high and the other front paw is permitted to hang free. The head of the rat is not allowed to rest on top of the cork. The stage IV response is determined on both right and left sides and one point is scored for each positive catatonic response. The maximum possible catatonic response for stage III or IV is three points.

The catatonic response was determined on each rat at 0.5-, 1-, 2-, and 3-h intervals after injection of the perphenazine. The percentage which the test drugs inhibited the catatonic response was calculated against the test scores of rats injected with a 5 mg/kg ip dose of perphenazine at the same time. The results of these tests are given in Table II.

Acknowledgment. This research was supported by NIH Training Grant GM-484. The authors wish to thank Dr. J. D. Smith for his helpful suggestions and A. S. Leeper, T. Dickerson, and Chung Ng for the technical assistance in this project. The authors are also indebted to Dr. L. G. Abood, who provided the glycolate ester samples on which partition coefficients were determined and the preliminary psycotomimetic data on compounds **13** and **14**, and to Dr. R. M. Quock, who provided the rabbit temperature studies.

References and Notes

(1) L. G. Abood in "Drugs Affecting the Central Nervous System", A. Burger, Ed., Marcel Dekker, New York, N.Y., 1968, p 127.
(2) L. G. Abood and J. H. Biel, *Int. Rev. Neurobiol.*, **4**, 218 (1962).
(3) L. Albanus, *Acta Pharmacol. Toxicol.*, **28**, 305 (1958).
(4) J. H. Biel, L. G. Abood, W. K. Hoya, H. A. Leiser, P. A. Nuhfer, and E. F. Kluchesky, *J. Org. Chem.*, **26**, 4096 (1961).
(5) H. Huller and W. Scheler, *Acta Biol. Med. Ger.*, **11**, 22 (1963).
(6) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengler, *J. Am. Chem. Soc.*, **74**, 1485 (1952).
(7) B. V. Franko and C. D. Lunsford, *J. Med. Pharm. Chem.*, **2**, 523 (1960).
(8) H. Kreiskott, G. Kimmerle, W. Wirth, H. Wollweber, and R. Heltmann, *Med. Chem. (Leverkusen, Ger.)*, **8**, 117 (1963).
(9) P. P. Denisenko and Y. M. Pratusevich, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **23** (T479 Trans. Suppl. No. 3, Part II) (1964).
(10) E. L. Engelhardt and C. A. Stone in "Medicinal Chemistry", 3rd ed, A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970, p 1538.
(11) R. M. Pinder, *Prog. Med. Chem.*, **9**, 191 (1973).
(12) C. C. Pfeiffer, *Int. Rev. Neurobiol.*, 1, 195 (1959).
(13) A. C. Sayers and H. R. Burki, *J. Pharm. Pharmacol.*, **28**, 252 (1976).
(14) H. H. Ong, Ph.D. Thesis, University of Virginia, Charlottesville, Va., 1964.
(15) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1351 (1965).
(16) F. G. Bordwell and K. M. Wellman, *J. Chem. Educ.*, **39**, 308 (1962).
(17) D. E. McGreer and M. M. Mocek, *J. Chem. Educ.*, **40**, 358 (1963).
(18) E. J. Ariens and J. M. Van Rossum, *Arch. Int. Pharmacodyn. Ther.*, **110**, 275 (1957).
(19) C. Morpurgo, *Arch. Int. Pharmacodyn. Ther.*, **137**, 84 (1962).
(20) D. B. Duncan, *Biometrics*, **11**, 1 (1955).
(21) A. Horita and R. M. Quock in "Temperature Regulation and Drug Action", P. Lomax, E. Schonbaum, and J. Jacobs, Ed., S. Kagar, Basel, 1974, pp 75–84.
(22) L. O. Randall, W. M. Benson, and P. L. Stefko, *J. Pharmacol.*, **104**, 284 (1952).
(23) L. F. Soyka and K. R. Unna, *Arch. Int. Pharmacodyn. Ther.*, **54**, 210 (1965).
(24) L. G. Abood, personal communication.
(25) H. J. Emeleus and H. G. Heal, *J. Chem. Soc.*, 1126 (1946).
(26) W. Wirth, R. Gosswald, U. Horlen, K. H. Risse, and H. Kreiskott, *Arch. Int. Pharmacodyn. Ther.*, **1958**, 115 (1958).

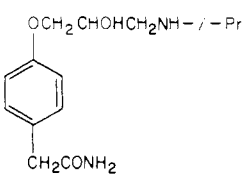
β-Adrenergic Blocking Agents. 16. 1-(Acylaminomethyl-, ureidomethyl-, and ureidoethylphenoxy)-3-amino-2-propanols

L. H. Smith

Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England.
Received January 18, 1977

The synthesis of a series of 1-(acylaminomethyl-, ureidomethyl-, and ureidoethylphenoxy)-3-amino-2-propanols is described. The compounds were screened as β-adrenergic receptor antagonists in cats and their partial agonist activity was evaluated in rats depleted of circulating catecholamines. Some of the compounds have a pharmacological profile similar to atenolol. Their structure–activity relationships are discussed.

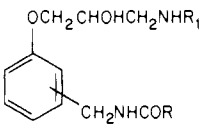
The addition of a methylene bridge between a carbamoyl moiety and the aromatic ring of an aryloxypropanolamine gave a β-blocking agent, atenolol (**1**, Tenormin[1]), that was potent, cardioselective, and without partial agonist activity.[2]



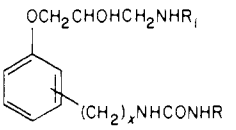
1

In an extension of this work we have synthesized a series of compounds that have a methylene or ethylene bridge interposed between the aromatic ring and an acylamino (**2**)[3] or ureido (**3**)[4] moiety.

The potency and selectivity of action found throughout the series was, in general, of a lower order than that observed with the parent acylamino[5] and ureido analogues.[6] Many of the compounds were similar to atenolol in that they had little or no partial agonist activity when examined in rats depleted of catecholamines. This paper describes the synthesis and discusses the structure–activity relationships found within this series of analogues.



2, R, R_1, see Tables I–IV

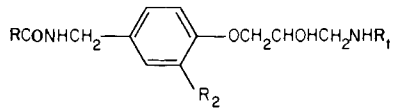


3, x = 1 or 2; R, R_1, see Tables I–IV

Chemistry. The compounds listed in Tables I–IV were prepared by previously described methods[5,7] and therefore the Experimental Section is limited to a typical example of each of the methods (A–C) outlined in Scheme I.

The various acylaminomethyl-, ureidomethyl-, and ureidoethylphenols used in the synthesis were made by

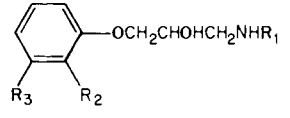
Table I. 1-(4-Acylaminomethylphenoxy)-3-amino-2-propanols



No.	R	R_1	R_2	Mp, °C	Crystn solvent	Yield,[a] %	Emp formula[b]	Method of prepn	Dose, μg/kg, giving 50% inhibn of tachycardia[c]	Inhibn, %, of depressor response[c]	Partial agonist act., BPM[c]
8	Me	*i*-Pr	H	90–92	EtOAc	3	$C_{15}H_{24}N_2O_3$	C	142	0	· 2
9	Me	*t*-Bu	H	146	EtOAc–EtOH	4	$C_{18}H_{30}N_2O_5 \cdot 1.25H_2O$	C	210	32	−7
10	Me	*t*-Bu	Cl	124	Me_2CO	3	$C_{18}H_{27}N_2O_5Cl \cdot H_2O$	A	21	30	−30
11	Me	2,4-(MeO)$(CH_2)_2C_6H_3$	Cl	204–206	Me_2CO–H_2O	2	$C_{13}H_{18}N_2O_5Cl$	B	1500	17	
12	Me	*i*-Pr	Br	86–88	EtOAc	4	$C_{15}H_{23}N_2O_3Br \cdot H_2O$	A	83	5	−17
13	Me	*i*-Pr	*n*-Pr	135	EtOAc	24	$C_{18}H_{30}N_2O_3$	A	40	51	−17
14	Me	*i*-Pr	$CH_2CH{=}CH_2$	114	EtOAc	5	$C_{18}H_{28}N_2O_3$	A	35	61	−16
15	Me	*i*-Pr	OMe	112–114	EtOAc	18	$C_{16}H_{26}N_2O_4$	A	312	5	−9
16	Me	*t*-Bu	OMe	102–104	EtOAc	23	$C_{17}H_{28}N_2O_4$	A	45	70	−16
17	Et	*i*-Pr	H	106–108	EtOAc	21	$C_{16}H_{26}N_2O_3$	C	658	16	−6
18	Et	*i*-Pr	Cl	106	EtOAc	13	$C_{16}H_{25}N_2O_3Cl$	A	630	83	−15
19	Et	*i*-Pr	Br	116	EtOAc	14	$C_{16}H_{25}N_2O_3Br \cdot 0.25H_2O$	B	269	7	−15
20	Et	*t*-Bu	Br	110–112	Me_2CO	7	$C_{19}H_{31}N_2O_5Br$	B	100	21	0
21	Et	*i*-Pr	*n*-Pr	128	EtOAc	26	$C_{19}H_{32}N_2O_3$	A	163	34	+4
22	Et	*i*-Pr	$CH_2CH{=}CH_2$	104	EtOAc	34	$C_{19}H_{30}N_2O_3$	A	98	3	−10
23	Et	*i*-Pr	OMe	108	EtOAc	29	$C_{17}H_{28}N_2O_4$	A	449	37	−19
24	Et	*t*-Bu	OMe	112	EtOAc	30	$C_{18}H_{30}N_2O_4$	A	1091	72	−12
25	Et	*i*-Pr	OEt	116	EtOAc	32	$C_{18}H_{30}N_2O_4$	A	331	48	−10
26	Et	*t*-Bu	OEt	114–116	Me_2CO	19	$C_{21}H_{36}N_2O_6$	A	1410	68	
27	*n*-Pr	*i*-Pr	H	116–117	EtOAc	45	$C_{17}H_{28}N_2O_3$	A	1404	51	
28	*n*-Pr	*t*-Bu	OMe	90–92	EtOAc	16	$C_{19}H_{32}N_2O_4$	A	282	17	−10
29	*i*-Pr	*i*-Pr	Br	138–140	EtOAc	10	$C_{17}H_{27}N_2O_3Br$	A	1099	43	−16
30	*i*-Pr	*i*-Pr	OMe	106	EtOAc	5	$C_{18}H_{30}N_2O_4$	A	1138	3	−16
31	*n*-C_6H_{13}	*t*-Bu	Cl	108	Me_2CO	7	$C_{23}H_{37}N_2O_7Cl$	A	1418	40	

[a] Overall yield, based on phenol. [b] Elemental analyses for C, H, and N were within ±0.4% of the theoretical values. [c] See Pharmacology section for description of method.

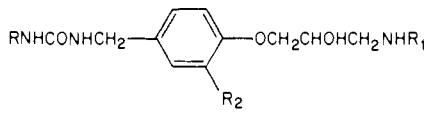
Table II. 1-(2- and 3-Substituted acylaminomethylphenoxy)-3-amino-2-propanols



No.	R_3	R_1	R_2	Mp, °C	Crystn solvent	Yield,[a] %	Emp formula[b]	Method of prepn	Dose, μg/kg, giving 50% inhibn of tachycardia[c]	Inhibn, %, of depressor response[c]	Partial agonist act., BPM[c]
32	2-$MeCONHCH_2$–	*t*-Bu	H	102–104	Me_2CO	10	$C_{18}H_{30}N_2O_5 \cdot 2H_2O$	B	130	63	+41
33	2-$EtCONHCH_2$–	*i*-Pr	H	88	EtOAc	9	$C_{16}H_{26}N_2O_3$	A	270	0	+44
34	2-*n*-$C_6H_{13}CONHCH_2$–	*i*-Pr	H	78–80	EtOAc	10	$C_{20}H_{34}N_2O_3$	A	1161	19	
35	2-*p*-Cl-$C_6H_4CONHCH_2$–	*i*-Pr	H	84–86	EtOAc	1	$C_{20}H_{25}N_2O_3Cl \cdot 0.25H_2O$	A	304	45	+14
36[d]	2-$MeCONHCH_2$–	*i*-Pr	4-Me	Oil (R_f 0.5)		1	$C_{16}H_{26}N_2O_3$	A	381	80	+5
37	3-$MeCONHCH_2$–	*i*-Pr	H	138	EtOAc		$C_{15}H_{24}N_2O_3$	A	383	83	

[a] Overall yield, based on phenol. [b] See footnote *b*, Table I. [c] See footnote *c*, Table I. [d] Isolated by TLC using Merck Kieselgel PF_{254} plate and 99:1 MeOH–NH_4OH (sp gr 0.98) solvent system.

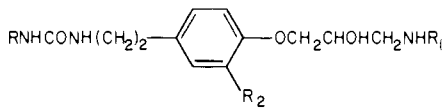
Table III. 1-(4-Ureidomethylphenoxy)-3-amino-2-propanols



No.	R	R_1	R_2	Mp, °C	Crystn solvent	Yield,[a] %	Emp formula[b]	Method of prepn	Dose, μg/kg, giving 50% inhibn of tachycardia[c]	Inhibn, %, of depressor response[c]
38	H	*i*-Pr	H	96-98	EtOAc	26	$C_{14}H_{23}N_3O_3$	A	117	48
39	H	*i*-Pr	Br	86-88	EtOAc	5	$C_{14}H_{22}BrN_3O_3$	A	106	25
40	H	*i*-Pr	OMe	138-140	EtOAc	7	$C_{15}H_{25}N_3O_4$	A	72	0
41	H	*t*-Bu	OMe	132-134	EtOAc	12	$C_{16}H_{27}N_3O_4$	A	75	68
42	Me	*i*-Pr	Cl	116-118	EtOAc	12	$C_{15}H_{24}ClN_3O_3$[d,e]	A	381	21
43	Me	*i*-Pr	Br	126-128	EtOAc	6	$C_{15}H_{24}BrN_3O_3$[f]	B	572	0
44	Me	*i*-Pr	OMe	122-124	EtOAc	8	$C_{16}H_{27}N_3O_4$	B	794	87
45	Et	*i*-Pr	Cl	119-121	EtOAc	35	$C_{16}H_{26}ClN_3O_3$	A	1757	63

[a] Overall yield, based on phenol. [b] See footnote *b*, Table I. [c] See footnote *c*, Table I. [d] C: calcd, 54.6; found, 54.1. [e] H: calcd, 7.8; found, 7.3. [f] C: calcd, 48.3; found, 48.8.

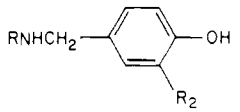
Table IV. 1-(4-Ureidoethylphenoxy)-3-amino-2-propanols



No.	R	R_1	R_2	Mp, °C	Crystn solvent	Yield,[a] %	Emp formula[b]	Dose, μg/kg, giving 50% inhibn of tachycardia[c]	Inhibn, %, of depressor response[c]
46	H	*i*-Pr	H	74-76	EtOAc	13	$C_{15}H_{25}N_3O_3$	101	47
47	Me	*i*-Pr	H	104-106	EtOAc	37	$C_{16}H_{27}N_3O_3$	193	399
48	Me	*i*-Pr	Br	98-100	EtOAc	28	$C_{16}H_{26}BrN_3O_3 \cdot 0.25H_2O$	880	97
49	Et	*i*-Pr	H	118-120	EtOAc	20	$C_{17}H_{29}N_3O_3$	1751	51
50	*n*-Pr	*i*-Pr	H	126-128	EtOAc	39	$C_{18}H_{31}N_3O_3 \cdot 0.25H_2O$	65	19
51	*n*-Pr	*t*-Bu	H	96-98	EtOAc	62	$C_{19}H_{33}N_3O_3 \cdot 0.25H_2O$	266	27
52	*n*-Pr	*i*-Pr	OMe	124-126	EtOAc	20	$C_{19}H_{33}N_3O_4$	867	6
53	*n*-Bu	*i*-Pr	H	114-116	EtOAc	10	$C_{19}H_{33}N_3O_3$	515	0
54	Practolol							167	8

[a] Overall yield, based on phenol. [b] See footnote *b*, Table I. All compounds were prepared by method A, see Experimental Section. [c] See footnote *c*, Table I.

Table V. 4-(Acylaminomethyl- and ureidomethyl)phenol Intermediates



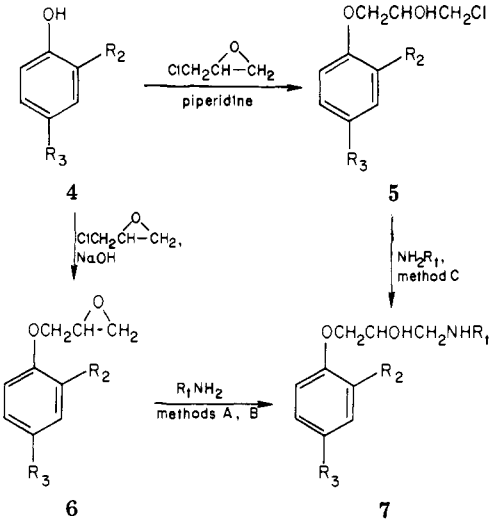
No.	R	R_2	Mp, °C	Crystn solvent	Yield, %	Emp formula[a]	Method of prepn
1	EtCO-	OEt	124-126	EtOAc	62	$C_{12}H_{17}NO_3$	E
2	*i*-PrCO-	OMe	118-120	EtOAc	35	$C_{12}H_{17}NO_2$[c]	E
3	n-$C_6H_{13}CO$-	Cl	88	EtOAc-petr ether[b]	53	$C_{14}H_{20}ClNO_2$	F
4	NH_2CO-	H	200-202	H_2O	61	$C_8H_{10}N_2O_2 \cdot 0.25H_2O$	D
5	NH_2CO-	OMe	174-176	H_2O	97	$C_{19}H_{12}N_2O_3$	D

[a] See footnote *b*, Table I. [b] Bp 60-80 °C. [c] N: calcd, 6.2; found, 5.6.

standard methods, and three typical preparations (D–F) are described in the Experimental Section. Many of the phenols were isolated as oils and most were used without further purification. Table V lists those which were crystalline solids and have satisfactory analytical data. The starting phenols that are novel are also described in the Experimental Section.

Pharmacology. β-Adrenoceptor blocking potency (ED_{50}) was estimated in vivo using the previously described cat preparation.[8] The results given in Tables I and II are expressed as the total dose, infused over a period of 30 min, causing 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 μg/kg 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 long units (i.e., a mean error of approximately 30%). The level of partial agonist activity was measured in rats depleted of catecholamines by pretreatment with syrosingopine and anesthetized with pentobarbital according to the method described by Barrett and Carter.[9] A standard dose of 2.5 mg/kg of compound was administered by intravenous injection and the increase in heart rate in beats per minute (BPM) was recorded.

Scheme I[a]



[a] R, R_1, R_2 have values shown in Tables I-IV; R_3 = $-CH_2NHCOR$, $-(CH_2)_xNHCONHR$ (x = 1 or 2)

Discussion

The purpose of this work was to observe the effect on potency, selectivity, and partial agonist activity of a methylene or ethylene bridge interposed between the aromatic ring and the acylamino and ureido moities used in our previous series of cardioselective β-blockers.[5,6]

Inspection of the data in Tables I–IV shows that, in general, the compounds in this series are less potent and less selective in their action on the isoproterenol-induced tachycardia and vascular response than the analogous parent compounds. Thus only compounds **8**, **12**, **22**, and **40** are comparable in both potency and selectivity with practolol **54**.

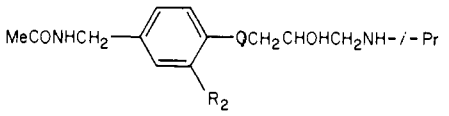
The amino substituent R_1 was limited, with the exception of compound **11**, to *i*-Pr and *t*-Bu groups which have shown optimum activity in our previous series. A comparison of seven pairs of analogous compounds, **8**, **9**; **15**, **16**; **19**, **20**; **23**, **24**; **25**, **26**; **40**, **41**; and **49**, **50**, substituted with *i*-Pr and *t*-Bu groups shows a random distribution in potency between these groups. The *i*-Pr group, however, appears to confer a greater selectivity of action than the *t*-Bu group, as shown by the smaller effects that it had on the depressor response.

An ortho substituent (R_2) favors potency and correlates well with the π value of the substituent, a finding observed in our previous series. Thus in Table VI potency can be seen to increase with the lipophilicity of R_2 and to be independent of its steric bulk, while selectivity of action is reduced.

The substituent on the para amidic moiety (R in the generic structures **2** and **3**) is, however, sensitive to steric bulk, with small groups being preferred for maximal potency. Thus, the increase in steric bulk of the amide substituent from a methyl group to an ethyl group reduces potency (cf. compounds **15** and **23**, **8** and **17**, **12** and **19**, **14** and **22**, and **13** and **21**). A similar reduction in potency can also be seen by increasing the length of the methylene bridge by the introduction of a further methylene moiety or an imino moiety (cf. compounds **12**, **43**, and **48**). These findings suggest that there is limited accommodation at the β-adrenergic receptor site for para substituents on the aryl ring.

Many of the compounds of general formula **2** (Tables I and II) were examined for partial agonist activity in rats which had been depleted of catecholamines. The results show that para-substituted compounds are devoid of this activity while the ortho-substituted analogues **32** and **33** possess a significant level of activity. This lack of partial agonist activity when a methylene bridge is interposed between an amide moiety and the aromatic ring of a β-blocking agent is in accordance with the finding made with atenolol,[2] which has a similar methylene bridge. No compound in this series, however, was found to have an overall pharmacological profile comparable to that of atenolol. Compounds of general formula **3** (Tables III and IV) were not of sufficient interest to merit examination in this test.

Table VI



No.	R_2	Dose, μg/kg, giving 50% inhibn of tachycardia[a]	Inhibn, %, of depressor response[a]	π[b]	MR[b]
15	OMe	312	5	−0.33	6.5
8	H	142	0	0	0
12	Br	83	5	0.84	7.6
14	$CH_2CH=CH_2$	35	61	1.10[c]	14.49[c]
13	*n*-Pr	40	51	1.85	14.0

[a] See Pharmacology for description of method. [b] See ref 10. [c] See ref 11.

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.

Method A. 3-Isopropylamino-1-(2-methoxy-4-propionamidomethylphenoxy)-2-propanol (23). A mixture of 2,3-epoxy-1-(2-methoxy-4-propionamidomethylphenoxy)propane (4.0 g, 0.015 mol), *i*-$PrNH_2$ (25 mL, 0.29 mol), and MeOH (25 mL) was heated under reflux for 3 h. The mixture was then evaporated under reduced pressure and the residue was crystallized from EtOAc: yield 1.4 g (29%); mp 108 °C.

Method B. 1-(2-Bromo-4-propionamidomethylphenoxy)-3-isopropylamino-2-propanol (19). A mixture of 1-(2-bromo-4-propionamidomethylphenoxy)-2,3-epoxypropane (2.0 g, 0.006 mol) and *i*-$PrNH_2$ (20 mL, 0.23 mol) was stirred at room temperature for 16 h. The mixture was evaporated to dryness and the residue was stirred with 2 N HCl (25 mL) and Et_2O (25 mL). The acidic phase was separated, basified with 11 N NaOH, and extracted twice with EtOAc (50 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was crystallized from EtOAc: yield 0.35 g (14%); mp 116 °C.

Method C. 1-Isopropylamino-3-(4-propionamidomethylphenoxy)-2-propanol (17). A mixture of 3-chloro-1-(4-propionamidomethylphenoxy)-2-propanol (3.4 g, 0.0125 mol), *i*-$PrNH_2$ (25 mL, 0.33 mol), and *n*-PrOH (25 mL) was heated under reflux for 18 h. The mixture was evaporated under reduced pressure and the residue was dissolved in 2 N HCl (25 mL) and extracted twice with Et_2O (25 mL). The acid phase was separated, basified with 11 N NaOH, and extracted twice with EtOAc (50 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was crystallized from EtOAc: yield 0.8 g (21%); mp 106–108 °C.

Method D. 2-Bromo-4-ureidomethylphenol. A solution of KCNO (4.45 g, 0.05 mol) in H_2O (20 mL) was added to a solution of 3-bromo-4-hydroxybenzylamine (11.95 g, 0.05 mol), in H_2O (75 mL), and the mixture was stirred at room temperature for 18 h and then filtered. The solid residue was crystallized from H_2O: yield 9.3 g (75%); mp 187–189 °C. Anal. ($C_8H_9BrN_2O_2$) C, H, N.

Method E. 4-Propionamidomethylphenol. A mixture of 4-hydroxybenzaldoxime (54.8 g, 0.4 mol), EtOH (300 mL), propionic anhydride (156 mL, 12.0 mol), and 5% Pd/C (5.5 g)

was hydrogenated at room temperature and atmospheric pressure until there was no further uptake of hydrogen. The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc (200 mL) and the solution was extracted with 2 N Na_2CO_3 (200 mL) and then washed with H_2O (200 mL). The EtOAc phase was dried ($MgSO_4$) and evaporated under reduced pressure and the residue was crystallized from a mixture of equal volumes of EtOAc and petroleum ether (bp 80–100 °C): yield 24 g (33.7%); mp 94–06 °C. Anal. ($C_{10}H_{13}O_2N$) C, H, N.

Method F. 4-Acetamidomethyl-2-chlorophenol. A mixture of 3-chloro-4-hydroxybenzylamine hydrochloride (4.9 g, 0.025 mol), H_2O (50 mL), NaOH (1.0 g, 0.025 mol), and acetic anhydride (10.0 mL, 0.1 mol) was heated on a steam bath for 4 h. The mixture was evaporated to dryness and the residue was dissolved in 2 N NaOH (25 mL) and then poured onto a mixture of ice and 11 N HCl (10 mL). The mixture was filtered and the solid residue washed with water and dried: yield 4.4 g (90%); mp 150 °C. Anal. ($C_9H_{10}ClNO_2$) C, H, N.

***N*-(4-Allyloxybenzyl)propionamide.** A mixture of 4-propionamidomethylphenol (7.1 g, 0.04 mol), allyl bromide (3.52 mL, 0.04 mol), acetone (100 mL), and K_2CO_3 (5.52 g, 0.04 mol) was heated under reflux with stirring for 6 h. The mixture was then filtered and evaporated to dryness under reduced pressure and the residue was stirred with ether (50 mL) and 1 N NaOH (50 mL). The ether phase was separated, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was crystallized from petroleum ether (bp 80–100 °C): yield 2.7 g (31%); mp 80–82 °C. Anal. ($C_{13}H_{17}NO_2$) C, H, N.

2-Allyl-4-propionamidomethylphenol. *N*-(Allyloxybenzyl)propionamide (2.5 g, 0.011 mol) was heated at 220 °C for 40 min, cooled, and dissolved in 1 N NaOH (20 mL). The solution was extracted twice with ether (20 mL), and the aqueous phase was acidified and extracted twice with ether (25 mL). The ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the solid residue was crystallized from petroleum ether (bp 80–100 °C): yield 1.5 g (62%); mp 86–88 °C. Anal. ($C_{13}H_{17}NO_2$) C, H, N.

2-*n*-Propyl-4-propionamidomethylphenol. A mixture of 2-allyl-4-propionamidomethylphenol (2.2 g, 0.01 mol), EtOH (50 mL), and 5% Pd/C (0.3 g) was hydrogenated at atmospheric pressure and room temperature until there was no further uptake of hydrogen. The mixture was filtered, the filtrate was evaporated to dryness, and the residue crystallized from a mixture of equal volumes of EtOAc and petroleum ether (bp 60–80 °C): yield 1.6 g (72%); mp 117–118 °C. Anal. ($C_{13}H_{19}NO_2$) C, H, N.

3-Chloro-4-hydroxybenzylamine Hydrochloride. A solution of 4-hydroxybenzylamine (8.0 g, 0.05 mol) in HOAc (200 mL) was cooled to 10 °C and a rapid stream of anhydrous Cl_2 was passed through the solution for 10 min. The mixture was filtered and the solid residue was washed with ether: yield 4.5 g (46%); mp 244–246 °C. Anal. ($C_7H_9Cl_2NO$) C, H, N.

3-Bromo-4-hydroxybenzylamine Hydrobromide. A solution of 4-hydroxybenzylamine (8.0 g, 0.05 mol) in HOAc (400 mL) was cooled to 10 °C and a solution of Br_2 (2.75 mL, 0.05 mol) in HOAc (100 mL) was added dropwise, with stirring, over 30 min. The mixture was evaporated under reduced pressure to a volume of 300 mL and cooled until the product crystallized. The mixture was filtered and the solid residue was crystallized from a mixture of equal volumes of ethanol and ether: yield 4.0 g (28%); mp 262 °C dec. Anal. ($C_7H_9Br_2NO$) C, H, N.

Acknowledgment. The author wishes to thank Mr. D. Griffiths and Mrs. E. Hadley for their expert technical assistance, Dr. J. D. Fitzgerald and Mr. J. Carter for providing the biological data, and Mr. C. J. Howarth for providing the analytical data.

References and Notes

(1) Tenormin is a trademark, the property of Imperial Chemical Industries Ltd.
(2) A. M. Barrett, J. Carter, J. D. Fitzgerald, R. Hull, and D. Le Count, *Br. J. Pharmacol.*, **48**, 3408 (1973).
(3) L. H. Smith, U.K. Patent 1 311 521 (1973).
(4) L. H. Smith, U.K. Patent 1 433 592 (1976).
(5) A. F. Crowther, R. Howe, and L. H. Smith, *J. Med. Chem.*, **14**, 511 (1971).
(6) L. H. Smith, *J. Med. Chem.*, **20**, 705 (1977).
(7) (a) A. F. Crowther and L. H. Smith, *J. Med. Chem.*, **11**, 1009 (1968); (b) A. F. Crowther, D. J. Gilman, B. J. McLoughlin, L. H. Smith, R. W. Turner, and T. M. Wood, *ibid.*, **12**, 638 (1969); L. H. Smith, *ibid.*, **19**, 1123 (1976).
(8) J. D. Fitzgerald and S. R. O'Donnell, *Br. J. Pharmacol.*, **43**, 222 (1971).
(9) A. M. Barrett and J. Carter, *Br. J. Pharmacol.*, **40**, 373–381 (1970).
(10) F. E. Norrington, R. M. Hyde, S. G. Williams, and R. Wootton, *J. Med. Chem.*, **18**, 604 (1975).
(11) C. Hansch and A. Leo, Computer Listing of Parameter Values, Pomona Medicinal Chemistry Project, Pomona College, Claremont, Calif.

Adrenergic Agents. 7.[1] Synthesis and β-Adrenergic Agonist Activity of Several 2-Pyridylethanolamines

Timothy Jen, James S. Frazee, Mark S. Schwartz, Carl Kaiser,*

Department of Chemistry

Donald F. Colella, and Joe R. Wardell, Jr.

Department of Biological Sciences, Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101. *Received October 28, 1976*

In a search for new selective bronchodilators, three 2-pyridylethanolamines, i.e., 2-*tert*-butylamino-1-(5-hydroxy-2-pyridyl)ethanol (**2b**), a related 6-methylsulfonylmethyl (**2c**), and a 6-methyl (**2d**) derivative, were prepared. These compounds were examined for potential bronchodilator activity in an in vitro test for relaxation of guinea pig tracheal tissue. Potential cardiac stimulant activity was evaluated in vitro by measuring changes in the rate of spontaneously beating guinea pig right atrial muscle. Comparison of potency in the tracheal test relative to that in the atrial procedure provides a measure of selectivity. Results of this study indicate that replacement of the phenyl ring of a para-hydroxylated phenylethanolamine with a 2-pyridyl system generally results in compounds which retain a high order of potency in the tracheal test; however, selectivity for tracheobronchial vs. cardiac tissue is markedly greater for the pyridyl derivatives. The α-picoline, 2-*tert*-butylamino-1-(5-hydroxy-6-methyl-2-pyridyl)ethanol (**2d**), which bears labile protons at a position meta to the ethanolamine side chain, was about equipotent with the corresponding 6-unsubstituted relative **2b**. The reason for the failure of these apparently appropriately located labile protons to enhance β-adrenoreceptor agonist activity is uncertain.

In previous publications, we described that replacing the *m*-hydroxyl group in isoproterenol with a ureido or methylsulfonylmethyl group led to potent and selective β_2-adrenergic receptor agonists as exemplified by carbuterol