$C_8H_{10}N_2O_2$	C, H, N
2	Me	Cl	195-196	MeCN	73	$C_8H_9ClN_2O_2$	C, H, N
3	Me	Me	223-224	MeCN	59	$C_9H_{12}N_2O_2$	C, H, N
4	Me	$COCH_3$	192-193	MeOH	91	$C_{10}H_{12}N_2O_3$	C, H, N
5	Et	H	174-176	*i*-PrOH	63	$C_9H_{12}N_2O_2$	C, H, N
6	Et	Cl	156-158	MeCN	64	$C_9H_{11}ClN_2O_2$	C, H, N
7	Et	Me	194-196	*i*-PrOH	59	$C_{10}H_{14}N_2O_2$	C, H, N
8	Et	$CH_2CH=CH_2$	141	EtOAc	39	$C_{12}H_{16}N_2O_2$	C, H, N
9	Et	OEt	156-158	MeCN	73	$C_{11}H_{16}N_2O_3$	C, H, N
10	Et	SMe	155-159	MeCN	40	$C_{10}H_{14}N_2O_2S$	C, H, N
11	*n*-Pr	Me	151-153	MeCN	35	$C_{11}H_{16}N_2O_2$	C, H, N
12	*n*-Bu	H	162-164	EtOAc	9	$C_{11}H_{16}N_2O_2$	C, H, N
13	*n*-Bu	Cl	147-149	MeCN	58	$C_{11}H_{15}ClN_2O_2$	C, H, N
14	*n*-Bu	Me	164-165	MeCN	32	$C_{12}H_{18}N_2O_2$	C, H, N
15	*n*-C_6H_{13}	H	132-134	EtOAc	91	$C_{13}H_{20}N_2O_2$	C, H, N
16	*n*-C_6H_{13}	$COCH_3$	159-160	MeOH	92	$C_{15}H_{22}N_2O_3$	C, H, N
17	$CH_2CH=CH_2$	H	150-152	EtOAc	72	$C_{10}H_{12}N_2O_2$	C, H, N
18	$CH_2CH=CH_2$	Cl	164-165	MeCN	47	$C_{10}H_{11}ClN_2O_2$	C, H, N
19	$CH_2CH=CH_2$	Me	153-154	MeCN	27	$C_{11}H_{14}N_2O_2$	C, H, N
20	c-C_6H_{11}	H	184-186	MeCN	28	$C_{13}H_{17}ClN_2O_2 \cdot H_2O$	C, H, N

[a] Yield based on aminophenol.

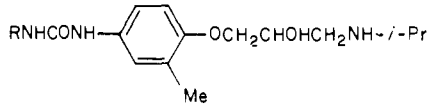
Table III



Compd	R_2	ED_{50}	M.R.[a]	π[a]	F[a]	R[a]
13	H	427	0	0	0	0
27	OEt	295	11.3	0.17	0.36	-0.44
18	Me	234	4.7	0.84	-0.05	-0.14
29	SMe	198	13.0	0.87	-0.33	-0.19
15	Cl	188	4.8	0.76	0.69	-0.16
21	Et	118	9.4	1.39	-0.07	-0.11
16	Br	69	7.6	0.84	0.76	-0.18

[a] See ref 9.

Table IV



Compd	R	ED_{50}	π[a]
9	Me	170	0.5
18	Et	234	1.0
55	$CH_2CH=CH_2$	107	1.2
49	*i*-Pr	438	1.37
33	*n*-Pr	61	1.5
39	*n*-Bu	46	2.0
43	*n*-C_6H_{13}	189	3.0
46	*n*-C_8H_{17}	169	4.0

[a] See ref 8.

(1.88 g, 0.01 mol), and EtOH (45 mL) was heated under reflux for 6 h. The mixture was evaporated to dryness and the product was isolated as described in method A: yield 0.1 g (3%); mp 112-114 °C.

4-(3-Ethylureido)-2-methylphenol. To a hot solution of 4-amino-2-methylphenol (6.0 g, 0.05 mol) in MeCN (60 mL) there was added, with stirring, a solution of EtNCO (3.4 g, 0.05 mol) in MeCN (20 mL). The mixture was heated under reflux for 10 min, cooled, and filtered. The solid residue was washed with water and crystallized from *i*-PrOH: yield 5.5 g (58%); mp 194-196 °C.

2-Acetyl-4-aminophenol. A mixture of 4-acetoxyacetanilide (14.5 g, 0.075 mol) and aluminum chloride (20.0 g, 0.15 mol) was heated at 175 °C for 3 h and cooled and ice (80.0 g) followed by 11 N HCl (80.0 mL) was added with stirring. The mixture was then heated under reflux for 1.5 h, cooled, brought to neutral pH with 11 N NaOH, and filtered. The solid residue was washed with water and crystallized from EtOAc: yield 6.0 g (53%); mp 112-113 °C. Anal. Calcd: C, 63.6; H, 6.0; N, 9.3. Found: C, 63.8; H, 5.7; N, 9.2.

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References and Notes

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