β-Adrenergic Blocking Agents. 3-(3-Substituted-amino-2-hydroxypropoxy)-4-substituted-1,2,5-thiadiazoles

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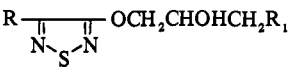
The synthesis of a number of 3-(3-substituted-amino-2-hydroxypropoxy)-4-substituted-1,2,5-thiadiazoles is described. The compounds were prepared by 3 general procedures, (A) by condensation of the appropriate 3-hydroxy-4-substituted-1,2,5-thiadiazole with epichlorohydrin, then formation of the epoxide, and condensation with an amine, (B) by treatment of 4-chloro-3-(3-substituted-amino-2-hydroxypropoxy)-1,2,5-thiadiazole with a heterocyclic compound containing a secondary N, or (C) by formation of a bromohydrin of a 3-substituted-4-allyloxy-1,2,5-thiadiazole, followed by treatment with an amine. A number of derivatives containing a 4 substituent such as Cl, Et, or EtO were potent β-adrenergic blocking agents but they were also short acting and possessed some sympathomimetic activity. 1-(2-Morpholinophenoxy)-3-isopropylamino-2-propanol was prepared and found to possess an extended duration of action. Following this lead a number of 1,2,5-thiadiazoles were made possessing a bulky group in the 4 position. Several of these substances were long acting, the outstanding member being 3-(3-*tert*-butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole. Resolution of this product showed that the bulk of activity resided in the (+) form. Structure–activity relationships of these compounds are presented.

The β-adrenergic blocking agents reported in the current literature possess either an ethanolamine side chain as in dichloroisoproterenol,[1] pronethalol,[2] and sotalerenol,[3] or an aminoisopropanoloxy side chain as in propranolol[4] and 1-(isopropylamino)-3-(*m*-tolyloxy)-2-propanol.[5] The aromatic portion of these compounds is either Ph, naphthyl, or an aromatic ring fused to a 5-membered heterocyclic system containing N,[6] O,[7] or S.[8] We now report the synthesis of a series of 3-(3-substituted-amino-2-hydroxypropoxy)-1,2,5-thiadiazoles (I) with a variety of substituents in the 4 position. These compounds provide the first examples of β-adrenergic blocking substances in which the conventional side chain is attached to a single heterocyclic ring.



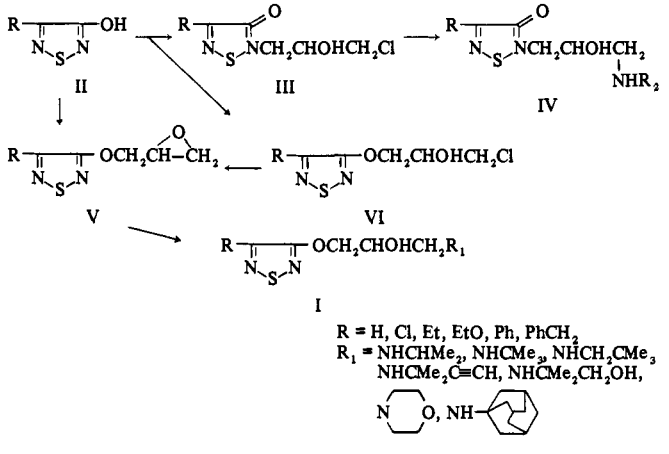
I

Pharmacological investigation has demonstrated that certain members of this series possessed β-adrenergic blocking properties and one of them, 3-(3-*tert*-butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole·HCl (24), received detailed pharmacological evaluation. Clinical evaluation of the levorotatory maleate salt **26** is now in progress.

Chemistry. A number of 3-(3-substituted amino-2-hydroxypropoxy)-4-substituted-1,2,5-thiadiazoles (I) were prepared by the reaction sequence shown in Scheme I and described as method A in the Experimental Section. Compounds prepared by this procedure were those wherein the 4 substituent was halogen, alkyl, alkoxy, aryl, and aralkyl. Thus treatment of a 3-hydroxy-1,2,5-thiadiazole (II) with epichlorohydrin containing a trace of piperidine[9] led to the formation of 2 products, N- and O-substituted derivatives (III and VI), respectively. In several instances (R = Cl, Et, or Ph) crystalline III were obtained. The O derivatives (VI) were separated from the less soluble N derivatives (III) by use of Et_2O. Treatment of the 3-(3-chloro-2-hydroxypropoxy)-4-substituted-1,2,5-thiadiazoles (VII) with NaOH solution afforded the epoxide V. V underwent facile condensation with the appropriate amine to give 3-(3-substituted-amino-2-hydroxypropoxy)-4-substituted-1,2,5-thiadiazoles (I) in yields of 50–80%. The products are listed in Table I. Although V could be obtained directly from II by treatment with epichlorohydrin and K_2CO_3 in Me_2CO, there was evidence from ir and nmr spectra that some of the corresponding chlorohydrin III was formed. The chlorohydrin III (R = Ph) readily condensed with the appropriate amine to afford 3-phenyl-4-oxo-5-(3-substituted-amino-2-hydroxypropyl)-Δ^2-1,2,5-thiadiazoline (IV). Treatment of the chlorohydrin III (R = Ph) with NaOH solution did not afford 3-phenyl-4-oxo-5-(2,3-epoxypropyl)-Δ^2-1,2,5-thiadiazoline. The chlorohydrin III (R = Cl or EtO) when treated with either *i*-$PrNH_2$ or *tert*-$BuNH_2$ failed to give the corresponding IV.

Examples of I were prepared wherein R was a piperidino, substituted piperidino, piperazino, or morpholino group by the treatment of I (R = Cl; R_1 = $NHCHMe_2$, $NHCMe_3$, or NH-adamantyl) with the appropriate heterocyclic amine (method B). These products are listed in Table I. The remaining compounds given in Table I were prepared by method C as depicted in Scheme II. Treatment of 3-

Scheme I



Scheme II

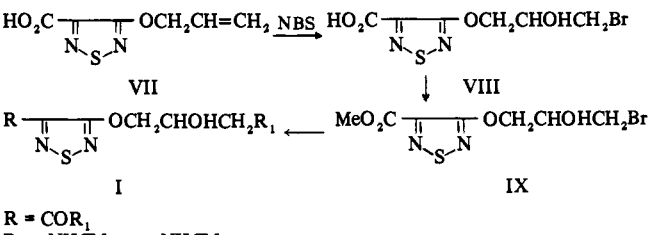
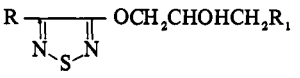


Table I



I

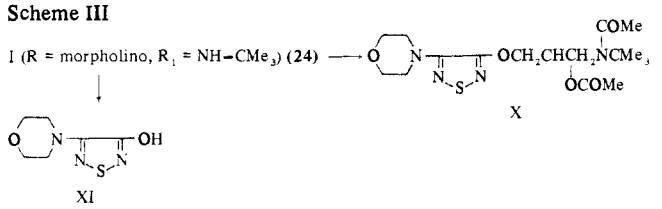
Compd	R	R_1	Method[a]	Form	Mp, °C	Crystn solvent[b]	Formula	Analyses	ED_{50}[c]
1	H	Morpholino	A	HCl	150-152	a	$C_9H_{16}ClN_3O_3S$	C, H, Cl, N	3.1
2	H	$NHCMe_2CHOH$	A	Base	94-96	l	$C_9H_{17}N_3O_3S$	C, H, N	4.8
3	Cl	$NHCHMe_2$	A	HCl	153-155	a	$C_8H_{15}Cl_2N_3O_2S$	C, H, Cl, N	0.12
4	Cl	$NHCMe_3$	A	HCl	160-163	a	$C_9H_{17}Cl_2N_3O_2S$	C, H, Cl, N	0.093
5[d]	Cl	$NHCMe_3$	D	HCl	146-147	a	$C_9H_{17}Cl_2N_3O_2S$	C, H, Cl, N, S	0.056
6[e]	Cl	$NHCMe_3$	D	HCl	148-149.5	a	$C_9H_{17}Cl_2N_3O_2S$	C, H, Cl, N, S	0.023
7	Cl	NH— 	A	HCl	239-242	a	$C_{15}H_{23}Cl_2N_3O_2S$	C, H, Cl, N, S	Slight and variable
8	Et	$NHCHMe_2$	A	HCl	144.5-145.5	a	$C_{10}H_{20}ClN_3O_2S$	C, H, Cl, N	0.04
9	Et	$NHCMe_3$	A	HCl	137-138	a	$C_{11}H_{22}ClN_3O_2S$	C, H, Cl, N	0.05
10	Et	$NHCMe_2CH_2OH$	A	HCl	125-127	k	$C_{11}H_{22}ClN_3O_3S$	C,[i] H, Cl, N	0.3
11	EtO	$NHCHMe_2$	A	HCl	167-170	a	$C_{10}H_{20}ClN_3O_3S$	C, H, Cl, N	0.035
12	EtO	$NHCMe_3$	A	HCl	147-149	a	$C_{11}H_{22}ClN_3O_3S$	C,[j] H, N	0.057
13	EtO	$NHCH_2CMe_3$	A	HCl	168-169	a	$C_{12}H_{24}ClN_3O_3S$	C, H, N, Cl	5.3
14	EtO	$NHCMe_2C{\equiv}CH$	A	HCl	130-131	j	$C_{12}H_{20}ClN_3O_3S$	C, H, Cl, N	0.08
15	EtO	Morpholino	A	HCl	124-126	c	$C_{11}H_{20}ClN_3O_4S$	C, H, Cl, N	1.95
16	Ph	$NHCHMe_2$	A	HCl	165-167	b	$C_{14}H_{20}ClN_3O_2S$	C, H, Cl, N, S	0.08
17	Ph	$NHCMe_3$	A	HCl	168-170.5	c	$C_{15}H_{22}ClN_3O_2S$	C, H, Cl, N, S	0.02
18	$PhCH_2$	$NHCMe_3$	A	HCl	122-123	c	$C_{16}H_{24}ClN_3O_2S$	C, H, N, Cl	0.12
19	Piperidino	$NHCHMe_2$	B	HCl	169.0-170.5	f	$C_{13}H_{25}ClN_4O_2S$	C, H, Cl, N, S	0.13
20	Piperidino	$NHCMe_3$	B	HCl	171-172	i	$C_{14}H_{27}ClN_4O_2S$	C, H, Cl, N, S	0.03
21	HO— 	$NHCMe_3$	B	Maleate	171-173	h	$C_{18}H_{30}N_4O_7S$	C, H, N, S	0.033
22	MeN 	$NHCMe_3$	B	2HCl	205	g	$C_{14}H_{29}Cl_2N_5O_2S\cdot H_2O$	C, H, Cl, N, S	0.35
23	Morpholino	$NHCHMe_2$	B	HCl	168.5-169.5	c	$C_{12}H_{23}ClN_4O_3S$	C, H,[k] Cl, N, S	0.013
24	Morpholino	$NHCMe_3$	B	HCl	161-163	c	$C_{13}H_{25}ClN_4O_3S$	C, H, Cl, N, S	0.013
25[f]	Morpholino	$NHCMe_3$	B	Maleate	201.5-202.5	d	$C_{17}H_{28}N_4O_7S$	C, H, N, S	0.088
26[g]	Morpholino	$NHCMe_3$	B	Maleate	201-202	d	$C_{17}H_{28}N_4O_7S$		0.0066
27[h]	Morpholino	NH— 	B	HCl	207-209	d	$C_{19}H_{31}ClN_4O_3S$	C, H, Cl, N, S	Inactive at dose levels studied
28	$Me_2CHNHCO$	$NHCHMe_2$	C	HCl	96-99	e	$C_{12}H_{23}ClN_4O_3S$	Cl, N, S	2.1
29	Me_3CNHCO	$NHCMe_3$	C	HCl	145-147	c	$C_{14}H_{27}ClN_4O_3S$	Cl, N, S	35.00

[a]For methods see Experimental Section. [b]a = EtOH-Et_2O, b = MeOH-Et_2O, c = Me_2CO-Et_2O, d = EtOH, e = EtOAc-MeOH-Et_2O, f = MeCN, g = MeOH, h = *i*-PrOH, i = Me_2CO-MeOH, j = EtOAc-Et_2O, k = C_6H_6, l = C_6H_6-Et_2O. [c]Iv dose (mg/kg) required to inhibit by 50% the cardioaccelerator repsonse to isoproterenol (0.12 μg/kg iv) in the ganglion-blocked anesthetized rat. [d]HCl salt of the (−) base. [e]HCl salt of the (+) base. [f]Hydrogen maleate salt of the (−) base. [g]Hydrogen maleate salt of the (+) base. [h]Free base, mp 124-125°. *Anal.* for C, H, N, S. [i]C: calcd, 42.37; found, 42.86. [j]C: calcd, 42.37; found 42.80; N: calcd, 13.48; found, 13.02. [k]H: calcd, 6.84; found, 7.48.

allyloxy-1,2,5-thiadiazole-4-carboxylic acid (VII)[10] with NBS gave the bromohydrin VIII. When treated with MeOH-AcCl, VIII gave the Me ester IX which afforded the amino amide I (R = COR_1) when treated with a primary amine. Reduction of I (R = $CONHCMe_3$; R_1 = $NHCMe_3$) with diborane in THF afforded the unknown 1-*tert*-butylamino-2,3-diaminopropane, isolated as its trihydrochloride (**30**). Thus ring-opening and reductive cleavage of the ether linkage had occurred in addition to reduction of the NHCO group.

When **24** was treated with DMSO-Ac_2O[11] the *N,O*-diacetyl derivative (X) was isolated (Scheme III) and there was no

Scheme III



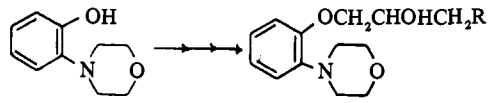
evidence of the oxidation of the CHOH group to CO. Treatment of **24** with $KOCMe_3$-C_6H_6-fluorenone[12] afforded a small amount of 3-hydroxy-4-morpholino-1,2,5-thiadiazole (XI) which was obtained in higher yield when fluorenone was omitted. XI was also obtained by treatment of 3-chloro-4-hydroxy-1,2,5-thiadiazole (**31**) with morpholine.

In order to obtain the optical isomers of **24** for pharmacological evaluation, (±)-3-(3-*tert*-butylamino-2-hydroxypropoxy)-4-chloro-1,2,5-thiadiazole (**4**) was resolved giving the HCl salts **5** and **6** of the pure (−) and (+) bases. The free bases of **5** and **6** were treated with morpholine to give (−)- and (+)-3-(3-*tert*-butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole, purified as their maleate salts **25** and **26**. A parallel resolution of **24** was performed by Erickson and Zabriskie† and the isomers **25** and **26** obtained by both routes were found to be identical. One would predict from the published data[13-16] on the stereo-

†A. E. Erickson and J. L. Zabriskie, Jr., Merck Sharp & Dohme Research Laboratories, Rahway, N.J., private communication.

chemistry of compounds interacting with the adrenergic receptor that the biologically active isomer of **24** would have the *S* configuration (corresponding to *R* in the phenylalkanolamine series). This has been confirmed by our colleagues at Merck Sharp & Dohme Research Laboratories at Rahway, N. J.‡

Simultaneously with this work, a parallel study was carried out on phenoxyisopropanolamines. It was observed that *o*-morpholinophenoxyisopropanolamines were more active than the corresponding meta and para isomers. The method is as follows. The facile synthesis of 2-morpholinophenol (XII) from 2-acetylfuran and morpholine by Birkofer and Daum[17] afforded starting material for a series of reactions by epichlorohydrination, epoxidation, and condensation with the appropriate amine to give 1-(2-morpholinophenoxy)-3-substituted-amino-2-propanols (XIII).



XII XIII

These substances exhibited high β-adrenergic blocking potency and persistance of action when tested in dogs. Similar procedures afforded the corresponding derivatives starting with 3- and 4-morpholinophenols. The desirable activities noted with XIII suggested to us the possibility of incorporating the morpholino moiety and other bulky groups in the 1,2,5-thiadiazole series, which was described under method B.

Biological Methods. Results of the screening test (C) were obtained as follows. Male Wistar rats (150-250 g) were anaesthetized with urethane (1.25-1.5 g/kg ip) and given mecamylamine·HCl (4 mg/kg sc). Heart rate was monitored by means of a calibrated rate meter or Beckman cardiotachometer from sc chest electrodes. The β-adrenergic stimulant, isoproterenol (*dl*-HCl), was administered *via* a femoral vein at 10-min intervals at a dose level of 0.12 μg/kg and the resulting tachycardia recorded in beats/min. Following stabilization of the responses, a dose of the test drug was given iv followed in 10 min by a further dose of isoproterenol. The resulting cardioacceleration was then expressed as per cent of control responses. For estimation of the ED_{50} at least 2 dose levels were used to produce between 16 and 84% inhibition and 3-4 rats were used at each dose level. The mean per cent inhibition of cardioacceleration was plotted against dose and the ED_{50} values were extrapolated from the graph. LD_{50}'s were obtained following ip administration in young adult rats (Charles River). Six dose levels were used and LD_{50}'s based on 14-day mortality were calcd according to the method of Weil.[18]

Structure-Activity Relationships. Biological results on compounds in the 1,2,5-thiadiazole series (Table I) indicate that the effect of substitution on the aminoisopropanoloxy side chain parallels that found for known β-adrenergic blocking agents.[1-8] In general the highest activity was observed in the compounds in which R_1 was $NHCMe_3$, $NHCHMe_2$, or $NHCMe_2C{\equiv}CH$, somewhat lower for $NHCMe_2CH_2OH$, and much lower for $NHCH_2CMe_3$ and NH-adamantyl. Not unexpectedly when R_1 was morpholino as in **15**, activity was greatly reduced. Compd **1** (R = H; R_1 = morpholino) was also found to have greatly reduced activity. Compounds wherein R was a small group such as Cl, Et, or EtO (**3-15**) exhibited marked activity, especially **4**, **8**, **9**, **11**, **12**, and **14**. These substances also possessed some sympathomimetic properties. In general the duration of action of **3-15** was relatively short, some being ultrashort acting compared to **24**. Substances having R as a bulky group (**16-26**) generally possessed marked β-adrenergic blocking activity. Four compounds (R_1 = Me_3CNH; R = C_6H_5, piperidyl, 4-hydroxypiperidyl, and morpholino, **17**, **20**, **21**, and **24**, respectively) were highly active. This was especially noted for **24**, which fulfilled the following requirements: high potency and specificity, minimal or no sympathomimetic effects, rapid onset, and reasonable duration of action. Compound **24** had 0.25 the activity of propranolol when tested in the guinea pig against ouabain-induced arrhythmias. When the resolved formed of **24** were tested the activity was shown to reside in the *l*-maleate salt, **26** (ED_{50}: 0.0066 mg/kg in the rat), prepared from the *d* base. The *d*-maleate salt (**25**) of the *l* base possessed only one-thirteenth of the activity of **26**. Compounds where R_1 = $NHCHMe_2$ and R = C_6H_5, C_6H_5NH, piperidyl, and morpholino (**16**, **18**, **19**, and **23**, respectively) were quite active, perhaps a little less so than **17**, **20**, **21**, and **24**. When R_1 = $NHCMe_3$ and R = 4-methylpiperazinyl (**22**) activity was greatly reduced. No activity was observed at the dosage level studied for **27** (R_1 = adamantylamino; R = morpholino). When R was a substituted amide as $CONHCHMe_2$ in **28** the activity was weak and with $CONHCMe_3$ **29** activity was also greatly reduced.

The discovery in this laboratory that 1-*o*-morpholinophenoxy-3-isopropylamino-2-propanol (**32**) and 1-*o*-morpholinophenoxy-3-*tert*-butylamino-2-propanol (**33**) possessed good duration of action plus reasonable potency as β-adrenergic blocking agents led to the extension of this concept to the 1,2,5-thiadiazole series (*i.e.*, the attachment of a bulky group at position 4) with the results being as described above.

The 2 examples of 3-phenyl-4-oxo-5-(3-substituted-amino-2-hydroxypropyl)-Δ^2-1,2,5-thiadiazolines wherein the 3-substituent is Me_2CH (**34**) and Me_3C (**35**) were found to be inactive as β-adrenergic blocking agents. Thus the isopropyl alcohol side chain must be attached through an ether linkage to the thiadiazole ring rather than directly to a ring N in order to achieve activity.

In conclusion, optimal activity in the 1,2,5-thiadiazole series was achieved by the presence of an Me_2CH or Me_3C group in the aminoisopropanoloxy side chain and inclusion of a bulky substituent, such as morpholino, in the 4 position.

Experimental Section§

3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-chloro-1,2,5-thiadiazole·HCl (4) (Method A). 1. 3-(2,3-Epoxypropoxy)-4-chloro-1,2,5-thiadiazole (36) and 3-Chloro-4-oxo-5-(3-chloro-2-hydroxypropyl)-Δ^2-1,2,5-thiadiazoline (37). A mixt of 30 g (0.22 mole) of 3-chloro-4-hydroxy-1,2,5-thiadiazole (**31**), 71 g (0.77 mole) of epichlorohydrin, and 0.6 ml of piperidine was maintained at 65-70° for 2 hr. Excess epichlorohydrin was removed at 95° at the aspirator. The 55 g of gummy residue was dissolved in Et_2O and refrigerated to give 18.3 g of cryst **37**, mp 95-103°. Recrystn from Et_2O provided pure **37**, mp 104.0-

‡R. Tull, L. Weinstock, and D. Mulvey, Merck Sharp & Dohme Research Laboratories, Rahway, N.J., private communication.

§All melting points were determined in capillary tubes and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. The ir spectra of all new compounds were consistent with the proposed structures. Optical rotations were detd on the isomers of **24** with a Zeiss photoelectric precision polarimeter. All others were detd visually with a Rudolph polarimeter.

105.5°. *Anal.* ($C_5H_6Cl_2N_2O_2S$) C, H, Cl, N, S.

The ethereal liquor from 37 was evapd to dryness giving 20.2 g of oil that was stirred for about 0.5 hr with 150 ml of 10% NaOH. The mixt was extd with Et_2O; the combined exts were washed with H_2O and evapd to yield 20.2 g of crude epoxide 36 suitable for use in the next procedure.

2. 3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-chloro-1,2,5-thiadiazole (4). A mixt of 40.2 g (0.21 mole) of crude 36 and 76 g (1.05 mole) of *tert*-$BuNH_2$ was heated with stirring at 60–70° for 2.5 hr. Excess *tert*-$BuNH_2$ was removed *in vacuo* and the 42.4 g of crude product dissolved by shaking with a mixt of Et_2O and H_2O contg 2.5 g of NaOH. The combined Et_2O exts were washed with H_2O and then with 3 *N* HCl. The aqueous acid layer was evapd to dryness and the dried solid recrystd from EtOH–Et_2O to give 31.3 g (49.5%) of the HCl salt 4, mp 159–161°. An analytical specimen had mp 161–163°. A sample of 4 when treated with aqueous Na_2CO_3 afforded the free base as colorless prisms from *i*-Pr_2O, mp 78–79°. *Anal.* ($C_9H_{16}ClN_3O_2S$) C, H, Cl, N, S. Equiv wt: calcd, 265.8; found, 268.6 ± 3.0.

3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole·HCl (24) (Method B). A mixt of 11.8 g (0.039 mole) of 4 and 65.5 ml (0.75 mole) of morpholine was heated with stirring at 125–135° for 4 hr and refrigerated overnight. The pptd morpholine HCl salt was collected and the filtrate evapd to dryness. The residue was shaken with 10 ml of H_2O contg 1.6 g of NaOH and extd with Et_2O. The combined dried Et_2O ext was treated with excess dry HCl to give 10.3 g of 24. Recrystn from anhyd Me_2CO–Et_2O gave an analytical specimen. Equiv wt: calcd, 352.9; found 353 ± 3.0. The free base was isolated as a cryst solid from *i*-Pr_2O, mp 71.5–72.5°. *Anal.* ($C_{13}H_{24}N_4O_3S$) C, H, N, S. Mass spectrum showed a mol wt of 316.

3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-*N*-*tert*-butylcarbamoyl-1,2,5-thiadiazole·HCl (29) (Method C). 1. 3-(3-Bromo-2-hydroxypropoxy-1,2,5-thiadiazole-4-carboxylic Acid (38). A mixt of 9.3 g (0.05 mole) of 3-allyloxy-1,2,5-thiadiazole-4-carboxylic acid (mp 138–139°) and 8.9 g (0.05 mole) of NBS was suspd in 50 ml of H_2O.[19] The mixt initially turned brown and evolved heat but after 1 min a colorless soln resulted. The soln was cooled and the pptd cryst solid was collected, washed with H_2O, and dried to give 8 g (56.5%) of the bromohydrin 38. *Anal.* ($C_6H_7BrN_2O_4S$) C, H, Br, N, S.

2. 3-(3-Bromo-2-hydroxypropoxy)-4-carbomethoxy-1,2,5-thiadiazole (39). A suspension of 5.66 g (0.02 mole) of 38 with a soln of 5 ml (excess) of AcCl in 40 ml of anhyd MeOH was stirred 18 hr at room temp. The resulting soln was evapd to dryness to afford a colorless oil whose ir spectrum was consistent with that for the ester 39. This material was used without further purification in the following step.

3. 3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-*N*-*tert*-butylcarbamoyl-1,2,5-thiadiazole·HCl (29). A mixt of 1.49 g (0.005 mole) of 39 in 6 ml (excess) of Me_3CNH_2 was refluxed 90 hr. The pptd *tert*-$BuNH_2$·HBr was collected and the filtrate evapd to dryness. The resulting oil was dissolved in $CHCl_3$, washed with H_2O, and evapd to dryness. The oil was dissolved in MeOH–Et_2O and treated with dry HCl to give pure 29 from MeOH–Et_2O.

1-*tert*-Butylamino-2,3-diaminopropane·3HCl (30). The amino-amide 29 (4.5 g, 0.015 mole) in 100 ml of dry THF was added during 15 min to 50 ml of a 1 *M* soln of borane in THF (0.055 mole) which was stirred at 0°. The mixt was refluxed 2.5 hr and left at room temp overnight. To this soln in the cold was added 5 ml of 6 *N* HCl, the excess THF distd, H_2O added, and the soln made alk. Et_2O extn afforded 0.9 g of unchanged 29, while extn with $CHCl_3$ gave 1.7 g of an oil. This oil was dissolved in MeOH–Et_2O and dry HCl passed in. The pptd solid was crystd from EtOH contg some HCl to give 0.6 g of the triamine·3HCl (30), mp 272–273°. *Anal.* ($C_7H_{19}N_3$·3HCl) H, Cl, N; C: calcd, 32.98; found, 32.52.

3-(3-*N*-Acetyl-*tert*-butylamino-2-acetoxypropoxy)-4-morpholino-1,2,5-thiadiazole (X). The HCl salt 24 converted to the free base (1 g, 3.1 mmoles) was stirred 26 hr in a 9 ml of Me_2SO with 6 ml of Ac_2O. Tlc indicated the disappearance of starting material and the presence of a new product. The isolated neutral fraction (1.25 g) was shown by ir spectroscopy to be an *O*,*N*-diacetyl deriv X. X was obtained by treatment of the base with Ac_2O alone. X (1.25 g) in 20 ml of MeOH left 1.25 hr with 4 ml of 1.25 *N* NaOH afforded 0.85 g of the free base of 24, identified by ir spectrum and tlc. Thus both Ac groups were removed. There was no indication of a preferential removal of one Ac group.

Attempted Oxidation of 3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole. A mixt of 4.5 g (0.025 mole) of fluorenone, 40 ml of C_6H_6 (anhyd), 1.58 g (0.005 mole) of free base, and 1.34 g (0.012 mole) of $KOCMe_3$ was stirred 4.5 hr at room temp. H_2O (50 ml) was added, the soln extd with Et_2O, the exts were evapd; the solids collected gave 0.3 g, mp 185° dec. Recrystn gave pure 3-hydroxy-4-morpholino-1,2,5-thiadiazole (XI), mp 196–198°. *Anal.* ($C_6H_9N_3O_2S$) C, H, N, S. No 3-(3-*tert*-butylamino-2-oxopropoxy)-4-morpholino-1,2,5-thiadiazole was isolated nor detected.

3-Hydroxy-4-morpholino-1,2,5-thiadiazole (XI). The free base from the HCl salt 24 (14.3 g, 0.043 mole) in 200 ml of C_6H_6 was stirred 16.5 hr at room temp with 0.11 mole of $KOCMe_3$. The mixt was poured over crushed ice and extd with Et_2O. The aqueous layer was acidified with HCl, and extd with Et_2O to give 3.7 g (44%) of XI.

(−)- and (+)-3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole Maleates (25 and 26). 1. Resolution of (±)-3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-chloro-1,2,5-thiadiazole (40). Racemic 40 (26.5 g, 0.1 mole) in 100 ml of EtOH added to a warmed soln of 38.6 g (0.1 mole) of *O*,*O*-di-*p*-toluoyl-(−)-tartaric acid in 225 ml of EtOH, and the mixt was left overnight at 5°. The pptd cryst solid was collected and recrystd 5 times from EtOH–MeOH (9:1) to give 21 g of enriched salt of the (+) base, mp 166.5–167.5°, $[\alpha]^{22}D$ 80.6° (*c* 2.5, MeOH). The free base was liberated as 7.9 g of a syrupy product that slowly solidified. Careful recrystn of this solid from hexane removed some racemic 40. Cropping of the filtrate gave 5.6 g of the (+) base 41, mp 58.5–62.5°. Further purification of 41 gave mp 58.5–59.5°, $[\alpha]^{20}D$ 7.22° (*c* 2.5, MeOH); HCl salt 6, mp 148–149.5°, $[\alpha]^{22}D$ 7.65° (*c* 2.5, MeOH). *Anal.* ($C_9H_{15}N_3O_2S$·HCl) C, H, Cl, N, S. All liquors and washings from the isolation of *O*,*O*-di-*p*-tolyoyl-(−)-tartrate of 40 were combined and treated with 5 *N* NaOH to give 14.3 g of solid, mp 58–76°. This solid was recrystd from C_6H_6 to afford 6.9 g of the (−) base 42, mp 57–60°. Further recrystn afforded pure 42, mp 58.5–59.5°, $[\alpha]^{20}D$ 7.31 (*c* 2.5, MeOH); HCl salt 5, mp 146–147°, $[\alpha]^{22}D$ 7.9° (*c* 2.5, MeOH). The mp of the purest samples of 41 and 42 was 58.5–59.5° whereas that of the racemate 40 was 79–80°.

2. (−)- and (+)-3-(3-*tert*-Butylamino-2-hydroxypropoxy-4-morpholino-1,2,5-thiadiazole Maleates (25 and 26). Treatment of 5.3 g of 41 with 5 vol of morpholine as in method B afforded the crude (+) base which was treated with maleic acid in *i*-PrOH to give 6.7 g (86%) of crude hydrogen maleate 26, mp 192–194° dec. Crystn from EtOH gave 3.8 g of 26, mp 201–202°, $[\alpha]^{21}D$ 5.55° (*c* 2.5, MeOH). Similarly 6.9 g of 42 was converted to (−)-3-(3-*tert*-butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole, and then converted to the hydrogen maleate 25 in 9.04 g (80%) yield. Recrystn of this material gave 5 g of 25, mp 201.5–202.5° dec $[\alpha]^{22}D$ 5.3° (*c* 2.5, MeOH).

3-Phenyl-4-oxo-5-(3-*tert*-butylamino-2-hydroxypropyl)-Δ^2-1,2,5-thiadiazoline·HCl (35). 1. 3-Phenyl-4-oxo-5-(3-chloro-2-hydroxypropyl)-Δ^2-1,2,5-thiadiazoline (III) and 3-Phenyl-4-(2,3-epoxypropoxy)-1,2,5-thiadiazole (43). A mixt of 7.5 g (0.042 mole) of 3-hydroxy-4-phenyl-1,2,5-thiadiazole, 11.7 g (0.126 mole) of epichlorohydrin, and 0.1 ml of piperidine was heated 1.5 hr at 84–91° until the tlc showed the absence of starting material. Excess epichlorohydrin was removed *in vacuo* and the residue crystd from C_6H_6 to give 3.65 g (32%) of III, mp 134–136.5°. *Anal.* ($C_{11}H_{11}ClN_2O_2S$) C, H, Cl, N, S. The structure was supported by nmr spectral data. The C_6H_6 liquors afforded 8.2 g of an oil which was treated with 25% NaOH to give the epoxide 43. 43 was condensed with *i*-$PrNH_2$ and *tert*-$BuNH_2$ to give 16 and 17, respectively.

2. 3-Phenyl-4-oxo-5-(3-*tert*-butylamino-2-hydroxypropyl)-Δ^2-1,2,5-thiadiazoline·HCl (35). A mixt of 3 g (0.011 mole) of the chlorohydrin III and 15 ml (5 mole) of Me_3CNH_2 was refluxed 3 hr, the mixt was left overnight, and the product was isolated as the HCl salt 35, mp 200–201°. *Anal.* ($C_{15}H_{21}N_3O_2S$·HCl) C, H, Cl, N, S. 3-Phenyl-4-oxo-5-(3-isopropylamino-2-hydroxypropyl)-Δ^2-1,2,5-thiadiazoline·HCl (34) was similarly obtained, mp 224–226° dec. *Anal.* ($C_{14}H_{19}N_3O_2S$) C, H, Cl, S, N: calcd, 12.74; found, 13.30. The free base had mp 84–85°. *Anal.* ($C_{14}H_{19}N_3O_2S$) C, H, N, S. The nmr and ir spectral data were consistent with this structure. 34 and 35 were inactive when tested for β-adrenergic blocking activity.

1-(2-Morpholinophenoxy)-3-isopropylamino-2-propanol (32). 1. *N*-[2-(2,3-Epoxypropoxy)phenyl]morpholine (44). 2-Morpholinophenol (35.8 g, 0.2 mole) was treated with 0.6 mole of epichlorohydrin as described in method A to give 21.6 g of crude epoxide 44, bp 113–120° (0.05 mm), which was suitable for the next procedure.

2. 1-(2-Morpholinophenoxy)-3-isopropylamino-2-propanol (32).

The epoxide 44 (4.7 g, 0.02 mole), 6.2 ml of *i*-PrNH$_2$ and 11 ml of MeOH, left 64 hr at room temp and worked up, gave 4.35 g of 32, mp 77.5–78.0° from Et$_2$O. *Anal.* ($C_{16}H_{26}N_2O_3$) C, H, N. 1-(2-Morpholinophenoxy)-3-*tert*-butylaminopropan-2-ol (33) was similarly prepd and isolated in 56.2% yield as the monophosphate monoethanolate, mp 175–176°. *Anal.* ($C_{17}H_{28}N_2O_2 \cdot H_3PO_4 \cdot C_2H_6O$) C, H, N, P. Similarly prepd were 1-(4-morpholinophenoxy)-3-isopropylamino-2-propanol, mp 98.5–99.5° (*i*-PrOH) [*Anal.* ($C_{16}H_{26}N_2O_3$) C, H, N] and 1-(3-morpholinophenoxy)-3-isopropylamino-2-propanol, isolated as the oxalate, mp 165–167.5° (EtOH) [*Anal.* ($C_{16}H_{26}N_2O_3 \cdot C_2H_2O_4$) C, H, N, O]. The last 2 compds were much less active in the β-adrenergic blocking screens than 32 and 33.

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Bisbenzimidazoles. Potent Inhibitors of Rhinoviruses[1]

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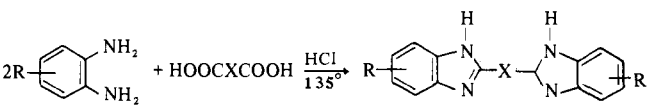
(*S*,*S*)-1,2-Bis(5-methoxy-2-benzimidazolyl)-1,2-ethanediol (**11**, Abbott 36683), reported in the literature as active against poliovirus type 1, was found in our laboratories to be a potent inhibitor of rhinoviruses in cell culture. A series of 27 bisbenzimidazoles and 11 related monobenzimidazoles were synthesized by the method of Phillips, namely, condensation of a substituted *o*-phenylenediamine with a carboxylic acid in 5 *N* HCl at 135°. None of the monobenzimidazoles was active against rhinoviruses. Eight bisbenzimidazoles in addition to **11** were active. Structural features of the bisbenzimidazoles essential for antiviral activity were: (1) no substituent in the 1 position of the benzimidazole; (2) a 5-methoxy or 5-ethoxy substituent; and (3) a two-carbon chain, unsubstituted or substituted by hydroxyl, connecting the two benzimidazoles.

Numerous derivatives of benzimidazole have been tested for antiviral activity.[2] In 1958, 2-(α-hydroxybenzyl)benzimidazole or HBB was reported to inhibit poliovirus type 1 in monkey kidney and HeLa cell cultures.[3] HBB has been extensively studied by Tamm and coworkers[4] and by others[2] and has been shown to inhibit several types of enteroviruses. More recently HBB has been found to inhibit rhinoviruses, although at relatively high concentrations.[5] In our laboratories HBB has been found to have weak activity against only a few serotypes of rhinovirus.

In 1963, O'Sullivan and Wallis[6] reported the antipoliovirus activity of 1,2-bis(2-benzimidazolyl)-1,2-ethanediol (**8**), an analog of HBB, and, in 1968, Akihama, *et al.*,[7] reported the synthesis and antipolio activity of three derivatives (**9**, **10**, **11**) of this compound which are substituted in the 5 position of the benzimidazole ring system. The percentage inhibitions of plaques of poliovirus type 1 by **8**–**11** at 10^{-5} *M* were 38, 33, 32, and 100, respectively. The minimal inhibitory concentration of the methoxy derivative **11** was 2×10^{-7} *M* compared with 10^{-4} *M* for HBB.

In our laboratories, Schleicher and coworkers[8] have found the methoxy derivative **11** to be a potent inhibitor of rhinoviruses in WI-38 cell culture: at a concentration of 0.1 μg/ml, **11** produced 100% inhibition of the cytopathic effect



(CPE). The chloro derivative **10** was inactive, but its hydrochloride salt was slightly active. The other two compounds (**8** and **9**), as well as their salts, were inactive. The potency and broad spectrum of inhibition of rhinoviruses by **11** encouraged us to synthesize a series of bisbenzimidazoles and some related monobenzimidazoles.

Results and Discussion

Chemistry. The benzimidazoles were synthesized by the method of Phillips,[9] namely, acid-catalyzed condensation of a substituted *o*-phenylenediamine with a carboxylic acid. The 27 bisbenzimidazoles synthesized are listed in Table I. All of the bisbenzimidazoles prepared in this study were symmetrically substituted, *i. e.*, with the same substituent on both benzimidazole moieties. Compound **3** was obtained by demethylation of **4**; we were unable to demethylate **11**. Compound **20** was obtained from an attempted oxidation of **11** with the use of nitric acid. Hydrochloride salts of