a series of agonists of membranes of the turkey erythrocyte containing mainly β-adrenoceptors.[36] Since the K_D values for pure isomers were available in a few cases only and our calculations were made for a definite configuration, we have used for correlations "corrected values", i.e., those given for the racemic mixture divided by two. This is justified, however, only for low receptor concentrations.[37]

Acknowledgment. One of the authors (I.L.) thanks the Slovenian Research Council for a postdoctoral fellowship.

(36) The formulas for metaraminol and ephedrine in ref 14 are incorrect. The K_D for PI 39 (9.7 μm) differs by a factor of 10 from what is given in a second paper[35] (0.97 μm). We have accepted the first value, but this does not affect the qualitative conclusion.

(37) G. Crippen, *J. Med. Chem.*, **24**, 198 (1981).

β-Adrenergic Blocking Agents. 24. Heterocyclic Substituted 1-(Aryloxy)-3-[[(amido)alkyl]amino]propan-2-ols

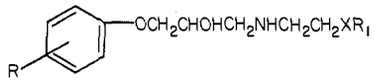
M. S. Large and L. H. Smith*

Imperial Chemical Industries PLC, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England.
Received December 28, 1981

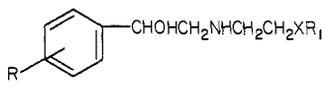
The synthesis of a series of 1-(aryloxy)-3-[[(amido)alkyl]amino]propan-2-ols where either the aryl moiety is heterocyclic or the amidic group is substituted by a heterocyclic moiety is described. Several of the compounds were more potent than propranolol when given intravenously to anesthetized rats. In contrast to previous findings with β-blockers based on heterocyclic moieties and with either an isopropylamino or *tert*-butylamino substituent on the side chain, several compounds proved to be cardioselective when further examined in anesthetized cats. The detailed structure–activity relationships shown by this series of compounds are discussed.

Heterocyclic moieties have been a structural feature of β-blockers for some considerable time; thus, pindolol[1] and timolol[2] are well-established β-blockers, and carazolol[3] and bufuralol[4] have undergone extensive clinical evaluation. All four compounds have either an isopropylamino or a *tert*-butylamino substituent on the side chain; none are cardioselective.

In earlier papers,[5-7] we have described the synthesis and structure–activity relationships of β_1-cardioselective blocking agents that incorporate an amidic moiety (X) into the side chain of an (aryloxy)propanolamine, **1**, or an arylethanolamine, **2**.



1

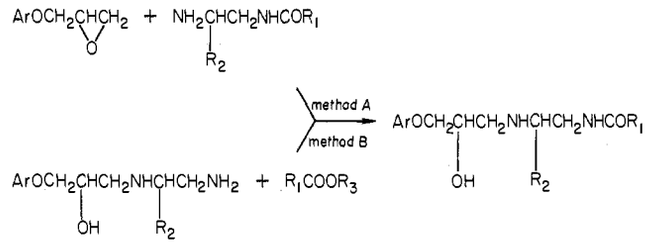


2

3, X = NHCO, NHCONH, $NHSO_2$

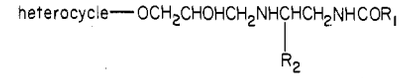
As an extension of this work, we considered it of interest to synthesize a further series of (aryloxy)propanolamines

Scheme I[a]

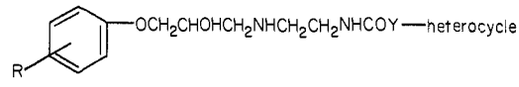


[a] Ar is a phenyl or heterocyclic moiety, R_1 relates to the substituents described in Tables I and II, R_3 is a suitable ester substituent, and R_2 is either a hydrogen atom or a methyl group.

in which either the aryl ring or the substituent R_1 in the above generic structure **1** is replaced by a heterocyclic moiety to give **4** and **5**, respectively.



4



5

We report here the β-blocking potency of these compounds in rats; some were also tested for β_1 cardioselectivity in cats.

Chemistry. The compounds listed in Tables I and II were synthesized by methods A and B illustrated in Scheme I.

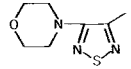
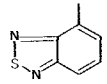
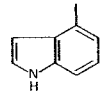
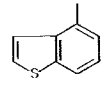
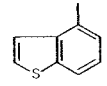
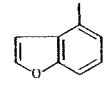
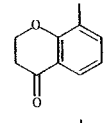
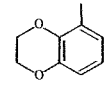
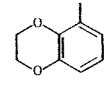
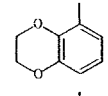
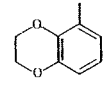
Method A was the most frequently used procedure, since it is widely applicable for the variants Ar and R_1. Method B is particularly useful when R_1 is a complex heterocycle. The designation C in the tables refers to a separately described method of preparation. The amidoalkylamine

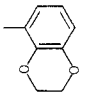
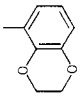
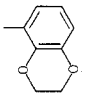
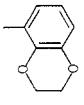
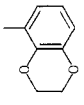
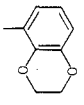
(1) J. F. Guidicelli, H. Schmidt, and J. R. Boissiers, *J. Pharmacol. Exp. Ther.* **1969**, *168*, 116.
(2) A. Seriabine, M. L. Torchiana, J. M. Stavorski, C. T. Ludden, D. H. Minsker, and C. A. Stone, *Arch. Int. Pharmacodyn. Ther.* **1973**, *205*, 76.
(3) W. Bartsch, K. Kietman, H. Leinert, and G. Spuner, *Arzneim.-Forsch.* **1977**, *27*, 1022.
(4) T. C. Hamilton and N. W. Parkes, *Arzneim.-Forsch.* **1977**, *27*, 1410.
(5) M. S. Large and L. H. Smith, *J. Med. Chem.* **1980**, *23*, 112.
(6) M. S. Large and L. H. Smith, *J. Med. Chem.*, **1982**, *25*, 1286.
(7) L. H. Smith, *J. Appl. Chem. Biotechnol.* **1978**, *28*, 201.
(8) J. D. Fitzgerald and S. R. O'Donnell, *Br. J. Pharmacol.* **1971**, *43*, 221.

0022-2623/82/1825-1417$01.25/0

Table I

heterocycle—$OCH_2CHOHCH_2NHCHCH_2NHCOR_1$ (with R_2 on the CH)

no.	heterocycle	R_2	R_1	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, mg/kg, giving 50% inhibn of tachycardia in rat
6		H	*i*-C_3H_7	158–160	EtOH–H_2O	17	$C_{12}H_{21}N_3O_3S \cdot C_2H_2O_4$	C, H, N	A	0.35
7		H	*i*-C_3H_7	194–196	EtOH	13	$C_{15}H_{27}N_5O_4S \cdot C_2H_2O_4$	C, H, N	A	0.17
8		H	*i*-C_3H_7	173–174	EtOH	28	$C_{15}H_{22}N_4O_3S$	C, H, N	A	10.00
9		H	*i*-C_3H_7	168–171	EtOH	7	$C_{17}H_{25}N_3O_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$	C, H, N	A	0.02
10		H	*i*-C_3H_7	121–123	EtOAc	19	$C_{17}H_{24}N_2O_3S$	C, H, N	C	0.5
11		H	NHC_6H_5	192–193	EtOH	10	$C_{20}H_{23}N_3O_3S \cdot C_2H_2O_4 \cdot 0.25H_2O$	C, H, N	A	5.0
12		H	NHC_6H_5	188–190	EtOH	8	$C_{20}H_{23}N_3O_4 \cdot 0.5C_2H_2O_4$	C, H, N	A	1.0
13		H	NHC_6H_5	184	EtOH	5	$C_{21}H_{25}N_3O_5 \cdot 0.5C_2H_2O_4 \cdot 0.25H_2O$	C, H, N	A	5.8
14		H	4-OH-C_6H_4	189–190	EtOH	26	$C_{20}H_{24}N_2O_6 \cdot C_2H_2O_4$	C, H, N	C	0.15
15		H	$CH_2C_6H_5$	114–116	toluene	9	$C_{21}H_{26}N_2O_5$	C, H, N	A	1.5
16[b]		CH_3	$CH_2C_6H_5$	93–94	EtOAc	20	$C_{22}H_{28}N_2O_5 \cdot 0.25H_2O$	C, H, N	A	0.03
17		H	4-NHCONHCH$_3$-C_6H_4	115–117	MeCN	15	$C_{23}H_{30}N_4O_6$	C, H, N	B	0.02

18		H	4-$COCH_3$-C_6H_4	129–131	EtOH	36	$C_{23}H_{28}N_2O_7 \cdot HCl \cdot H_2O$	C, H, N	B	0.2
19		H	4-NO_2-C_6H_4	162–164	EtOH	27	$C_{21}H_{25}N_3O_8$	C, H, N	B	0.74
20		H	4-NH_2-C_6H_4	200–202	EtOH	30	$C_{21}H_{27}N_3O_6 \cdot 2HCl$	C, H, N	C	1.2
21		H	2-$CH_2CH{=}CH_2CH_2OC_6H_4$	87–90	EtOAc	18	$C_{24}H_{30}N_2O_6 \cdot C_2H_2O_4 \cdot 0.75H_2O$	C, H, N	A	10.0
22		H	NHC_6H_5	154–155	EtOH	11	$C_{20}H_{25}N_3O_5$	C, H, N	A	0.5
23		H		165–167	MeCN	12	$C_{18}H_{22}N_2O_5S \cdot C_2H_2O_4$	C, H, N	A	a

[a] Examined in cat only. [b] Presumed to be a mixture diastereoisomers.

precursors used in method A were made by acylating an alkylenediamine with the appropriate ester or acid chloride, and the Experimental Section describes a typical acylation procedure and three amidic alkylamines that are novel.

Discussion

The majority of the compounds presented in Tables I and II were examined for potency in the rat preparation, described under "Pharmacology" in the Experimental Section; data for propranolol and practolol have been included at the end of Table II for comparison purposes. Seven compounds (**22**, **23**, **27**, **32**, **34**, **36**, and **42**) were examined for potency and selectivity in the cat preparation. Of these, three compounds, i.e., **22**, **32**, and **42**, were examined in both rat and cat preparations, and their relative potencies are similar in both species. This observation is in accord with our findings in a previous series.[1]

Table I lists 18 compounds, 10 of which have a 1,4-benzodioxanyl moiety as the aromatic nucleus, since this proved to be a readily accessible nucleus for examining structure–activity relationships at R_1. In addition, previous experience with conventional isopropylamino β-blockers showed this nucleus to give high potency.[9] The rat data confirmed our expectations; thus, compounds **14** and **16–18** have similar potency to propranolol (**45**). Within this series, **14–22**, we found it surprising that the benzamides **14** and **17–20** were more potent than the phenylacetamide **15** or the phenoxyacetamide **21**, two substituents that conferred high potency in our previous work.[2] Branching at R_2 with a methyl substituent led to a substantial increase in potency (compare **15** and **16**), an effect that we have observed in an eariler series.[1]

The remaining compounds in Table I are derived from heterocycles other than 1,4-benzodioxan. The most potent of these compounds, the indole **9**, is 10 times more potent than propranolol (**45**), while the thiazole **6** and the thiadiazole **7** have similar potencies to **45**. The three compounds, **11–13**, with phenylurea as the amidic group are all less potent than the analogous benzodioxan **22**.

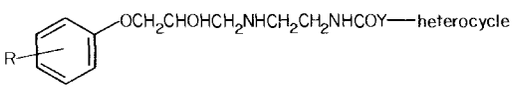
Table II describes those compounds in which the heterocycle is attached to the amidic function either by a direct link or by a methylene group. The compounds with a direct link are all less potent than propranolol **45**. Of the four heterocyclic amides (**24**, **27**, **37**, and **40**) that are unsubstituted in the phenoxy ring, the thiophene derivative is the most potent. Substitution in the ortho or meta positions of the phenoxy ring of a series of furoamides (**25–29**) gives less potent compounds than the parent **24**. The replacement of the phenoxy group in **24** by 1-naphthyloxy to give **30** also leads to a decrease in potency.

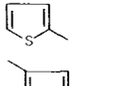
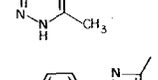
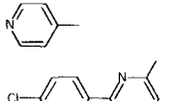
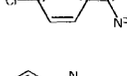
In marked contrast, four of the six compounds derived from heterocyclic acetic acids (**33**, **39**, **42**, and **44**) were more potent than propranolol (**45**). A comparison of the indole acetamide **42** and the indole carboxamide **41** shows the former to be approximately 70 times more potent than the latter.

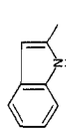
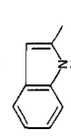
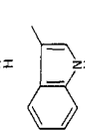
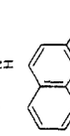
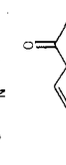
The seven compounds listed in Table III were tested for potency and cardioselectivity in the cat preparation. All were cardioselective, with compounds **22**, **34**, **36**, and **42** showing a higher degree of cardioselectivity than practolol (**46**), and, with the exception of **34**, these four compounds were all more potent than practolol (**46**). One bis-heterocyclic compound (**23**) that has a 1,4-benzodioxanyl ring as the nucleus and a 2-thienyl substituent on the

(9) A. F. Crowther, R. Howe, B. J. McLoughlin, K. B. Mallion, B. S. Rao, L. H. Smith, and R. W. Turner, *J. Med. Chem.* **1972**, *15*, 260.

Table II



no.	heterocycle	Y	R	mp, °C	crystn solvent	yield, %	emp formula	anal.	method of prepn	dose, mg/kg, giving 50% inhibn of tachycardia in rat
24		D[a]	H	154–156	EtOH	15	$C_{16}H_{20}N_2O_4 \cdot C_2H_2O_4 \cdot 0.25H_2O$	C, H, N	A	1.0
25		D	2-CH_3	183–184	EtOH–H_2O	37	$C_{17}H_{22}N_2O_4 \cdot C_2H_2O_4$	C, H, N	A	1.3
26		D	3-CH_3	170–171	EtOH	30	$C_{17}H_{22}N_2O_4 \cdot C_2H_2O_4$	C, H, N	A	4.0
27		D	2-CN	168–170	EtOH	19	$C_{17}H_{19}N_3O_4 \cdot 0.5C_2H_2O_4$	C, H, N	A	6.0
28		D	2-I	203–204	EtOH–H_2O	19	$C_{16}H_{19}IN_2O_4 \cdot 0.5C_2H_2O_4$	C, H, N	A	2.3
29		D	2-$OCH_2CH{=}CH_2$	123–125	EtOH–MeCN	22	$C_{19}H_{24}N_2O_5 \cdot C_2H_2O_4 \cdot 0.5H_2O$	C, H, N	A	3.0
30		D	2,3-CH=CHCH=CH	209–211	EtOH–H_2O	18	$C_{20}H_{22}N_2O_4 \cdot C_2H_2O_4$	C, H, N	A	6.5
31		D	2-OH	176–178	EtOH–H_2O	68	$C_{16}H_{24}N_2O_5 \cdot C_2H_2O_4$	C, H, N	C	2.2
32		D	H	169–171	EtOH	3	$C_{16}H_{20}N_2O_3S \cdot C_2H_2O_4$	H, N; C[c]	A	0.38
33		CH_2	2-CN	157–158	MeCN	41	$C_{18}H_{21}N_3O_3S$	C, H, N	B	0.04
34		D	2-$CONH_2$	189–190	EtOH	33	$C_{17}H_{21}N_3O_4S$	C, H, N	A	6.0
35		D	2-CN	160–161	EtOH	38	$C_{17}H_{21}N_5O_3$	C, H, N	B	5.6
36		CH_2	2-CN	113–114	EtOH	20	$C_{23}H_{23}ClN_4O_3S$	C, H, N	B	6.0
37		D	H	154–156	*i*-PrOH	4	$C_{17}H_{21}N_3O_3 \cdot C_2H_2O_4$	C, H, N	A	0.5
38		CH_2	2-CN	195–197	MeOH–H_2O	26	$C_{25}H_{26}ClN_5O_4 \cdot 0.5C_2H_2O_4$	C, H, N	B	10.0
39		CH_2	2-Cl	123–126	MeOH	10	$C_{20}H_{23}ClN_4O_3 \cdot 2C_2H_2O_4$	C, H, N	B	0.05

40		D	H	144–145	EtOAc	17	$C_{20}H_{23}N_3O_3$	C, H, N	A	10.0
41		D	2-CN	163–165	EtOH	26	$C_{21}H_{22}N_4O_3 \cdot C_2H_2O_4$	C, H, N	A	10.0
42		CH_2	2-CN	200–202	EtOH–H_2O	26	$C_{22}H_{24}N_4O_3 \cdot 0.5C_2H_2O_4$	C, H, N	B	0.14
43		D	2-CN	179–180	H_2O	17	$C_{22}H_{22}N_4O_3 \cdot C_2H_2O_4 \cdot 0.25H_2O$	C, H, N	B	10.0
44		CH_2	2-CN	171–173	MeOH	37	$C_{24}H_{26}N_4O_5 \cdot 0.25H_2O$	C, H, N	B	0.1
45	propranolol									0.2
46	practolol									0.5

[a] Direct link. [b] C: calcd, 52.7; found, 52.1.

Table III. β-Blocking Potency and Cardioselectivity in Cats

no.	dose, μg/kg, giving 50% inhibn of tachycardia in cat	% inhibn of depressor response
22	111	0
23	702	40
27	272	28
32	104	28
34	461	0
36	87	0
42	49	6
45	62	85
46	167	8

amidic moiety was synthesized; it had poor potency and moderate cardioselectivity when tested in the cat preparation.

In summary, our studies show that the incorporation of a heterocyclic ring into a 1-(aryloxy)-3-[[(amido)alkyl]-amino]propan-2-ol, either replacing the aryl group or as the amidic substituent, can lead to potent and, in some instances, highly cardioselective β-adrenoreceptor blocking agents.

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 HA 100D or a Varian A60 with tetramethylsilane as the internal standard and were consistent with the assigned structures.

3-[(2-Isobutyramidoethyl)amino]-1-(thiazol-2-yloxy)-propan-2-ol (6) Hydrogen Oxalate. Method A. A mixture of 1-(thiazol-2-yloxy)-2,3-epoxypropane[10] (1.1 g, 0.007 mol), *N*-(2-aminoethyl)isobutyramide[11] (0.91 g, 0.007 mol), and *i*-PrOH (40 mL) was refluxed for 4 h and then evaporated to dryness. The residue was partitioned between 1 N HOAc and EtOAc, and the aqueous phase was separated and neutralized with $NaHCO_3$. The mixture was extracted with ethyl acetate, and the extract was dried and evaporated to dryness. A solution of the residue in Me_2CO was added to a solution of oxalic acid in Me_2CO, and the precipitated oxalate was collected and recrystallized from EtOH–H_2O: yield 0.45 g (17%); mp 158–160 °C dec.

3-[[2-(2-Thien-2-ylacetamido)ethyl]amino]-1-(2-cyanophenoxy)propan-2-ol (33). Method B. An intimate mixture of 3-[(2-aminoethyl)amino]-1-(2-cyanophenoxy)propan-2-ol[6] (2.35 g, 0.01 mol) and ethyl 2-(thien-2-yl)acetate (1.7 g, 0.01 mol) was heated at 100 °C for 18 h. The cooled mixture was crystallized from MeCN: yield 1.48 g (41%); mp 159–160 °C.

3-[(2-Isobutyramidoethyl)amino]-1-(benzothien-4-yloxy)propan-2-ol (10). A solution of 1-chloro-2,3-epoxypropane (4.6 g, 0.05 mol) in *i*-PrOH (10 mL) was added over 0.5 h to a solution of *N*-(2-aminoethyl)isobutyramide[11] (6.5 g, 0.05 mol) in *i*-PrOH, and the resulting solution was kept at room temperature for 18 h. The solution was added to a solution of oxalic acid in EtOAc, and the precipitated solid was collected and recrystallized from EtOH to give *N*-[[2-[(3-chloro-2-hydroxypropyl)amino]-ethyl]amino]isobutyramide hydrogen oxalate: yield 5.5 g (35%); mp 129–130 °C. Anal. ($C_9H_{19}ClN_2O_2 \cdot C_2H_2O_4$) C, H, N.

A mixture of 4-hydroxybenzothiophene[12] (1.5 g, 0.01 mol), *N*-[[2-[(3-chloro-2-hydroxypropyl)amino]ethyl]amino]isobutyramide hydrogen oxalate (3.12 g, 0.01 mol), NaOH (1.6 g, 0.04 mol),

(10) A. P. Roszkowski, A. M. Strosberg, L. M. Miller, J. A. Edwards, B. Berkoz, G. S. Lewis, O. Halpern, and J. H. Fried, *Experentia* **1972**, *28*, 1336.
(11) L. H. Smith, U.K. Patent 145516 (1976).
(12) L. F. Fiser and R. G. Kennelly, J. *Am. Chem. Soc.* **1935**, *57*, 1611.

H_2O (5 mL), and *i*-PrOH (50 mL) was refluxed for 18 h and then evaporated to dryness. The residue was partitioned between H_2O and $CHCl_3$, the $CHCl_3$ phase was dried and evaporated to dryness, and the residue was crystallized from EtOAc: yield 0.65 g (19%); mp 121–123 °C.

3-[[2-(4-Hydroxybenzamido)ethyl]amino]-1-[(1,4-benzodioxan-5-yl)oxy]propan-2-ol Hydrogen Oxalate (14). A solution of 3-[[2-[4-(benzyloxy)benzamido]ethyl]amino]-1-[(1,4-benzodioxan-5-yl)oxy]propan-2-ol oxalate (1.7 g, 0.0032 mol) in HOAc (40 mL) was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure. The mixture was diluted with water (40 mL) and then filtered, and the filtrate was evaporated to dryness. The residue was crystallized from EtOH: yield 0.4 g (26%); mp 189–190 °C.

The 3-[[2-[4-(benzyloxy)benzamido]ethyl]amino]-1-[(1,4-benzodioxan-5-yl)oxy]propan-2-ol oxalate used as starting material was prepared by method A: yield 38%; mp 187–189 °C (EtOH). Anal. ($C_{20}H_{24}N_2O_6 \cdot C_2H_2O_4$) C, H, N.

3-[[2-[(4-Aminophenoxy)acetamido]ethyl]amino]-1-[(1,4-benzodioxan-5-yl)oxy]propan-2-ol Dihydrochloride (20). A solution of 19 (1.3 g, 0.0029 mol) in EtOH was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in MeCN, and the solution was acidified with a solution of HCl in Et_2O. The precipitated hydrochloride was collected and crystallized from EtOH: yield 0.5 g (30%); mp 200–202 °C.

3-[[2-(2-Tetrahydrofuramido)ethyl]amino]-1-(2-hydroxyphenoxy)propan-2-ol Hydrogen Oxalate (31). A solution of 3-[[2-(2-furamido)ethyl]amino]-1-[2-(benzyloxy)phenoxy]-propan-2-ol (1.05 g, 0.0025 mol) in EtOH (40 mL) was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure until uptake of hydrogen was complete. The mixture was filtered, and the filtrate was evaporated to dryness. A solution of the residue in MeCN was added to a solution of oxalic acid in MeCN, and the precipitate was collected and recrystallized from EtOH–H_2O: yield 0.7 g (68%); mp 176–178 °C.

The 3-[[2-(2-furamido)ethyl]amino]-1-[2-(benzyloxy)phenoxy]propan-2-ol used as starting material was prepared by method A: yield 30%; mp 84–85 °C (EtOAc–cyclohexane). Anal. ($C_{23}H_{26}N_2O_5$) C, H, N.

***N*-(2-Aminoethyl)thien-2-ylcarboxamide Hydrogen Oxalate.** A mixture of ethyl 2-thiophenecarboxylate (15.6 g, 0.1 mol) and ethylenediamine (24 g, 0.4 mol) was heated at 100 °C for 18 h, cooled, and then diluted with water (250 mL). The mixture 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 precipitate was collected and recrystallized from EtOH: yield 10.5 g (40%); mp 175–177 °C. Anal. ($C_7H_{10}N_2OS \cdot C_2H_2O_4$) C, H, N. *N*-(2-Aminoethyl)furan-2-ylcarboxamide hydrochloride [mp 155–159 °C (EtOH). Anal. ($C_7H_{10}N_2O_2 \cdot HCl$) C, H, N] and *N*-(2-aminoethyl)pyridine-4-carboxamide dihydrochloride [mp 263–265 °C (EtOH). Anal. ($C_8H_{11}N_3O \cdot 2HCl$) C, H. N] were prepared in a similar manner with the appropriate ester.

Pharmacology. We measured β-adrenoceptor blocking potency in vivo using a rat preparation, and some compounds were examined in the previously described cat preparation.[8] 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 was recorded. A saline solution of the compound under investigation was injected subcutaneously at four different doses, 10, 1.0, 0.1, and 0.01 mg, groups of four rats being used for each dose level. The rats were then anesthetized in a similar manner to the control group; 30 min later, they were challenged with 0.1 μg/kg of isoproterenol, and the heart rate was recorded. The percentage blockade of the isoproterenol response for each dose level was calculated as follows:

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

From these results a dose–response curve was constructed, and from this the ED_{50} values quoted in the tables were calculated. 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., mean error of approximately 25–30% for each experiment). The results from the cat preparation given in Table III are the estimated dose, infused over a period of 30 min, which would cause a 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 μg/kg dosed iv). The estimated degree (percent) of blockade of the vasodepressor response at that dose level is also given. Three to five dose levels of each compound were used to calculate these estimates. The relative potencies in these two systems give an indication of selectivity for β-1 (cardiac) as opposed to β-2 (vascular) receptors. Mean log ED_{50}'s were calculated for each compound on the basis of two or three tests, and the standard errors of the means were computed. On average, these mean values had an error of 30%. Previous data[11] has 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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