obtained at 750 μg/rat. The Sar residue consists of a Gly residue in which the α-NH is methylated; it lacks an asymmetric α-carbon. Alkylation of the α-NH moiety of the residue in position 3 may be one factor contributing to the potency of inhibition of ovulation.

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Synthesis of Heteroaromatic Potential β-Adrenergic Antagonists by the Glycidol Route[1]

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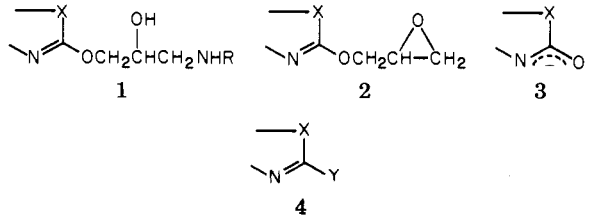
The synthesis of several 3-alkylamino-2-hydroxypropyl heteroaryl ethers (**13**–**15**, **17**, and **18**) is described. These compounds were prepared by the alkylamination of the corresponding glycidyl ethers (**6**–**8**, **10**, and **11**), which in turn were obtained from the requisite heteroaryl halides and the sodium salt of glycidol. The above basic ethers exhibited β-blocking activity, but the potency of the tested compounds was considerably less than that of propanolol. Only 3-*tert*-butylamino-2-hydroxyl-1-(1,2,4-thiadiazol-5-yl) propyl ether (**13**) showed some selective myocardial β-blocking activity.

Aromatic compounds in which are incorporated the 1-alkylamino-2-hydroxypropoxy moiety are frequently found to elicit β-adrenergic antagonist activity in vivo.[2] In view of the known[3] myocardial selectivity of 1-alkylamino-3-(2-thiazolyloxy)-2-propanols, it became of interest to determine if this feature, particularly selective myocardial β-blockade, could be found in other heteroaromatic ethers of type **1** where X = O, S, NC_6H_5, or =CH and R = isopropyl or *tert*-butyl.

Chemistry. The synthesis of compounds of type **1** is usually accomplished by the alkylamination of the corresponding glycidyl ethers **2**, which in turn can be obtained from a salt of the oxo compound **3** and an epihalohydrin, provided that alkylation of this ambident anionic system occurs on oxygen.[4] In the event that alkylation of **3** takes place on nitrogen (as is certainly the case for thiazolin-2-ones,[5] 1,2,4-oxadiazolin-5-ones,[6] 1,2,4-thiadiazolin-5-ones,[7] and 1-substituted tetrazol-5-ones[7]), then it is possible to prepare the glycidyl ether **2** via a four-step synthesis from **4** (Y = Cl, Br, etc.) and a salt of glycerol acetonide.[3] It has now been found that the glycidyl ethers **2** can be prepared *in one step* from **4** and glycidol, provided that the nucleophilic displacement of Y occurs easily and that conditions are followed which avoid or minimize the base-induced destruction[8] of glycidol. For example, a solution of the compound to be alkylated (see Table I) and glycidol, in a suitable solvent, was added *slowly* to a suspension of sodium hydride in the same solvent. The crucial aspect of this process is that the concentration of the sodium salt of glycidol is maintained at a low level and thus the self-polymerization thereof is largely averted. The yields of the glycidyl ethers were, in general, satifactory, although on occasion the isolation of a pure product from the reaction mixture was difficult. In those cases (compounds **5**–**7**, Table I) it was expedient to convert the crude epoxide directly into the desired amino compound (see Table II). For the examples cited herein, the overall yields of the amino alcohols (Table II) were equivalent to, or better than, those obtained by the glycerol acetonide route.



The reaction of *tert*-butylamine with the glycidyl ether **9** gave 3-phenyl-5-*tert*-butylamino-1,2,4-oxadiazole (**16**) instead of the required amino alcohol. A similar dis-

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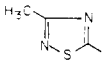
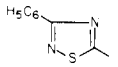
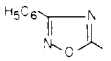
Table I. Yields and Physical Constants of Some Heteroaromatic Glycidyl Ethers

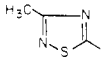
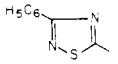
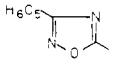
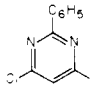
$ArX^a \rightarrow ArOCH_2CH\text{-}CH_2$ (O)

Ar	Compd	Mp, °C	Crystn solvent	% yield	Formula	Analyses
	5	Oil		*b*	$C_6H_7NO_2S$[c]	
	6	Oil		78[d]	$C_5H_6N_2O_2S$	*b*
	7	Oil		75[d]	$C_6H_8N_2O_2S$	*b*
	8	32.5	CH_2Cl_2-hexane	39	$C_{11}H_{10}N_2O_2S$	C, H, N, S
	9	36-38	Hexane	62	$C_{11}H_{10}N_2O_3$	C, H, N
	10	83-84	Hexane	80	$C_{13}H_{11}ClN_2O$	C, H, N
	11	83-84	Pentane	62	$C_{10}H_{10}N_4O_2$	C, H, N

[a] Compounds 5 and 6 were prepared from the bromides; all of the others were synthesized from the aryl chlorides. 2-Bromothiazole and 1-phenyl-5-chlorotetrazole were commercially available (Aldrich). 5-Bromo-1,2,4-thiadiazole,[10a] 3-methyl-5-chloro-1,2,4-thiadiazole,[10b] 3-phenyl-5-chloro-1,2,4-thiadiazole,[10b] 3-phenyl-5-chloro-1,2,4-oxadiazole,[10c] and 2-phenyl-4,6-dichloropyrimidine[10d] were prepared by literature procedures. [b] The epoxide was used without purification in the next step. [c] Known compound, see ref 2b. [d] Crude yield. The NMR spectrum indicated a purity of >90%.

Table II. Yields and Physical Properties of Some Heteroaryloxy Amino Alcohols

$ArOCH_2\underset{OH}{CH}CH_2NHR^a$

Ar	Compd	Mp, °C	Crystn solvent	% yield	Formula	Analyses
	12	160-162[b,c]	MeOH-acetone	17[d]	$C_9H_{17}ClN_2O_2S$[e]	
	13	148[c]	2-Propanol-ether	63	$C_9H_{18}ClN_3O_2S$	C, H, N
	14	149[c]	2-Propanol	89	$C_{10}H_{20}ClN_3O_2S$	C, H, N
	15	123	Pentane	61	$C_{15}H_{21}N_3O_2S$	C, H, N
	16	83-85[f]	Hexane	83[f]	$C_{12}H_{15}N_3O$	C, H, N[f]
	17	115-116	CH_2Cl_2-ether	35[g]	$C_{16}H_{20}ClN_3O_2$[e]	C, H, N
	18	156-158[c]	Acetone	20[g]	$C_{14}H_{22}ClN_5O_2$	C, H, N

[a] R = *tert*-butyl unless specified otherwise. [b] Reported[2b] mp 163–164 °C. [c] Hydrochloride salt. [d] Overall yield from 2-bromothiazole. [e] R = isopropyl. [f] Yield, melting point, and analysis refer to 2-phenyl-5-*tert*-butylamino-1,2,4-oxadiazole. [g] Several unidentified products were obtained in this reaction. See Experimental Section.

placement reaction in the 1,2,4-oxadiazole series has been reported by Moussebois and Eloy.[9]

The direct alkylation of glycidol has several important synthetic implications which are not encompassed by this study.

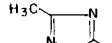
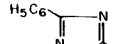
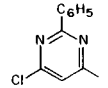
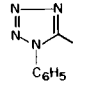
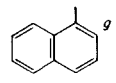
Structure–Activity Relationships. The β-blocking activities of the heteroaromatic β-adrenergic antagonists are listed in Table III. The data indicate that these compounds exhibit weak β-blocking activity in comparison to propanolol. Only compound **13** exhibited some selective myocardial β-blocking activity in that the heart rate response to isoproterenol was inhibited at a much lower dose level than that which inhibited the diastolic blood pressure response. Compounds **14**, **15**, **17**, and **18** exhibited general β-blocking activity. The incorporation of methyl or phenyl groups in the 3 position of the thiadiazole moiety (compounds **14** and **15**) decreased activity. The phenylpyrimidyl compound **17** exhibited so little β-blocking activity that it was not possible to accurately quantify it at the dose levels administered.

Experimental Section

All melting points were determined in a Mel-Temp apparatus and are uncorrected. Elemental analyses, indicated by symbols

Table III. Pharmacological Activity of Heteroaromatic Potential β-Adrenergic Antagonists

OH
ArOCH$_2$CHCH$_2$NHR

Ar	R	Compd	N^f	% inhibn of isoproterenol HR response at dose, mg/kg					% inhibn of isoproterenol DBP response at dose, mg/kg					ED_{50} (HR),[a] mg/kg	ED_{50} (DBP),[b] mg/kg
				0.1	0.42	1.42	4.58	14.58	0.1	0.42	1.42	4.58	14.58		
	*t*-Bu	13	2	23.5 ± 6.5	49.5 ± 8.5	70.0 ± 2.0	91.0 ± 1.0	97.5 ± 0.5	3.0 ± 3.0	1.0 ± 1.0	13.5 ± 11.5	50.0 ± 2.0	76.5 ± 1.5	0.4 ± 0.1	5.7 ± 1.3
	*t*-Bu	14	4	15.0 ± 4.9	24.2 ± 8.4	39.5 ± 13.4	59.8 ± 15.3	92.3 ± 2.0	7.7 ± 5.0	12.8 ± 4.4	35.5 ± 14.1	55.5 ± 6.0	85.3 ± 4.6	3.6 ± 2.6	3.5 ± 1.0
	*t*-Bu	15	4	7.0[c] ± 4.4	5.7 ± 3.0	9.5 ± 3.6	23.8 ± 2.6	68.0[d]	3.7[c] ± 3.7	5.3 ± 5.3	16.5 ± 9.2	41.5 ± 18.7	100[d]	19.3[c] ± 5.7	4.9[c] ± 2.9
	*i*-Pr	17	3	3.0 ± 3.0	6.0 ± 6.0	18.0 ± 11.4	16.7 ± 6.6	49.0[d]	5.0 ± 0	16.5 ± 3.5	10.3 ± 6.1	21.0 ± 7.6	19.0[d]	>14.58[e]	>14.58[e]
	*t*-Bu	18	4	5.7 ± 3.3	10.5 ± 4.0	32.5 ± 9.9	63.0 ± 8.6	91.0 ± 0	6.7 ± 3.8	21.2 ± 3.6	44.8 ± 6.5	76.2 ± 4.6	98.7 ± 1.3	3.0 ± 1.0	1.5 ± 0.3
				Dose, mg/kg					Dose, mg/kg						
				0.03	0.13	0.45	1.45	4.61	0.03	0.13	0.45	1.45	4.61		
	*i*-Pr	19	6	24.7 ± 4.4	62.0 ± 3.5	85.2 ± 2.1	95.8 ± 0.5	98.4 ± 0.2	40.5 ± 1.7	63.5 ± 2.3	80.8 ± 1.8	90.7 ± 0.5	96.6 ± 1.2	0.09 ± 0.01	0.06 ± 0.01

[a] Dose producing 50% inhibition of the heart rate (HR) increase to 0.5 μg/kg of isoproterenol. [b] Dose producing 50% inhibition of the diastolic blood pressure (DBP) decrease to 0.5 μg/kg of isoproterenol. [c] Each value is expressed as the mean ± SE. [d] Only one experiment done at this dose level. [e] Compound minimally active. Dose levels high enough to permit calculation of ED_{50}'s were not administered. [f] N = number of studies. [g] Propranolol.

of the elements, were within ±0.3% of the theoretical values for all crystalline compounds. The IR spectra were measured on a Perkin-Elmer Model 21 infrared spectrophotometer or a Perkin-Elmer Model 267 grating infrared spectrophotometer in chloroform solutions or as solids in potassium bromide disks. The UV spectra were recorded in methanol solution with a Perkin-Elmer UV-visible spectrophotometer. The NMR spectra were measured with a Varian T-60, NMR spectrometer in $CDCl_3$ or D_2O solutions. The spectral data for all new compounds were consistent with the assigned structures.

Synthesis of the Glycidyl Ethers. A solution of the heteroaryl halide (10 mmol) and freshly distilled glycidol (10 mmol) in dry dimethylformamide (50 mL) was added dropwise over a 2–3-h period to a stirred suspension of sodium hydride (10 mmol, obtained from a 55% dispersion of sodium hydride in mineral oil which was washed free of the carrier with dry hexane) in the same solvent (50 mL) which was maintained at 0 °C (compounds **6**, **7**, and **10**) or 25 °C (compounds **5**, **8**, **9**, and **11**). Stirring was then continued at the specified temperature for a further 0.5–2 h and then the solution was poured into ice water. The product was extracted into benzene; the extract was washed well with water, dried over sodium sulfate, and evaporated in vacuo. The residue was then purified by crystallization from a suitable solvent (see Table I) or by preparative TLC on silica gel. In some instances the epoxide was used without purification in the next step.

Synthesis of the Amino Alcohols. A solution of the glycidyl ether in *tert*-butylamine or isopropylamine (10 equiv) containing *tert*-butyl alcohol or isopropyl alcohol (0.1 vol of the amine), respectively, was left at room temperature until the reaction was seen to be complete (1–5 days) by TLC. The excess amine and alcohol were removed in vacuo and the residue was crystallized directly or after conversion to the crystalline hydrochloride salt with dry HCl in ether.

In the case of compound **12**, after evaporation of the reaction mixture, the residue was dissolved in 10% hydrochloric acid and the neutral contaminants were removed by extraction with dichloromethane. The aqueous phase was made basic with dilute sodium hydroxide solution and the product was extracted into ether. The normal work-up was then followed.

The amine produced from **9** was 3-phenyl-5-*tert*-butylamino-1,2,4-oxadiazole (**16**), identical with the product obtained from 3-phenyl-5-chloro-1,2,4-oxadiazole and *tert*-butylamine.

The product from the reaction of **10** with *tert*-butylamine contained several more and less polar impurities which were removed by preparative TLC on silica gel (chloroform–methanol, 85:15).

The product from the reaction of **11** with *tert*-butylamine was a mixture of compounds from which the required more polar amine could be separated by preparative TLC on silica gel (chloroform–methanol, 90:10). It was converted to the crystalline hydrochloride in the usual manner.

Pharmacological Method. The β-blocking activities of the heteroaromatic potential β-adrenergic antagonists were studied in bilaterally vagotomized open chest mongrel dogs of both sexes (weight 7.2–18 kg) which were anesthetized intravenously with 30 mg/kg of sodium pentobarbital and supplemented by an additional 5 mg/kg at hourly intervals. The heart rate was recorded by a cardiotachograph triggered by the R wave of a limb lead II EKG and the systemic blood pressure from a cannulated femoral artery. Each drug was administered intravenously, as a bolus, into a cannulated femoral vein.

The general β-stimulant, (±)-isoproterenol sulfate dihydrate (0.5 μg/kg), was administered before and 10–20 min following each dose of the test compound or propranolol (the comparison compound). Four or five cumulative doses of the test compound (0.1–14.58 mg/kg) were administered at hourly intervals. Dogs treated with propranolol received five cumulative doses (0.0316–4.61 mg/kg) at hourly intervals.

The means and standard errors were calculated using standard statistical procedures.[11] ED_{50} inhibitory values of isoproterenol induced heart rate increases and diastolic blood pressure decreases were determined for each β-blocker by a computer program which fitted an unweighted least-squares regression line through the logit transformed responses. These data appear in Table III.

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