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β-Adrenergic Blocking Agents. 18. 1-(Aryloxy)-3-(arylthioalkylamino)propan-2-ols and 1-Substituted Alkylthioamino-3-(aryloxy)propan-2-ols

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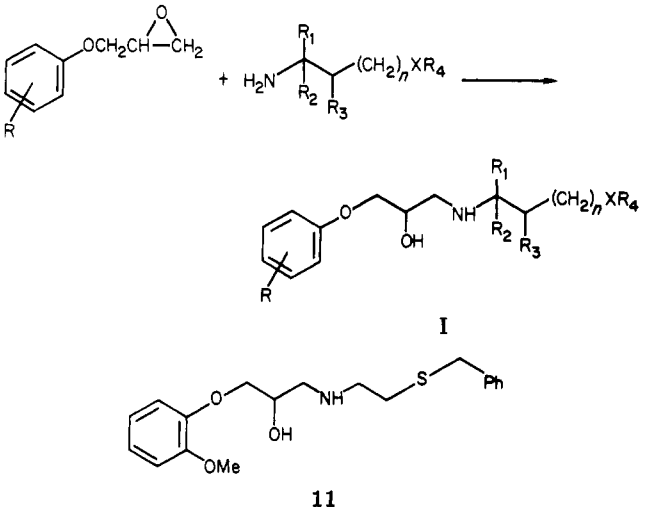
The synthesis is described of a series of derivaties of 1-(aryloxy)-3-(arylthioalkylamino)propan-2-ols and 1-(alkylthioamino)- and 1-(aralkylamino)-3-(aryloxy)propan-2-ols. These compounds were investigated for their β-adrenoreceptor blocking properties and their selectivity of action for the cardiac β_1 receptor. The structure–activity relationships are discussed with particular reference to the effects of the sulfur, sulfoxide, and sulfone groups on β-adrenoreceptor blocking potency and selectivity.

In an earlier publication[1] we discussed the structural features of β-adrenergic receptor antagonists which confer selectivity for the cardiac β_1 receptor compared to the vascular β_2 receptor and, in particular, we showed that in a series of general structure I, where X = O, it was this oxygen atom which played the major role in determining the cardioselectivity. In an extension of these studies we have investigated the influence of the group X in structure I on β-adrenoreceptor blocking potency and cardioselectivity and report here our findings for a series of compounds in which X is the sulfur, sulfoxide, or sulfone moiety.[2] In general, these compounds show a high degree of selectivity for the cardiac β_1 receptor although their potency overall is lower than that of the corresponding oxygen series. A closely related compound, the benzylthioethylamino derivative **11**, has already been described by a Parke Davis group as part of their work on the radioprotective actions of 2-aminoethanethiol derivatives, but no cardiovascular data were reported.[3]

Chemistry. The compounds were prepared by the previously described method[4] of reacting a 1,2-epoxy-3-substituted phenoxypropane with the appropriate amine as shown in Scheme I. Where the amine used was nonvolatile some difficulty was experienced in removing the excess amine from the reaction mixture, but it was found that the lipophilic secondary amine was extracted into the chloroform phase on partitioning of the reaction mixture between hydrochloric acid and chloroform while the primary amine remained in the aqueous phase. A typical preparation is given in the Experimental Section. The various substituted arylthio-, alkylthio-, and aralkylthioalkylamines and oxidized analogues were prepared

Scheme I[a]



I

11

[a] See tables for R, R_1, R_2, R_3, and R_4.

by standard synthetic routes and representative syntheses of novel amines used are described in the Experimental Section.

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

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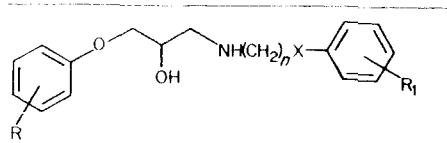
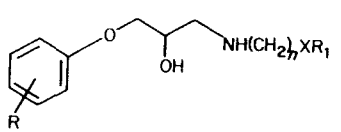
Table I



no.	R	R_1	*n*	X	mp, °C	salt	crystn solvent	yield,[a] %	emp formula	analyses	dose, μg/kg, giving 50% inhibn of tachycardia[b]	inhibn, %, of depressor response
1	H	H	2	S	85–86.5	base	cyclohexane	13	$C_{17}H_{21}NO_2S$	C, H, N, S	138	13
2	H	H	2	SO	103–104.5	base	EtOAc	6	$C_{17}H_{21}NO_3S$	C, H, N	44	0
3	H	H	2	SO_2	118–120	base	EtOAc	18	$C_{17}H_{21}NO_4S$	C, H, N	1329	53
4	H	H	3	S	155–158	HCl	*i*-PrOH	14	$C_{18}H_{24}ClNO_2S$	C, H, N	415	
5	2-Me	H	2	S	71.5–73.5	base	cyclohexane	3	$C_{18}H_{23}NO_2S$	C, H, N	1553	53
6	2-Me	H	2	SO	173–175	$(COOH)_2$	MeOH	22	$C_{20}H_{25}NO_7S$	C, H, N	799	54
7	2-Me	H	3	S	95–100	HCl	EtOAc–cyclohexane	10	$C_{19}H_{26}ClNO_2S$	C, H, N	NA	
8	3-Me	H	2	S	176–178	$(COOH)_2$	MeOH	13	$C_{20}H_{25}NO_6S$	C, H, N	NA	
9	2-Cl	H	2	S	168–169	$(COOH)_2$	MeOH	2	$C_{19}H_{22}ClNO_6S$	C, H, N, S	1463	0
10	2-CN	H	2	S	151–153	$(COOH)_2$	EtOH	11	$C_{20}H_{22}N_2O_6S$	C, H, N	NA	
11	2-MeO	H	2	S	169–170	$(COOH)_2$	MeOH–H_2O	19	$C_{20}H_{25}NO_7S$	C, H, N	NA	
12	4-MeO	H	2	S	82–92	base	EtOH	8	$C_{18}H_{23}NO_3S$	C, H, N	NA	
13	H	4-Cl	2	S	98.5–99.5	base	EtOAc	31	$C_{17}H_{20}ClNO_2S$	C, H, N, S	NA	
14	H	4-Cl	2	SO	116–119	base	EtOAc	5	$C_{17}H_{20}ClNO_3S$	C, H, N	90	0
15	H	4-Me	2	S	83.5–85.5	base	EtOAc–cyclohexane	21	$C_{18}H_{23}NO_2S$	C, H, N	289	43
16	H	4-Me	2	SO	125–128	base	EtOAc	3	$C_{18}H_{23}NO_3S$	C, H, N	121	13
17	H	4-Me	3	S	149–152	HCl	MeOH–EtOAc	29	$C_{19}H_{26}ClNO_2S$	C, H, N	1264	11
18	2-NO_2	4-Me	3	S	93–97	HCl	EtOAc	16	$C_{19}H_{25}ClN_2O_4S$	C, H, N	NA	
19	H	2-MeO	2	S	189–192	$(COOH)_2$	MeOH–H_2O	3	$C_{20}H_{25}NO_7S$	C, H, N, S	482	24

[a] Yield based on epoxide. [b] NA indicates that the compound was inactive when dosed at 200 μg/kg/min for 30 min.

Table II

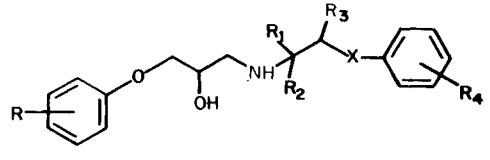


no.	R	R_1	*n*	X	mp, °C	salt	crystn solvent	yield,[a] %	emp formula	analyses	dose, μg/kg, giving 50% inhibn of tachycardia[c]	inhibn, %, of depressor response
26	H	Et	2	S	130–131.5	HCl	MeOH–Et_2O	11	$C_{13}H_{22}ClNO_2S$	C, H, N	332	0
27	H	Et	2	SO	154–156	$(COOH)_2$	EtOH–Et_2O	3	$C_{15}H_{23}NO_7S \cdot 0.5H_2O$	C, H, N	195	10
28	H	Et	3	S	175–177	$(COOH)_2$	MeOH–EtOH	6	$C_{16}H_{25}NO_6S$	C, H, N	838	14
29	2-CN	Et	2	S	138–139	0.5$(COOH)_2$	MeOH–Et_2O	7	$C_{15}H_{21}N_2O_4S \cdot 0.25H_2O$	C, H, N	200	
30	2-CN	Et	3	S	120–122	$(COOH)_2$	MeOH–EtOAc	4	$C_{17}H_{24}N_2O_6S$	C, H, N	135	0
31	2-NO_2	Et	2	S	64.5–67.5	base	petr ether[d]–Et_2O	24	$C_{13}H_{20}N_2O_4S$	C, H, N	NA	
32	2-NO_2	Et	3	S	142.5–145	$(COOH)_2$	MeOH–EtOAc	26	$C_{16}H_{24}N_2O_8S$	C, H, N	130	12
33	4-NO_2	Et	3	S	60–64	base	Et_2O	7	$C_{14}H_{22}N_2O_4S$	C, H, N	NA	

34	2-Cl	Et	3	S	oil	base		3	$C_{14}H_{22}ClNO_2S$		269	52
35	2-Br	Et	3	S	137–139.5	$(COOH)_2$	EtOH–Et_2O	1	$C_{16}H_{24}BrNO_6S$	C, H, N	212	0
36	2-MeO	Et	3	S	129.5–132.5	$(COOH)_2$	MeOH–EtOAc	3	$C_{17}H_{27}NO_7S$	C, H, N	285	70
37	4-MeO	Et	3	S	127–130	$(COOH)_2$	MeOH–EtOAc	12	$C_{17}H_{27}NO_7S$	C, H, N	NA	
38	2-allyl	Et	3	S	146–149	$(COOH)_2$	EtOH–Et_2O	3	$C_{19}H_{29}NO_6S$	C, H, N	720	65
39	2-propyl	Et	3	S	147–149	$0.5(COOH)_2$	EtOH	8	$C_{18}H_{30}NO_4S$	C, H, N	NA	
40	4-CH_2-$CONH_2$	Et	3	S	139–143	base	H_2O	29	$C_{16}H_{26}N_2O_3S$	C, H, N	NA	
41	4-NH-COMe	Et	3	S	168.5–171	HCl	EtOAc	8	$C_{16}H_{27}ClN_2O_3S$	C, H, N	NA	
42	H	cyclohexyl	2	S	108–110	HCl	EtOAc	32	$C_{17}H_{28}ClNO_2S$	C, H, N	162	0
43	H	cyclohexyl	3	S	149–151	$(COOH)_2$	EtOH–Et_2O	13	$C_{20}H_{31}NO_6S \cdot 0.25H_2O$	C, H, N	781	37
44	H	cyclohexyl	3	SO	125–127.5	$(COOH)_2$	EtOH–Et_2O	18	$C_{20}H_{31}NO_7S \cdot 0.5H_2O$	C, H, N	162	68
45	2-NO_2	cyclohexyl	2	S	140–143	$0.5(COOH)_2$	EtOH	33	$C_{18}H_{27}N_2O_6S$	C, H, N	427	37
46	2-NO_2	cyclohexyl	3	S	138–141	$(COOH)_2$	EtOAc	27	$C_{20}H_{30}N_2O_8S \cdot 0.25H_2O$	C, H, N	NA	
47	2-NO_2	cyclohexyl	3	SO	100–103	$(COOH)_2$	EtOH–Et_2O	56	$C_{20}H_{30}N_2O_9S \cdot 0.5H_2O$	C, H, N	NA	
48	2-NO_2	cyclohexyl	3	SO_2	131–133	$(COOH)_2$	EtOH	13	$C_{20}H_{30}N_2O_{10}S$	C, H, N	1457	75
49[b]	H	CH_2Ph	2	S	160–161	$(COOH)_2$	EtOH–MeOH	1	$C_{20}H_{25}NO_6S \cdot 0.5H_2O$	C, H, N	207	
50	H	CH_2Ph	2	SO	149–151	$(COOH)_2$	MeOH	6	$C_{20}H_{25}NO_7S \cdot 0.5H_2O$	C, H, N, S	156	20
51	2-NO_2	CH_2Ph	2	S	117–120	base	EtOAc	41	$C_{18}H_{22}N_2O_4S$	C, H, N	946	0
52	2-Me	CH_2Ph	2	S	106–108	HCl	EtOAc	5	$C_{19}H_{26}ClNO_2S$	C, H, N, S	NA	
53	2-Cl	CH_2Ph	2	S	124–126	HCl	EtOAc	14	$C_{18}H_{22}ClNO_2S$	C, H, Cl, N	NA	
54	H	$CH_2C(Me_2)$-CH_2CH_3	3	S	149–152	$(COOH)_2$	EtOH–Et_2O	14	$C_{19}H_{31}NO_6S$	C, H, N	83	0
55	H	*i*-Pr	3	S	147–149	$(COOH)_2$	$Me_2C{=}O$	5	$C_{17}H_{27}NO_6S$	C, H, N	333	0
56	tolamolol										133	81

[a] Yield based on epoxide. [b] Kindly provided by Dr. M. Wharmby. [c] NA indicates that the compound was inactive when dosed at 200 μg/kg/min for 30 min. [d] Bp 60–80 °C.

Table III



no.	R	R_1	R_2	R_3	R_4	X	mp, °C	salt	crystn solvent	yield,[a] %	emp formula	analyses	dose, μg/kg, giving 50% inhibn of tachycardia	inhibn, %, of depressor response
20	H	H	Me	H	H	S	77–80	$(COOH)_2$	EtOAc	1	$C_{20}H_{25}NO_6S$	C, H, N	16	0
21	H	Me	Me	H	H	S	95–98	$(COOH)_2$	EtOH–Et_2O	4	$C_{21}H_{27}NO_6S \cdot 0.5H_2O$	C, H, N, S	65	40
22	H	Me	Me	H	H	SO	90–94	$(COOH)_2$	EtOH–Et_2O	3	$C_{21}H_{27}NO_7S$	C, H, N	185	84
23	H	Me	H	Me	H	S	138–140	$(COOH)_2$	EtOH–Et_2O	2	$C_{21}H_{27}NO_6S$	C, H, N	195	32
24	H	H	H	Me	H	S	159–162	$(COOH)_2$	MeOH–Et_2O	6	$C_{20}H_{25}NO_6S$	C, H, N	559	18
25	2-Cl	H	Me	H	H	S	77–79	$(COOH)_2$	EtOAc	2	$C_{20}H_{24}ClNO_6S$	C, H, N, S	58	60

[a] Yield based on epoxide.

these two systems give some indication of selectivity for β_1 (cardiac) as opposed to β_2 (vascular) receptors. Mean log ED_{50} values 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%.

Discussion

For convenience the compounds can be divided into two main groups, namely, the arylthioalkylamines and the alkylthioalkylamines. In some respects the factors influencing biological activity mirror those found in the oxygen series. Thus for the arylthioalkylamines (Table I), ortho substituents, R, decreased potency, e.g., **5–7**, **9–11**, but with the exception of **5**, cardioselectivity was retained. Substituents R_1 both in the ortho (compound **19**) and para positions (compounds **13–17**) reduce potency with, for the most part, retention of cardioselectivity.

In the alkylthioalkylamine series (Table II), however, the influence of the ortho substituent, R, depends on the length of the alkyl chain linking the sulfur and nitrogen atoms, i.e., the value of n; when n = 2 an ortho R group had a detrimental effect on potency (compare **26** with **31** and **42** with **45**) (the *o*-cyano analogue **29** is exceptional in this respect) and the same holds true for the aralkyl series, e.g., **51–53**. The active compounds, however, were still cardioselective. On the other hand, when n = 3, the potency is improved by ortho substitution e.g., compare **28** with **30**, **32**, **34**, **36**, and **38** (**46** is an exception), but there is a variable effect on cardioselectivity which is difficult to explain given the relatively small number of substances studied. This is in contrast to the findings in the oxygen series, structure I (X = O), where for n = 3, ortho substitution led to a reduction in potency. In the arylthioalkylamines, the optimum value for n is 2 (compare **1** with **4**, **5** with **7**, and **15** with **17**). In both series substitution in the para position resulted in a complete loss of activity, e.g., **12**, **33**, **37**, **40**, and **41**. The one example with a meta substituent, **8**, was also inactive.

Another variable which had a considerable effect on potency in the alkylthioalkylamine series was the nature of the group R_1 (Table II). Thus, when n = 2 the cyclohexyl compounds were more potent than the corresponding ethyl compounds (compare **26** with **42**, **31** with **45**), while the opposite is true when n = 3 (compare **32** with **46**) (**28** and **43** are virtually equipotent). The best activity was found when R_1 is branched, e.g., **54** and **55**. With the exception of **43**, the active compounds in this group were cardioselective.

Compounds with branched alkyl chains linking the sulfur and nitrogen atoms are shown in Table III. Compounds in which R_2 is alkyl showed improved potency (compare **1** with **20**, **21** and **9** with **25**). The sulfoxide **22**, however, is less potent than its thio analogue but this could be due to steric overcrowding. Branching on both the α- and β-carbon atoms dropped potency (**23**) and there was a considerably larger drop in potency for branching at the β-atom alone (**24**). *gem*-Dimethyl substitution α to the nitrogen atom gave nonselective compounds, whereas the other α-branched analogues were cardioselective with the exception of **25**.

In general, the sulfoxide analogues were considerably more potent than the corresponding sulfur compounds and they were cardioselective (compare **1** with **2**, **5** with **6**, **13** with **14**, **15** with **16**, **26** with **27**, **43** with **44**, and **49** with **50**). As mentioned earlier, the *gem*-dimethyl analogue **22** is not selective. Of the two sulfones prepared, the aryl sulfone **3** was less potent than its parent sulfur compound **1**, whereas the cyclohexyl sulfone **48** exhibited marginal activity compared to its inactive sulfur analogue **46**. Neither sulfone showed selectivity for the cardiac β_1 receptor.

A comparison of the biological properties of the sulfur and sulfoxide compounds with their corresponding oxygen analogues, which were described in an earlier publication,[1] shows that the sulfur compounds are much less potent than their oxygen analogues, whereas the sulfoxides are roughly equipotent.

Thus compound **1** is less potent than **2** which is equipotent with its oxygen analogue (ED_{50} = 54) and, similarly, compound **13** is inactive but the sulfoxide **14** is as potent as its oxygen analogue (ED_{50} = 80). All of these active compounds were cardioselective. The sulfones generally showed only marginal activity.

In conclusion, this study has shown that compounds of structure I in which X = S or SO exhibit good cardioselectivity. However, compounds where X = S are less potent than the corresponding oxygen analogues. This drop in potency is unlikely to be due solely to the increased steric bulk of the sulfur atom since compounds with the even bulkier sulfoxide groups are generally equipotent with the oxygen analogues. Thus, it is evident from our structure–activity relationships that the nature of the group X in structure I plays a significant role in determining both potency and cardioselectivity, and this is in agreement with our previously reported findings.

Experimental Section

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 and IR data were consistent with the structures. NMR spectra were recorded either on a Varian HA-100 or a Varian A-60 using tetramethylsilane as the internal standard. IR spectra were recorded on a Perkin-Elmer 157 infrared spectrophotometer.

Preparation of 1-(3-Methylphenoxy)-3-(2-phenylthioethylamino)propan-2-ol Oxalate (8). A mixture of 1-(3-methylphenoxy)-2,3-epoxypropane (1.2 g, 0.007 mol), 2-(phenylthio)ethylamine hydrochloride (3.0 g, 0.016 mol), and triethylamine (3 mL) in 50 mL of aqueous 2-propanol (10:1) was heated under reflux for 5 h. The mixture was evaporated to dryness and the residue was partitioned between excess dilute 2 N hydrochloric acid and chloroform (25 mL). The chloroform layer was separated and evaporated to dryness. The residue was partitioned between dilute 2 N hydrochloric acid (25 mL) and ether (25 mL). The acid layer was basified with dilute sodium hydroxide and extracted three times with chloroform (25 mL each time). The chloroform extracts were dried over anhydrous magnesium sulfate. Removal of the solvent gave an oil which was converted into its oxalate salt with ethereal oxalic acid. The crude oxalate was crystallized from methanol to give 1-(3-methylphenoxy)-3-(2-phenylthioethylamino)propan-2-ol oxalate: yield 0.4 g (13%); mp 176–178 °C. Anal. [$C_{18}H_{23}NO_2S \cdot (COOH)_2$] C, H, N.

1-Methyl-2-(phenylthio)propylamine (57). A solution of thiophenol (12.4 g, 0.112 mol), 3-aminobutan-2-ol (10.0 g, 0.112 mol), and propionic acid (8.3 g, 0.112 mol) in benzene (15 mL) was heated under reflux for 12 h, the water formed during the reaction being continuously removed. The mixture was cooled and the *N*-(1-methyl-2-phenylthiopropyl)propionamide was filtered off: yield 11.8 g (55%); mp 88.5–90 °C. Anal. ($C_{13}H_{19}NOS$) C, H, N.

A mixture of *N*-(1-methyl-2-phenylthiopropyl)propionamide (11.8 g, 0.05 mol) and concentrated hydrochloric acid (50 mL) was heated under reflux for 15 h, cooled, basified with aqueous sodium hydroxide solution, and extracted with chloroform (3 × 75 mL). The chloroform extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amine, yield 8.3 g, a sample of which was converted into its hydrochloride salt with ethereal HCl and crystallized from an ethyl acetate–ethanol

mixture to give 1-methyl-2-(phenylthio)propylamine hydrochloride, mp 138–140 °C. Anal. ($C_{10}H_{16}ClNS$) C, H, N.

1,1-Dimethyl-2-(phenylsulfinyl)ethylamine (58). 1,1-Dimethyl-2-(phenylthio)ethylamine hydrochloride (1.1 g, 0.005 mol) was added in one portion to an ice-cold stirred solution of sodium periodate (1.1 g, 0.005 mol) in aqueous methanol (30 mL, 1:1). The reaction mixture was stirred at ambient temperature for 48 h and filtered. The filtrate was concentrated under reduced pressure and the residue was basified with aqueous NaOH and extracted with chloroform (3 × 50 mL). The chloroform extracts were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was converted into its oxalate salt with ethereal oxalic acid and was crystallized from an EtOAc–EtOH mixture to give 1,1-dimethyl-2-(phenylsulfinyl)ethylamine oxalate: yield 1.2 g (37%); mp 221–223 °C. Anal. [$C_{10}H_{15}NOS\cdot(COOH)_2$] C, H, N.

Using this method there was also prepared 2-(4-chlorophenylsulfinyl)ethylamine hydrochloride (**59**) [mp 157–158.5 °C; yield 53%. Anal. ($C_8H_{10}ClNOS\cdot HCl$) C, H, N] and 2-(4-methylphenylsulfinyl)ethylamine oxalate (**60**) [mp 174–176 °C; yield 70%. Anal. [$C_9H_{13}NOS\cdot(COOH)_2\cdot 0.5H_2O$] C, H, N].

3-(Cyclohexylthio)propylamine (61). A solution of sodium methoxide (prepared from 4.6 g of sodium in 80 mL of methanol) was added dropwise over 60 min to a stirred solution of 3-bromopropylamine hydrobromide (21.9 g, 0.1 mol) and cyclohexanethiol (11.6 g, 0.1 mol) in methanol (80 mL) maintained at −15 °C. The reaction mixture was then stirred at −10 °C for 30 min and allowed to warm to room temperature. Stirring was continued for a further 16 h. The methanol was distilled off and the residue was stirred with ether (200 mL) and filtered. The ether was evaporated off under reduced pressure and the residue was treated with ethereal HCl to give hygroscopic 3-(cyclohexylthio)propylamine hydrochloride, yield 18.3 g (88%).

A sample of the hydrochloride was converted into the free base and treated with ethereal oxalic acid to give the oxalate salt which was crystallized from aqueous MeOH: mp 151–153 °C. Anal. [$C_9H_{19}NS\cdot(COOH)_2$] C, H, N.

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Synthesis and Hypotensive Activity of *N*-Alkyl-*N''*-cyano-*N'*-pyridylguanidines

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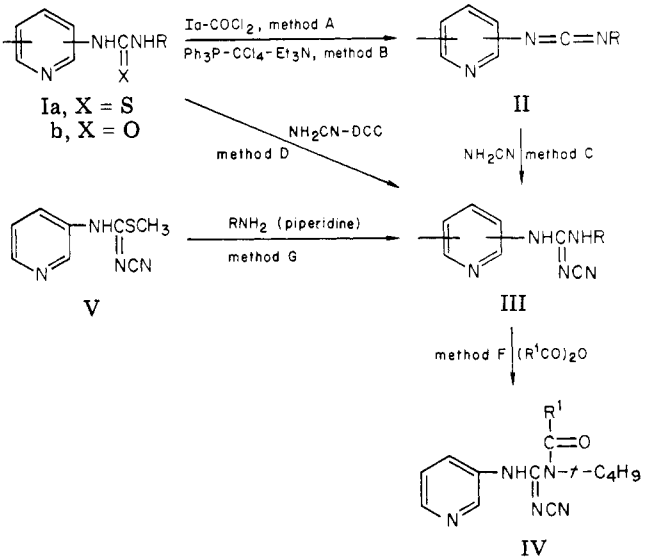
A variety of *N*-alkyl-*N'*-pyridyl-*N''*-cyanoguanidines III was prepared as potential bioisosteres of hypotensive *N*-alkyl-*N'*-pyridylthioureas Ia. Optimal activity of the N,N'-disubstituted cyanoguanidines III was associated with the presence of four to seven carbon branched alkyl and 3- or 4-pyridyl groups. Maximum potency was displayed by *N-tert*-pentyl-*N'*-3-pyridyl-*N''*-cyanoguanidine (**20**). This compound proved to be 200 times more potent than the corresponding thiourea in hypertensive rats and dogs. In comparison with guancydine, which is the de-3-pyridyl analogue of **20**, a 150-fold increase of potency in spontaneously hypertensive rats was obtained with **20** and its *tert*-butyl analogue **19**. The observed activity appears to be due to direct vascular relaxation. On a weight basis compounds **19**, **20**, **50**, and **101** compared favorably with hydralazine.

Several years ago we synthesized a series of *N*-alkyl-*N'*-2-, 3-, and 4-pyridylthioureas[1] Ia (Scheme I) which were found to have pronounced hypotensive activity in rats and dogs.[2] The hypotensive effect of *N-tert*-pentyl-*N'*-3-pyridylthiourea was comparable to that of hydralazine. Urea analogues Ib (Scheme I) were less potent. With the objective of increasing the potency and improving on the therapeutic ratio found with the thioureas, we were led to consider potentially bioisosteric replacements. Our previous finding that the cyanoimino group can function as a biological equivalent of carbonyl oxygen as part of the 6-carboxamide group of penicillins[3] encouraged us to prepare a number of cyanoguanidines[1] III (Scheme I). Meanwhile, a similar approach to molecular modification of gastric antisecretory *N*-imidazolylalkyl-*N'*-alkylthioureas has resulted in a promising cyanoguanidine, cimetidine.[4,5] The appreciation of the structural relation of the title compounds to guancydine, *N*-cyano-*N'*-*tert*-pentylguanidine, drew our attention to an earlier study, evaluating guancydine as the most active antihypertensive compound of a group of monosubstituted *N*-alkyl-*N'*-cyanoguanidines.[6] It was reported that slight structural modification, such as methylation of the unsubstituted amino group, leads to loss of activity. Therefore, it was of interest to assess the activity of the cyanoguanidines III as derivatives of guancydine.

Scheme I



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