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1,4-Benzodioxanes as Reversible and Irreversible Antagonists at Adrenergic Receptors

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A series of 1,4-benzodioxanes has been synthesized and examined for activity at adrenergic receptors. The prototype of this series is 2-*N*,*N*-diethylaminomethyl-1,4-benzodioxane (I). The corresponding *N*-2-chloroethyl derivative was found to be an irreversible α-receptor antagonist, and this irreversible activity was maintained or abolished by the 6- and 7-$MeSO_2NH$ substituents, respectively. I, its 6- and 7-$MeSO_2NH$ derivatives and related nonalkylating compounds showed competitive or potentiating activity toward norepinephrine (NE) in the rat and guinea pig vas deferens. I was the most active competitive antagonist. Additionally, I and some analogs increased the maximum contractile response to NE. Since a similar effect was also exerted by certain compounds on carbachol-induced responses in the guinea-pig vas deferens, it is unlikely that this augmenting effect is exerted at the receptor level and it is speculated that it may be related to increased Ca^{2+} mobilization in the E-C coupling process.

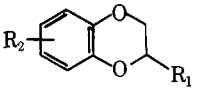
Our continuing concern with structure-activity relationships of ligands active at adrenergic receptors[1,2] and of the mechanisms by which ligand-receptor interactions are linked to the physiological response[3,4] has prompted us to examine a series of 1,4-benzodioxanes. These were chosen because this structure includes well-known α-receptor antagonists as Prosympal (I). However, as with many other α-receptor antagonists the structural relationship of I and its analogs to norepinephrine is far from clear[5] and it appeared of interest to determine whether I could, like Dibenamine and related 2-halogenoethylamine antagonists, be exhibiting its antagonism, in whole or in part, by interacting at a site other than the norepinephrine recognition site of the α receptor.[2,3,6]

To pursue this aim we have synthesized a number of potential irreversibly acting analogs of I. Additionally, we have attempted to determine the binding requirements of the benzodioxane antagonists relative to the catecholamine agonists at the α receptor. Methanesulfonamido derivatives both of I and its alkylating analog have been prepared and examined to determine whether this substitution produces effects in these compounds that parallel the effects in the substituted phenylethanolamines.[5,7,8]

Results and Discussion

A number of the compounds prepared exhibited irreversible α-adrenergic receptor antagonism in the rat vas deferens (Table I) and this was of long duration. This activity is, however, substantially lower than that of phenoxybenzamine, one of the best known of this class of antagonists.[5,9,10] Despite this limitation it is of obvious interest that 2-*N*-ethyl-*N*-(2-chloroethyl)aminomethyl-6-methanesulfonamido-1,4-benzodioxane (VIII) and not the corresponding 7-substituted isomer VI produces irreversible antagonism (Table I); this finding is highly reminescent of the work of Larsen, *et al.*,[7,8] showing a similar de-

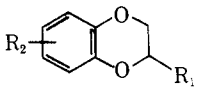
Table I. Duration of Irreversible Blockade in Rat Vas Deferens α-Receptor Preparation



No.	R_1	R_2	Block (90–100%)	$t_{1/2}$,[a] min	Blocking concn (M)/ time, min	$t_{1/2}$ (DMPEA),[b] min
II	$CH_2N(C_2H_5)C_2H_4Cl$	H	Yes	337 ± 40	10^{-4}/12	37 ± 5
III	H	6-$CH_2N(C_2H_5)C_2H_4Cl$	Yes	310 ± 30	10^{-4}/11	45 ± 5
VIII	$CH_2N(C_2H_5)C_2H_4Cl$	6-$NHSO_2CH_3$	Yes	250 ± 20	10^{-4}/11	48 ± 7
VI	$CH_2N(C_2H_5)C_2H_4Cl$	7-$NHSO_2CH_3$	No		10^{-4}/15	
X	H	6-$CHClCH_2N(CH_3)_2$	No		10^{-4}/15	

[a] $t_{1/2}$ ± S.E.M. There was no significant difference between these values as determined by Student's t test at $p < 0.01$. [b] $t_{1/2}$ following tissue pretreatment with DMPEA (10^{-6} M, 5 min). This concentration neither affected the NE dose-response curve nor changed the initial degree of blockade produced by the benzodioxane antagonist. There was no significant difference between these values at the $p = 0.01$ level.

Table II. Action of 1,4-Benzodioxane Derivatives on Rat Vas Deferens α-Receptor Preparation



No.	R_1	R_2	Max response to NE, % of control (± S.E.M.), dose, M 10^{-4}	10^{-5}	Dose ratio[a] 10^{-4}	10^{-5}
I	$CH_2N(C_2H_5)_2$	H	165 ± 6.7	127.0 ± 1.9	18	4.99
IV	H	6-$CH_2N(C_2H_5)_2$	123.2 ± 9.8	102.9 ± 2.77	1.11	1.24
V	$CH_2N(C_2H_5)_2$	7-$NHSO_2CH_3$	152.0 ± 4.4	119 ± 3.7	2.40	1.42
VII	$CH_2N(C_2H_5)_2$	6-$NHSO_2CH_3$	145.9 ± 4.5	141.6 ± 5.1	−1.32	−2.10
VII	$CH_2N(C_2H_5)_2$[b]	6-$NHSO_2CH_3$	179 ± 14.4		−1.93	

[a] Dose ratio is the antilog of the difference between the log ED_{50} control and the log ED_{50} drug; a negative sign preceding dose indicates a shift to the left. Dose ratio values close to one indicate that there is no effect of the drug on the ED_{50}. [b] Reserpine pretreated, see Experimental Section.

terminant role of the $MeSO_2NH$ group for agonist and antagonist activities in the arylethanolamines, meta or para substitution conferring agonist or antagonist activity, respectively. A similar distinction has been made[11] with the meta and para $MeSO_2NH$ derivatives of *N,N*-dimethyl-2-bromo-2-phenylethylamine (DMPEA) where only the meta derivative exhibited irreversible antagonist activity. The apparently determinant role of a common substituent group in the two series of antagonists may be suggestive of a common binding pattern at the α receptor. If it is assumed that a common binding site is occupied by the $MeSO_2NH$ group and benzene ring of the DMPEA and benzodioxane antagonists, then examination of molecular models shows, however, that it is impossible for both 3-$MeSO_2NH$ DMPEA and VIII to alkylate the same site. Quite possibly alkylation by these two agents is directed at different areas or residues of the α receptor.

Our previous studies[2,3,6] have indicated that the 2-halogenoethylamine irreversible α-adrenergic antagonists appear to exert their antagonism at two distinct sites: one of these sites appears to be concerned with Ca^{2+} binding/mobilization while the other may be the NE recognition site. The evidence for this is discussed in full in our previous work and a model proposed (for the rat vas deferens) in which the NE recognition site is allosterically linked to the Ca^{2+} binding/mobilization site such that the whole constitutes the functional α receptor and that blockade of either site will eliminate response. Using the same experimental procedure as previously described,[2,3,6] the data of Table I show that the DMPEA pretreatment converts the antagonism of II, III, and VIII from long duration to short duration *without* affecting the initial degree of blockade produced. Apparently the benzodioxane antagonists listed behave similarly to dibenamine, phenoxybenzamine, and related compounds in that they exert their antagonism at two kinetically distinguishable sites of action.

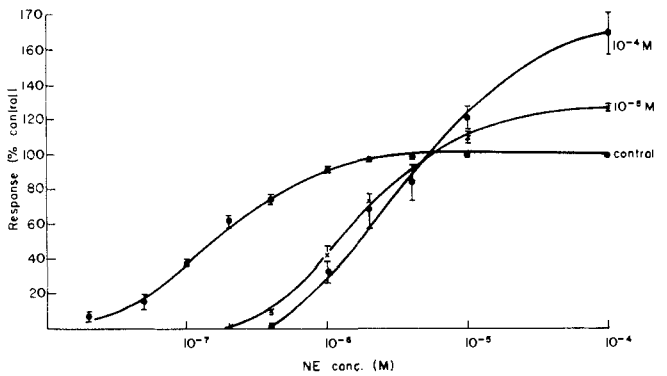


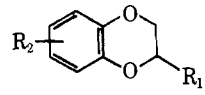
Figure 1. The effects of Prosympal (I, 10^{-4} and 10^{-5} M) on the dose-response relationship of NE in the rat vas deferens preparation. Each point is the mean of at least six preparations.

Examination of a number of nonalkylating analogs of I revealed them to have, in addition to their α-adrenergic antagonism that was most pronounced with I itself, the ability to increase or augment the maximum response to NE (Table II, Figure 1). Since both the 6- and 7-$MeSO_2NH$ derivatives of I possessed augmenting activity but were weak competitive antagonists (the 6-$MeSO_2NH$ derivative was actually a potentiating agent causing a leftward shift of the NE dose-response curve), it is unlikely that this augmenting activity is related to events at the α-adrenergic receptor itself. This is further suggested by a comparison of the action of I on rat and guinea-pig vas deferens (Tables II and III); augmenting activity to NE is seen in both preparations but Prosympal is almost ineffective as an antagonist in the guinea-pig vas deferens. This suggests also that the α receptors in the rat and guinea pig vas deferens may be distinguished by antagonist action.[12] The guinea pig vas deferens is also sensitive to muscarinic agonists and the finding that compounds I, V, and IX also significantly increased the response to carbamylcholine (CCh) in this preparation makes it even less probable that this activity is related to events at a specific receptor.

One plausible explanation is that this augmenting activity is related to an ability to permit increased mobilization of Ca^{2+}, the key element in excitation-contraction coupling. To test this proposal three compounds that significantly increased the maximum response of NE were tested for their ability to modify the Ca^{2+} dose-response curve in the rat vas deferens (in the constant presence of 10^{-4} NE). No increase in maximum response to Ca^{2+} was found although significant leftward shifts of the Ca^{2+} dose-response curve were seen with dose ratios of −3.7, −2.9, and −10.7 for compounds I, V, and VII, respectively. Since, however, the control response to Ca^{2+} was some 60% above that of NE, a further increase in maximum response may have been mechanically impossible. At present the basis of the enhanced responses must remain a subject for further inquiry.

A number of compounds synthesized were examined for their activity in a β-receptor preparation, the guinea pig tracheal chain; IX (of unknown stereochemistry) exhibited significant antagonist activity with a pA_2 value of 7.3. Tertiary amines are usually associated with much reduced β-antagonist activity and a pA_2 value of 7.3 for IX is quite comparable with that for a number of β antagonists of other series, including pronethalol, in the guinea-pig tracheal chain preparation. However, in view of the extremely high β antagonism found for secondary amines in the benzodioxane series, such as 2-(2-*N*-*tert*-butylamino-1-

Table III. Effect of 1,4-Benzodioxanes on Responses to NE and CCh in Guinea-Pig Vas Deferens



No.	R_1	R_2	Max responses[a] as % of control (100) to CCh	Max responses[a] as % of control (100) to NE	Dose ratio CCh	Dose ratio NE	p[b]
I	$CH_2N(C_2H_5)_2$	H	130.8 ± 10.5	151.3 ± 10.9	1.50	1.00	<0.01
IV	H	6-$CH_2N(C_2H_5)_2$	102.9 ± 2.83	115.47 ± 7.4	3.18		>0.01
V	$CH_2N(C_2H_5)_2$	7-$NHSO_2CH_3$	111.7 ± 1.33	107.2 ± 5.5	2.0	−1.18	<0.01
VII	$CH_2N(C_2H_5)_2$	6-$NHSO_2CH_3$	100.2 ± 0.6	101.7 ± 3.4	3.10	1.15	<0.01
IX	$CHOHCH_2N(CH_3)_2$	H	112.3 ± 1.7	147.3 ± 9.6	1.26	−1.94	>0.01

[a]Drug concentration was 10^{-4} M with equilibration time 5 min (n = 4). [b]Comparison of maximal responses for both agonists in the presence of each drug by Student's t test. $p < 0.01$ indicates CCh and NE responses are not significantly different. $p > 0.01$ indicates CCh and NE responses are significantly different.

hydroxyethyl)-1,4-benzodioxane[13] in the perfused heart preparation, it seems probable that IX actually does have reduced activity relative to its secondary amine counterpart.

Experimental Section

A. Synthetic Methods.† **2-*N,N*-Diethylaminomethyl-1,4-benzodioxane Hydrochloride (Prosympal, I).** This was prepared according to the method of Fourneau, *et al.*[14] It had mp 127–129° (Me_2CO) (lit.[14] 127–129°).

2-*N*-Ethyl-*N*-(2-chloroethyl)aminomethyl-1,4-benzodioxane Hydrochloride (II). 2-Chloromethyl-1,4-benzodioxane (10 g, 0.05 mol) was placed in a steel bomb with excess (10–15 ml) *N*-ethylethanolamine and heated at 140–150° for 12 hr. The contents were diluted with ether, filtered, and distilled to give *N*-ethyl-*N*-(2-hydroxyethyl)-2-aminomethyl-1,4-benzodioxane, bp 130–132° (0.1 mm) in 50% yield. The HCl salt had mp 131–133° (Me_2CO). *Anal.* ($C_{13}H_{20}ClNO_3$) C, H, Cl, N. The free base was converted to II by $SOCl_2$–$CHCl_3$ in 20% yield: mp 132–135° (Me_2CO). *Anal.* ($C_{13}H_{19}Cl_2NO_2$) C, H, Cl, N.

6-*N*-Ethyl-*N*-(2-chloroethyl)aminomethyl-1,4-benzodioxane Hydrochloride (III). This was prepared similarly to II using 6-chloromethyl-1,4-benzodioxane (employed crude) obtained by the method of Danksas and Kadzicarskas.[15] The yield was poor (5%) because of polymerization of the chloromethyl derivative. III had mp 201–203° (*i*-PrOH). *Anal.* ($C_{13}H_{19}Cl_2NO_2$) C, H, Cl, N.

6-*N,N*-Diethylaminomethyl-1,4-benzodioxane Hydrochloride (IV). This was prepared similarly to I in 10% yield and had mp 235–237° (*i*-PrOH). *Anal.* ($C_{13}H_{20}ClNO_2$) C, H, Cl, N.

2-*N,N*-Diethylaminomethyl-7-methanesulfonamido-1,4-benzodioxane Hydrochloride (V). 7-Nitro-2-chloromethyl-1,4-benzodioxane[16] (5 g, 0.024 mol) and diethylamine (15 ml, excess) were heated at 150° as described for II and worked up to give 7-nitro-2-*N,N*-diethylaminomethyl-1,4-benzodioxane hydrochloride (40%), mp 168–173° (EtOH). *Anal.* ($C_{13}H_{19}ClN_2O_4$) C, H, Cl, N. This was reduced, as the free base in EtOH, catalytically with 5% Pd/C at 3 atm and the crude oil (12 g, 0.05 mol) dissolved in $CHCl_3$ (20 ml) cooled at 0° and treated dropwise with $MeSO_2Cl$ (15 g, 0.13 mol). The mixture was stirred 4 hr at room temperature and poured into excess Et_2O and triturated. Repeated treatment with Me_2CO–Et_2O gave colorless extremely hygroscopic crystals with mp 115–120°. *Anal.* ($C_{14}H_{23}ClN_2O_4S$) C, H, Cl, N.

2-*N*-Ethyl-*N*-(2-chloroethyl)aminomethyl-7-methanesulfonamido-1,4-benzodioxane Hydrochloride (VI). Reaction of 7-nitro-2-chloromethyl-1,4-benzodioxane with *N*-ethylethanolamine under the conditions described for II gave 2-*N*-ethyl-*N*-(2-hydroxyethyl)aminomethyl-7-nitro-1,4-benzodioxane in 20% yield. The HCl salt had mp 153–156° (*i*-PrOH). *Anal.* ($C_{13}H_{19}ClN_2O_5$) C, H, Cl, N. The free base was reduced and reacted with $MeSO_2Cl$ as described for V. The $CHCl_3$ solution was stripped and stirred with saturated $NaHCO_3$ for 24 hr and then reextracted into $CHCl_3$ to give 2-*N*-ethyl-*N*-(2-hydroxyethyl)aminomethyl-7-methanesulfonamido-1,4-benzodioxane (VIa) as an oil. The HCl salt had mp 120–125°. *Anal.* ($C_{14}H_{23}ClN_2O_5S$) C, H, Cl, N. The free base was converted to VI with $SOCl_2$–$CHCl_3$ and had mp 197–201°. *Anal.* ($C_{14}H_{22}Cl_2N_2O_4S$) C, H, Cl, N, S.

2-*N,N*-Diethylaminomethyl-6-methanesulfonamido-1,4-benzodioxane Hydrochloride (VII). 2-Chloromethyl-6-nitro-1,4-benzodioxane was prepared from 2-hydroxymethyl-6-nitro-1,4-benzodioxane[17] by treatment with $SOCl_2$ and the crude material, after removal of excess $SOCl_2$, reacted directly with $HNEt_2$ as described for II. 2-*N,N*-Diethylaminomethyl-6-nitro-1,4-benzodioxane hydrochloride had mp 177–179° (*i*-PrOH) [*Anal.* ($C_{13}H_{19}ClN_2O_4$) C, H, Cl, N] and was reduced as the free base with Pd/C and reacted with $MeSO_2Cl$ as described for V. VII was very hygroscopic and had mp 105–110°. *Anal.* ($C_{14}H_{23}ClN_2O_4S$) C, H, Cl, N.

2-*N*-Ethyl-*N*-(2-chloroethyl)aminomethyl-6-methanesulfonamido-1,4-benzodioxane Hydrochloride (VIII). This was prepared similarly to VI from 2-chloromethyl-6-nitro-1,4-benzodioxane. The intermediate 2-*N*-ethyl-*N*-(2-hydroxyethyl)aminomethyl-6-nitro- and 2-*N*-ethyl-*N*-(2-hydroxyethyl)aminomethyl-6-amino-1,4-benzodioxanes were not characterized. 2-*N*-Ethyl-*N*-(2-hydroxyethyl)aminomethyl-6-methanesulfonamido-1,4-benzodioxane was obtained in 20% overall yield and as the HCl salt had mp 130–135°. *Anal.* ($C_{14}H_{23}ClN_2O_5S$) C, H, Cl, N, S. Treatment of the free base with $SOCl_2$–$CHCl_3$ gave VIII with mp 160–165°. *Anal.* ($C_{14}H_{22}Cl_2N_2O_4S$) C, H, Cl, N, S.

2-(2-Dimethylamino-1-hydroxy)ethyl-1,4-benzodioxane Hydrochloride (IX). 2-(2-Bromo-1-hydroxy)ethyl-1,4-benzodioxane[18] (5 g, 0.02 mol) was heated with Me_2NH (10 ml, excess) at 110° for 6 hr to give IX in 72% yield: mp 145–149° (MEK). *Anal.* ($C_{12}H_{18}ClNO_3$) C, H, Cl, N.

6-(1-Chloro-2-*N,N*-dimethylamino)ethyl-1,4-benzodioxane Hydrochloride (X). 6-Bromoacetyl-1,4-benzodioxane[19] dissolved in EtOH (250 ml) and H_2O (15 ml) was added to Me_2NH (120 ml of a 20% EtOH solution). After 5 days (25°) the ethanol was removed, and the amino ketone was extracted into Et_2O and reduced with $NaBH_4$–MeOH at 10° to give 6-(1-hydroxy-2-dimethylamino)ethyl-1,4-benzodioxane in 68% yield: bp 148° (0.3 mm). The HCl salt had mp 160–162° (Me_2CO). *Anal.* ($C_{12}H_{18}ClNO_3$) C, H, Cl, N. Chlorination of the free base with $SOCl_2$–$CHCl_3$ gave XIII, mp 141–144° (*i*-PrOH). *Anal.* ($C_{12}H_{17}Cl_2NO_2$) C, H, Cl, N.

B. Pharmacology. Male albino rats (Sprague–Dawley, 160–300 g) were killed by a blow on the head. The vasa deferentia were removed, slit at the bottom, and suspended in 10-ml jacketed tissue baths in Tyrodes solution (composition: NaCl, 137.5 mM; KCl, 2.66 mM; $CaCl_2$, 1.8 mM; $MgCl_2$, 1.05 mM; $NaHCO_3$, 11.9 mM; NaH_2PO_4, 0.41 mM; glucose, 5.8 mM) maintained at 37 ± 0.5° and aerated with 95% O_2–5% CO_2. Isotonic contractions were recorded on smoked paper and this procedure together with that for measuring α-receptor blockade and rate of recovery of pharmacological response have been described previously.[2,3] The guinea-pig vasa deferentia were prepared similarly but suspended in Krebs bicarbonate (NaCl, 113 mM; KCl, 4.7 mM; $CaCl_2$, 2.5 mM; KH_2PO_4, 1.19 mM; $MgSO_4$, 1.19 mM; glucose, 11.53 mM; $NaHCO_3$, 2.5 mM) since the higher Ca^{2+} appeared to stabilize the tissue and decrease rhythmic contractions when agonists were employed.

The guinea-pig tracheal chain was prepared according to the procedure described by Castillo and deBeer.[20] Six to eight cartilage rings were tied together to form each chain and the pair of chains suspended in Krebs bicarbonate solution and tied to light isotonic levers weighted at 300 mg with 15× magnification. Carbachol (CCh) was used to produce contractions of the tracheal chain and *dl*-isopropylnorepinephrine (ISO) as the β agonist to induce relaxation. Potential β antagonists were added after CCh

†Melting points were determined on a Thomas-Hoover Kofler hot stage and are corrected. Analyses were by Dr. A. E. Bernhardt and are within ±0.4% of the calculated values.

contractions were complete; for IX a 5-min incubation was employed and a dose ratio plot using four antagonist concentrations constructed.

Calcium free experiments were conducted on rat vas deferens equilibrated in Ca^{2+} free Tyrode's solution for 1 hr. Norepinephrine (10^{-4} *M*) was then without affect on the tissue and in its presence Ca^{2+} dose–response curves could be determined.

For the study of catecholamine-depleted systems rats were injected with 3 mg/kg of reserpine (Serpasil) ip 20 hr prior to use.

The Student's t test was used to test the null hypothesis that both the drug-treated and control responses were from the same population or represented identical responses. The standard error of the mean was determined for all points in each dose–response curve representing 4–8 experiments.

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1-Alkylamino-3-(2-thiazolyloxy)-2-propanols. A Novel Class of Mixed Myocardial β-Stimulants/β-Blockers†

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The synthesis of a series of 1-alkylamino-3-(2-thiazolyloxy)-2-propanols is described. Several compounds in this series, *e.g.*, (±)-1-isopropylamino-3-(2-thiazolyloxy)-2-propanol, are selective myocardial β-stimulants with a prolonged duration of action. The structure–activity relationships of these compounds are described.

Extensive investigations by the Imperial Chemical Industries (ICI) group have demonstrated that 1-amino-3-naphthoxy-2-propanols and 1-amino-3-(substituted phenoxy)-2-propanols possess potent β-adrenergic blocking properties.[2,3] Synthesis and evaluation of other compounds based on the ICI lead by various laboratories have indicated that the ability of 1-amino-3-aryloxy-2-propanols to antagonize the action of isoproterenol hydrochloride (a general β-stimulant) is a general pharmacological property of this class of compounds.[4-8]

The present communication describes the synthesis and pharmacology of a series of 1-alkylamino-3-(2-thiazolyloxy)-2-propanols which were prepared at Syntex Research in connection with a general program aimed at the development of agents useful in treating cardiovascular disease. In contrast to the known 1-amino-3-aryloxy-2-propanols[2-8] which exhibit β-blocking properties, a number of the title compounds are selective myocardial β-stimulants with β-blocking properties as well.‡ They have a prolonged duration of action [in some cases, *e.g.*, **15a** (Table I), greater than 6 hr]. These compounds increase the contractile force of the heart and heart rate but produce minimal or no effects on blood pressure. They are largely or completely devoid of vascular β-receptor stimulant properties. Because of their prolonged and selective action on the heart and their lack of effect on blood pressure, compounds of the thiazolyl-2-oxy series may be useful in the treatment of heart failure and myocardial depression.

Chemistry. The synthesis of the title compounds, starting from readily available 2-bromothiazole (**1**),[9] is outlined in Scheme I. Treatment of **1** with the Na alkoxide of (±)-glycerol 1,2-acetonide in DME yielded the ether **2** which was hydrolyzed to the diol **3a** with dilute HCl. Reaction of **3a** with 1 equiv of CH_3SO_2Cl in C_5H_5N gave a mixture containing predominantly the requisite monomesylate **3b**. This mixture was then allowed to react with an excess of NaOMe to yield the liquid epoxide **4**. Exposure of the resulting epoxide **4** to the appropriate amine furnished the corresponding 1-amino, 1-alkylamino, or 1-dialkylamino-3-(2-thiazolyloxy)-2-propanol (see Table I).

This procedure appeared to afford an efficient route to the optically active forms of 1-alkylamino-3-(2-thiazolyloxy)-2-propanols by starting with (+)- or (−)-glycerol

† For a preliminary account of this work, see ref 1.

‡ Studies in dogs pretreated with β-blockers (propranolol or practolol) and in reserpinized dogs indicate that the compounds act *via* a direct β-adrenergic receptor mechanism. These studies will be published elsewhere by Dr. A. Strosberg and colleagues.