Acidic Epinephrine Analogues Derived from 1*H*,3*H*-2,1,3-Benzothiadiazole 2,2-Dioxide and from Trifluoromethanesulfonanilide. A New Synthesis of 1*H*,3*H*-2,1,3-Benzothiadiazole 2,2-Dioxide

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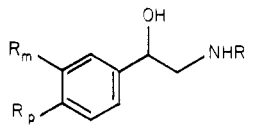
Treatment of *N,N'*-dibenzyl-1,2-diaminobenzene (**2**) successively with thionyl chloride and then *m*-chloroperbenzoic acid gave *N,N'*-dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxide (**4**), which gave (via routes analogous to standard epinephrine syntheses) four bicyclic catecholamine analogues **7a–d**. Hydrogenolysis of **4** yielded the parent heterocycle **5** in the first practicable synthesis avoiding expensive sulfamide (Scheme I). The trifluoromethanesulfonamidoacetophenones **8m** and **8p** on similar elaboration gave triflanilide catecholamine analogues **14m**, **14p**, **17m**, and **17p** (Scheme II). 4,4'-Dimethoxybenzhydrylamine (**15**) is recommended for the regiospecific synthesis of primary amines from epoxides (Scheme II). Series **7**, **14**, and **17** were inactive in animal cardiovascular screens. Selected compounds were also screened in bronchodilator and in in vitro dopamine–, clonidine–, and prazosin–receptor binding assays as appropriate; again no activity was observed. Steric, lipophilicity, and acidity factors are discussed, and the inactivity is ascribed to the high acidity of both systems ($pK_a \approx 4$).

Analogues of epinephrine (**1a**) containing the bioisosteric



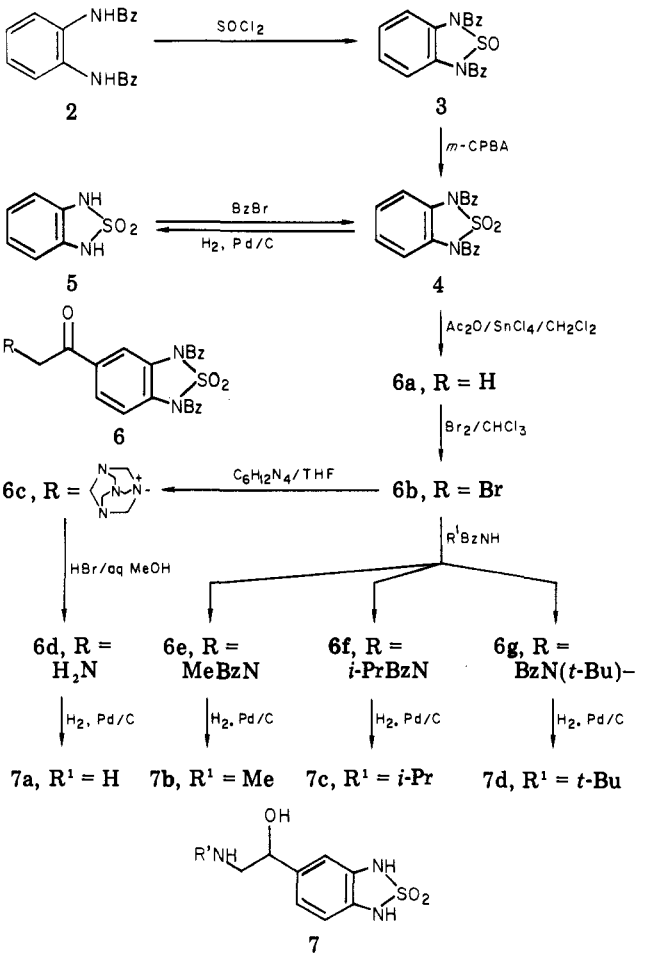
1a, R = Me; R_m = R_p = OH
b, R = *i*-Pr; R_m = $MeSO_2NH$; R_p = OH
c, R = *i*-Pr; R_m = H; R_p = $MeSO_2NH$
d, R = *i*-Pr; R_m = H; R_p = $BuSO_2NH$
e, R = *i*-Pr; R_m = H; R_p = $BzSO_2NH$

methanesulfonamido moiety, whose NH group has similar geometry and acidity to a phenolic OH group, include the β-agonist soterenol[1-3] (**1b**), the β-antagonists sotalol[3-6] (**1c**), and congeners **1d** and **1e**. We now report analogues of the above compounds containing the little-known 1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxide ring.[7,8] We also describe related triflanilides **14** and **17**, which we made in order to assess the separate influences of steric and electronic factors in catecholamine analogues.

Results and Discussion

Chemistry. Benzothiadiazoles (Scheme I). Benzimidazole was quaternized[9] with benzyl bromide, and the quaternary salt was hydrolyzed[9,10] to give *N,N'*-dibenzyl-1,2-diaminobenzene (**2**), which was elaborated according to Scheme I. Thus, the diamine **2** with thionyl chloride (compare Wright's procedure for aliphatic thiadiazoline monoxides)[11] yielded the new monoxide **3**, which was oxidized in good yield (*m*-chloroperbenzoic acid) to the key intermediate **4**. (We originally made **4** by benzylation of

Scheme I



5, but this latter compound was not readily accessible.[7,8,12,13] Indeed, our new synthesis of **4**, followed by *debenzylation*,[14] provides the first good route to **5**.) Friedel–Crafts

(1) Larsen, A. A.; Lish, P. M. *Nature (London)* **1964**, *203*, 1283.
(2) Larsen, A. A.; Gould, W. A.; Roth, H. R.; Comer, W. T.; Uloth, R. H.; Dungan, K. W.; Lish, P. M. *J. Med. Chem.* **1967**, *10*, 462.
(3) Uloth, R. M.; Kirk, J. R.; Gould, W. A.; Larsen, A. A. *J. Med. Chem.*, **1966**, *9*, 88.
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(10) Fischer, O. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 320.
(11) Wright, W. B. U.S. Patent 3 584 004, 1971.
(12) In our hands, the sulfamide procedure[7,8] was unreliable even when the diglyme was rigorously dried. Furthermore, sulfamide[13] is expensive and only intermittently available commercially.
(13) Brauer, G. "Handbook of Preparative Inorganic Chemistry"; Academic Press: New York and London, 1963; Vol. 1, p 482.

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Table I. Compounds Prepared by Reactions of Amines with Epoxides or Bromohydrins (Procedure A)

compd	S.M. (wt, g)	amine (wt, g)	solvent	vol, mL	temp, °C	time, h	yield, %	mp, °C	formula	anal.
6e	**6b** (4.71)	HNBzMe (2.42)	MeCN	50	reflux	3	42	197–212 [a]	$C_{30}H_{29}N_3O_3S$·HCl	C, H, N
6f	**6b** (4.71)	HNBz-*i*-Pr (2.98)	MeCN	50	reflux	3	70	125–144 [a]	$C_{32}H_{33}N_3O_3S$·HCl·AcOH·0.75H_2O	C, H, N
6g	6b (4.71)	HNBz-*t*-Bu (3.26)	MeCN	50	reflux	3	62	50–60 [a]	$C_{33}H_{35}N_3O_3S$·HCl·AcOH·H_2O	C, H, N
13m	11m (3.3)	H_2N-*i*-Pr (2.3)	EtOH	15	20	48	82	160–162 [b]	$C_{19}H_{23}F_3N_2O_3S$·HCl	C, H, N
13p	11p (0.5)	H_2N-*i*-Pr (0.35)	EtOH	20	20	48	35	209–212 [b]	$C_{19}H_{23}F_3N_2O_3S$·HCl	C, H, N
16m	12m (2.032)	15 (1.382)	*i*-PrOH	3	reflux	10	99	oil	$C_{31}H_{31}F_3N_2O_5S$	acc mass
16p	12p (1.433)	15 (0.977)	*i*-PrOH	2.6	reflux	7.3	18	oil [c]	$C_{31}H_{31}F_3N_2O_5S$	acc mass

[a] Converted to HCl salt (HCl/MeOH) and recrystallized from AcOH. [b] Converted to the HCl salt (HCl/Et_2O) and recrystallized from *i*-PrOH. [c] Isolated by column chromatography, Et_2O/SiO_2, R_f 0.48.

Table II. Compounds Prepared by Catalytic Hydrogenation (Procedure B)

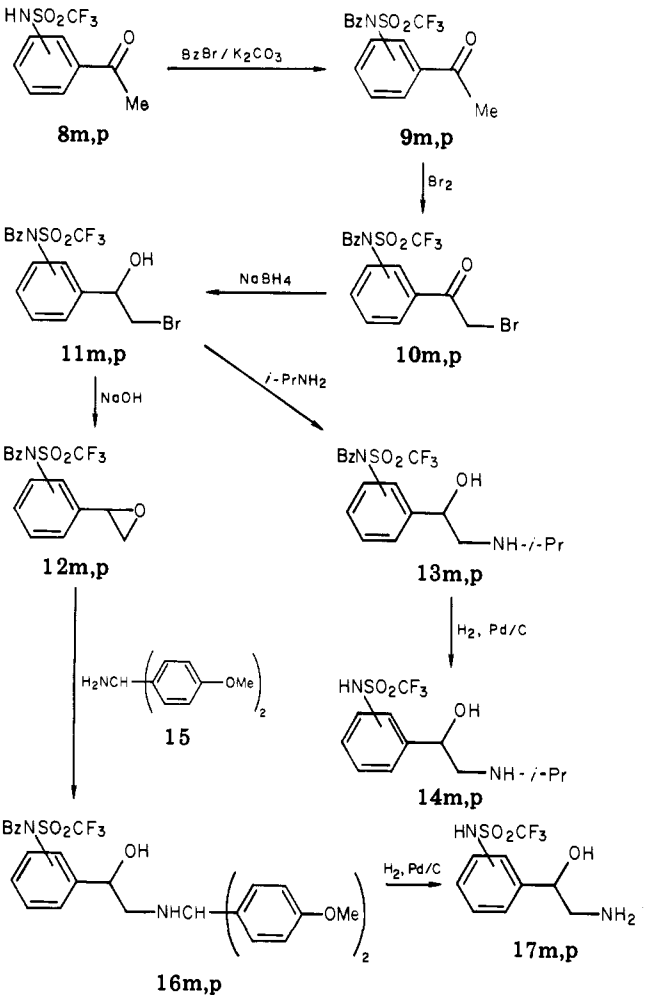
compd	S.M. (wt, g)	Pd/C, g	EtOH, mL	H, atm	temp, °C	time, h	yield, %	mp, °C	formula	anal.
5	4 (1.0)	2.0	20	3.5	50	5	94	175–180 [a]	*b*	
7a	6d (2.0)	2.0	200	1	65	3.5	16	glass	$C_8H_{11}N_3O_3S$·HBr·H_2O	C, H, N
7b	6e (1.5)	1.2	200	1	40	4	89	glass	$C_9H_{13}N_3O_3S$·HCl	C, N; H [c]
7c	6f (3.0)	1.5	200	1	60	4	50	glass	$C_{11}H_{17}N_3O_3S$·HCl	C, H, N
7d	**6g** (1.12)	1.75	200	1	60	5	57	glass dec 150	$C_{12}H_{19}N_3O_3S$·HCl	H, N; C [d]
14m	13m (2.65)	~1	100	3.3	50	~6	47	glass	$C_{12}H_{17}F_3N_2O_3S$·HCl	C, H, N
14p	13p (2.0)	~1	100	3.3	50	~6	34	172–174 [e]	$C_{12}H_{17}F_3N_2O_3S$·HCl	C, H, N
17m	16m (2.036)	2.0	75	3.6	50	6	57	glass	$C_9H_{11}F_3N_2O_3S$·0.75HCl	C, H, N
17p	16p (1.0)	1.0	200	3.3	50	6	49	glass	$C_9H_{11}F_3N_2O_3S$·HCl	*f*

[a] Triturated with toluene. [b] Reference 7. [c] H: calcd, 5.0; found, 5.5 [d] C: calcd, 44.78; found, 44.3. [e] Recrystallized from EtOAc. [f] Anal. calcd: C, 33.70; H, 3.77; N, 7.35. Found: C, 34.22; H, 4.31; N, 8.13.

acetylation of 4 gave ketone **6a**, which was readily brominated to **6b**; subsequent reaction with hexamethylenetetramine gave intermediate **6c**, which on hydrolysis with hydrobromic acid gave the primary amino ketone **6d**. Additionally, **6b** with the appropriate *N*-alkylbenzylamines gave the tertiary amino ketones **6e–g** (Table I). All four amines **6d–g** on catalytic hydrogenation were debenzylated with concurrent reduction of the ketone to the amino alcohol, yielding the desired final compounds **7a–d** (Table II).

Triflanilides. Two series were prepared from the known[15] meta- and para-substituted trifluoromethanesulfonamidoacetophenones **8** according to Scheme II. These triflanilides **8** were N-benzylated,[16] yielding ketones **9**, which were readily brominated in the side chain (confirmed by NMR). Bromo ketone **10** yielded (with sodium borohydride) bromo alcohols **11**, which with base gave epoxides **12**. Either **11** or **12**, with the appropriate amine (Table I) yielded amino alcohols **13** and **16**, requiring only hydrogenative deprotection to give the final compounds **14** and **17** (Table II). We used and strongly recommend 4,4′-dimethoxybenzhydrylamine[17–22] (**15**) for the regio-

Scheme II [a]



[a] Abbreviations used: m, meta substituted; p, para substituted.

(14) Catalytic debenzylation of sulfonamides was introduced by Kaiser, C.; Schwartz, M. S.; Colella, D. F.; Wardell, J. R. *J. Med. Chem.* **1974**, *17*, 49.

(15) Trepka, R. D.; Harrington, J. K.; McConville, J. W.; McGurran, K. T.; Mendel, A.; Pauly, D. R.; Robertson, J. E.; Waddington, J. T. *J. Agr. Food Chem.* **1974**, *22*, 1111.

(16) A reviewer has prepared **14p**, mp 173.5–174.5 °C, independently from **8** treated successively with Br_2, *i*-$PrNH_2$, and then $NaBH_4$, i.e., without benzyl blocking groups (personal communication). Our own usage of benzyl protection in the triflanilides had been prompted by our previous experience with the benzothiadiazoles **7**, where we had found it essential. The reviewer's and our own biological data on **14p** are in accord.

(17) Reductive removal of 4,4′-dimethoxybenzhydryl is reported in ref 18–20; preparations of 4,4-dimethoxybenzhydryl chloride[21] and amine **15**[22] have been reported, though we found it more convenient to make these intermediates by procedures inspired by ref 20.

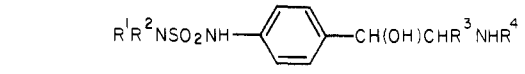
specific preparation of primary amines from epoxides (Scheme II): it has an ideal blend of bulk and reactivity, and the dimethoxybenzhydryl group is more readily removed than benzyl or benzhydryl from the intermediate secondary amines.

Pharmacology. Series **7**, **14**, and **17** were tested in vivo in the dog at 0.25 mg/kg iv for changes in heart rate, blood pressure, and left ventricular pressure. Most compounds were also tested for bronchodilator activity[23] in the guinea pig at 30 mg/kg. Series **7** were screened for dopamine-receptor binding,[24] and **14m** and **14p** were screened for clonidine-receptor[25] and prazosin-receptor[26] binding also. The effect of **7c** on isoprenaline-induced cardiac stimulation in the guinea pig atria was also investigated. No significant activity was observed (see paragraph at the end of paper concerning supplementary material).[16]

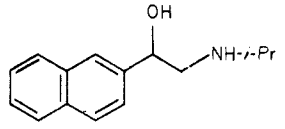
Acidities. Spectrometrically determined[27,28] pK_a values were as follows: **7a**, 4.68; **7b**, 4.67; **7c**, 4.68; **7d**, 4.70; **14m**, 3.63; **14p**, 3.65.

Discussion

The failure of the benzothiadazole ring to function as a catechol bioisostere was unexpected. Precedent includes not only soterenol and sotalol[1-6] but also active *acyclic sulfamides* **18**[29] (β-blockers of varying selectivity) and *nonsulfamide bicyclic analogues*, such as the early β-blocker pronethalol[30] (**19**), and various heterocyclic analogues, including the benzimidazolones **20a**,[31] **20b**,[32] and certain benzimidazoles.[33-37] These latter compounds include the hypertensive dopamine analogue 5-(2-aminoethyl)benzimidazole reported[33] in 1914, the more recent α-agonist **21a**,[34] and the β_2-agonist **21b**.[34,35] Also noteworthy are the peripheral vasodilator and hypotensive[38] cyclized practolol analogues **22**. Substantial activity is retained in the bulkier sulfonanilides **23a** (α stimulants and β blockers)[3] and **23b** (α or β agonists or α blockers).[2]



18, R^1–R^4 = various alkyl



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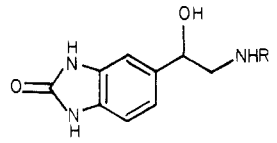
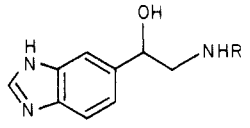
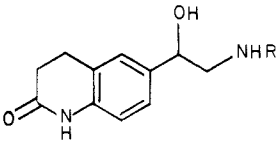


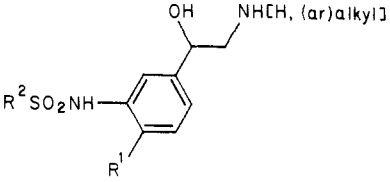
20a, R = *i*-Pr
b, R = Me

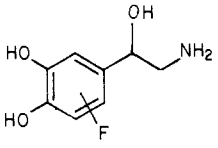


21a, R = H
b, R = *i*-Pr



22a, R = H
b, R = *i*-Pr





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23a, R^1 = H; R^2 = (ar)alkyl
b, R^1 = OH; R^2 = (ar)alkyl
c, R^1 = OH; R^2 = CH_2F

In view of the activities of **18–23**, it was clear that the inactivity of series **7a–d** was unlikely to be associated with steric hindrance or conformational restriction. A possible explanation was the unforeseen high acidity (pK_a = 4.7) of the benzothiadiazole ring. An additional factor, consequential on this high acidity though unlikely to be decisive in itself (especially in the in vitro tests), was solution instability due to autoxidation of the anion at physiological pH, observed by us and by Rees and co-workers[8] on the parent heterocycle **5** and related systems. This is likely to be of only marginal significance: biological activity is readily demonstrable[39] in the fluorinated norepinephrines **24** which, with pK_a = 7.8–8.5, are also largely ionized at physiological pH and are known to be readily autoxidized.

The trifluoromethanesulfonanilides **14** and **17** (also inactive) provide a powerful test of the influence of high acidity, provided that we can again legitimately dismiss steric and lipophilic effects of the CF_3 group. Inspection of the multidimensional steric parameters[40] suggest that CF_3 has the "length" of Cl and the "width" of I; overall its steric effect approximates to that of a bromine atom or a cyclopropyl group. The lipophilicities (octanol/water log *P* values) and acidities of relevant "parent molecules" are given in Table III. The steric and lipophilic properties of series **14** and **17** are clearly of the same magnitude as in active compounds **1d**, **1e**, **19**, and **23**.

Since active catecholamine analogues, including fluoromethanesulfonanilide[44] **23c**, have pK_a values greater than

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(22) Lattrell, R.; Lohaus, G. *Liebigs Ann. Chem.* **1974**, 870, report **17c** as an oil: in our hands this solidified, mp 50–54 °C.
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(36) Arnett, C. D.; Callery, P. S.; Zenker, N. *Biochem. Pharmacol.* **1977**, *26*, 377.
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(41) Hansch, C.; Leo, A. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; Wiley Interscience: New York, 1979; pp 203, 205, 203, 222, 214, and 249, respectively, and loc. cit.
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(43) Calculated from $k = 1.06 \times 10^{-10}$ (Washburn, E. W., Ed. "International Critical Tables"; McGraw-Hill: New York, 1929; Vol VI, p 273).

Table III. Log P and pK_a of "Parent Molecules"

	PhOH	o-$C_6H_4(OH)_2$	5	PhNH-SO_2Me	PhNH-SO_2CH_2F	PhNH-SO_2CF_3	naphthalene
log P	1.49[a]	0.85[a]	1.12[a]	0.95[b]	1.35[b]	3.03[b]	3.36[a]
pK_a	9.97[c]	9.50[c]	5.26[d]	8.85[b]	7.53[b]	4.45[b]	

[a] Reference 41. [b] Reference 42. [c] Reference 43. [d] This work.

7 (except **19** which has no acidic proton), the *aromatic ring* is substantially un-ionized at physiological pH, though the compounds are cationic due to the *side-chain nitrogen*. However, our triflanilides (and benzothiadiazoles) are almost totally ionized at both sites and are zwitterions. It seems very possible that these zwitterions may bind, unproductively, at sites other than the adrenergic receptors. Alternatively, but less likely, the consequent changes in partitioning and solubility properties may disrupt bioactivity.

In conclusion, our work suggests that compounds of acidities around pK_a = 4.8 are far too acidic to function as catecholamine agonists or antagonists, and the continuing search for useful adrenergic drugs should thus be conducted among compounds of substantially higher pK_a.

Experimental Section

Melting points were observed using a Reichert microscope RCH Kofler Micro heating stage and are quoted uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 Infracord grating spectrophotometer, 60-MHz proton magnetic resonance spectra were recorded on a Perkin-Elmer R12 instrument fitted with a double-resonance accessory and operating at 34 °C, and 100-MHz double-resonance spectra of compounds **6a**, **6b**, **14m**, and **14p** were obtained on a Varian XL-100 instrument. Mass spectra were recorded on a VG MM 16F machine or on a VG MM 7070F machine using direct-insertion probes. IR, UV, NMR, and MS were recorded for most compounds and were in accord with the structures proposed. The key NMR spectra (only compounds **6a**, **6b**, and **10**) are quoted below. Analyses were within ±0.4% of theoretical values when indicated by symbols of elements; occluded solvents were always confirmed by NMR. A few oils, containing variable amounts of occluded solvents, were characterized by accurate MS in conjunction with NMR and TLC confirmation of essential purity. Observed masses were within 9 ppm of calculated values. The pK_a determinations were obtained spectroscopically using a Gilford 250 UV spectrophotometer with matched 1-cm quartz cells and a Radiometer (Copenhagen) 4K 23216 KCl electrode and pH meter 26. Reference spectra were made on a Perkin-Elmer 137 UV grating spectrometer. Reaction mixtures and product purities were monitored qualitatively by TLC using either Merck precoated silica gel 60F-254 (glass-backed) plates or Polygram precoated SIL N-HR/UV254 (plastic back) plates with various suitable mobile phases. "ESD catalyst" refers to Engelhard Special Debenzylation Catalyst, code no. 4573, 5% palladium on carbon. Other catalysts worked but were less uniformly satisfactory.

Procedure A. Reactions of Amines with Epoxides or Bromo Compounds (Table I). The starting amine plus epoxide (**12**) or bromo compound (**6** or **11**) in an inert solvent were stirred at room temperature or refluxed, then the mixture was evaporated to dryness, and the product obtained was used crude (**16m**) or further processed according to Table I.

Procedure B. Catalytic Hydrogenations (Table II). Engelhard special debenzylation catalyst, 5% Pd/C, code no. 4573, was added to a small portion of ethanol and prehydrogenated in a Parr apparatus at 20 °C and 1 atm until uptake ceased. The starting material, dissolved in the remainder of the ethanol, was added, and hydrogenation was carried out according to Table II. The mixture was cooled and filtered through "Hyflo" filter aid, and the filtrate was evaporated to dryness. The residue was analyzed and tested without further treatment (for hygroscopic products) or processed further (Table II, footnotes *a* and *d*).

1,3-Dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole 2-Oxide (3). *N*,*N*'-Dibenzyl-1,2-diaminobenzene (**2**; 105.5 g, 0.33 mol) and triethylamine (75 g, 103 mL, 0.74 mol) in tetrahydrofuran (500 mL) in a 1-L three-necked flask equipped with a stirrer, a drying tube, and a low-temperature thermometer were cooled to −70 °C in a CO_2/acetone bath, and $SOCl_2$ (40 g, 24 mL, 0.34 mol) in THF (20 mL) was added with vigorous stirring over 45 min. The temperature was allowed to rise to ambient, and the mixture was stirred for a further 20 h and heated on a steam bath for another 2 h. After cooling, the suspension was diluted with a little toluene and filtered, and the solid collected was washed well with toluene (3 × 100 mL). The filtrates were combined and the solvent was evaporated. The residue was partitioned between toluene (1000 mL) and water (500 mL), and the toluene layer was dried ($MgSO_4$). Evaporation gave crude 1,3-dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole 2-oxide (96.2 g, 76%) as brown crystals, mp 115–117 °C. A sample recrystallized from ether gave white crystals, mp 119–120.5 °C. Anal. ($C_{20}H_{18}N_2OS$) C, H, N.

1,3-Dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-Dioxide (4). 1,3-Dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole 2-oxide (34.5 g, 0.1 mol) and 3-chloroperbenzoic acid (*m*-CPBA) (22 g, 85% techn, 0.1 mol) were stirred in 1,2-dichloroethane (400 mL) for 48 h at room temperature. The precipitated 3-chlorobenzoic acid formed was filtered off, a solution of *m*-CPBA (22 g) in 1,2-dichloroethane (150 mL) was added to the filtrate, and the mixture was stirred for a further 24 h at room temperature and then refluxed for 5 h. The precipitated 3-chlorobenzoic acid was filtered off, a further portion of *m*-CPBA (22 g) in 1,2-dichloroethane (150 mL) was added to the filtrate, and the mixture was stirred for 23 h at room temperature and filtered. The filtrate was shaken with saturated sodium bicarbonate solution (300 mL), dried ($MgSO_4$), and evaporated to yield a brown solid (30 g), which was recrystallized from toluene to give pure 1,3-dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxide (**4**; 24.2 g, 66%) as a white powder, mp 126–131 °C (lit.[7] 128–131 °C).

5-Acetyl-1,3-dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-Dioxide (6a). Stannic chloride (44.6 g, 20 mL, 0.17 mol) was added to a solution of acetic anhydride (8.8 g, 8.0 mL, 0.087 mol) and 1,3-dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxide (20 g, 0.06 mol) in 1,2-dichloroethane (200 mL). The mixture was stirred at room temperature for 1 h, during which time a deep green color developed. The mixture was poured into a mixture of concentrated HCl (20 mL) and ice–water (200 mL), and the two layers were vigorously stirred for 10 min. The brown 1,2-dichloroethane layer was poured off, dried ($MgSO_4$), and evaporated to give a crimson gum (20 g), which was crystallized from toluene/methanol (4:1) to give 5-acetyl-1,3-dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxide (19.3 g, 86%) as white crystals, mp 119–121 °C. A sample recrystallized from methanol/chloroform (5:1) gave the pure compound, mp 120–122 °C; NMR (100 MHz, $CDCl_3$) δ 2.41 (s, Me), 5.00 (s, 2 CH_2), 6.55 (d, J = 8.3 Hz, H-7), 7.22 (d, J = 1.6 Hz, H-4), 7.3–7.6 (m, H-6 + 2 Ph). The assignments weere confirmed by double irradiation, which located H-6 at δ 7.46. Anal. ($C_{22}H_{20}N_2O_3S$) C, H, N.

5-(2-Bromoacetyl)-1,3-dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-Dioxide (6b). A solution of bromine (2.4 g, 0.82 mL) in chloroform (25 mL) was added dropwise over 5 min to a solution of **6a** (6.0 g, 0.0153 mol) in chloroform (200 mL). The bromine color faded over 10 min, and stirring was continued for a further 30 min. Hydrogen bromide was evolved. The solvent was removed, and the residual gum was stirred vigorously with methanol (30 mL), causing product (4.4 g, 61%) to crystallize as a white powder. Recrystallization of a sample from methanol/ethanol acetate (1:1) gave the pure product **6b** as white crystals, mp 137–139 °C; NMR (100 MHz, $CDCl_3$) δ 4.26 (s, CH_2), 5.05 (s, 2 CH_2), 6.61 (d, J = 9.0 Hz, H-7), 7.26 (d, J = 1.8 Hz, H-4), 7.35–7.65 (m, H-6 + 2 Ph). Anal. ($C_{22}H_{19}BrNO_3S$) C, H, N.

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5-(2-Aminoacetyl)-1,3-dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-Dioxide (6d). Hexamethylenetetramine (0.9 g) was added to a solution of **6b** (3.0 g, 0.0064 mol) in THF (200 mL). The mixture was stirred for 3 h at room temperature and filtered, the residue (crude **6c**) was dissolved by heating in a mixture of methanol (50 mL) and 48% aqueous HBr (5 mL), and the solution was refluxed for 3 h. The hot solution was cooled and water (25 mL) was added. The precipitate formed was filtered off and recrystallized from methanol to yield pure **6d** as the hydrobromide (1.55 g, 52%) as white crystals, mp 210–222 °C. Anal. ($C_{22}H_{21}N_3O_3S$·HBr) C, H, N.

***N*-Benzyl-*N*-(3-acetylphenyl)trifluoromethanesulfonamide (9m).** *N*-(3-Acetylphenyl)trifluoromethanesulfonamide[16] (8m; 6.75 g, 0.025 mol), benzyl bromide (4.7 g), and anhydrous potassium carbonate (13.8 g) in acetone (125 mL) were refluxed for 2 h, evaporated to low bulk, and partitioned between ether (50 mL) and water (50 mL); the organic layer was evaporated to yield the product **9m** (9.7 g, 112%) containing a little occluded solvent. Prolonged drying gave a pure sample, with satisfactory spectra. Anal. ($C_{16}H_{14}F_3NO_3S$) C, H, N.

***N*-Benzyl-*N*-(4-acetylphenyl)trifluoromethanesulfonamide (9p)** was obtained similarly to **9m**, starting from **8p**:[16] mp 55–57 °C (from petrol, bp 60–80 °C); yield 86%. Anal. ($C_{16}H_{14}F_3NO_3S$) C, H, N.

***N*-Benzyl-*N*-[3-(bromoacetyl)phenyl]trifluoromethanesulfonamide (10m).** Compound **9m** (0.025 mol) in chloroform (80 mL) was treated with 40% hydrogen bromide in acetic acid (1 mL) and then bromine (4 g in 20 mL chloroform) was added dropwise over 3 min. (The bromine was decolorized instantaneously; if the HBr/AcOH initiator was omitted, the reaction was unreliable.) After 5 min, the mixture was evaporated to dryness to give the desired product (quantitative) as an oil. Side-chain bromination was confirmed by NMR ($CDCl_3$), showing CH_2Br at δ 4.26 (compare **9m** CH_3 at δ 2.45). Anal. TLC, accurate MS.

The 4-(bromoacetyl) isomer (10p) was obtained similarly from **9p**. Anal. TLC, MS.

***N*-Benzyl-*N*-[3-(2-bromo-1-hydroxyethyl)phenyl]trifluoromethanesulfonamide (11m).** Bromo ketone **10m** (9.6 g, 0.022 mol) was stirred in methanol (100 mL) at 0–5 °C and sodium borohydride (0.83 g, 0.022 mol) was added portionwise over 5 min. The mixture was allowed to warm to ambient temperature over 0.50 h. The mixture was evaporated to dryness and the residue was triturated with chloroform (2 × 50 mL); the chloroform layer was evaporated to low bulk and filtered, and the filtrate (~5 mL) was diluted with petrol, bp 40–60 °C (30 mL), depositing product (6.2 g, 64%) in two crops. This product slowly solidified (mp 61–63 °C) and was of adequate purity for conversion to **12m**. The mother liquors slowly deposited a pure sample of **11m**, mp 66–67 °C. Anal. ($C_{16}H_{15}BrF_3NO_3S$) C, H, N.

***N*-Benzyl-*N*-[4-(2-bromo-1-hydroxyethyl)phenyl]trifluoromethanesulfonamide (11p)**, an oil, was prepared (analogously to **11m**) from **10p** in 77% yield. Anal. TLC, accurate MS.

***N*-Benzyl-*N*-[3-(2-oxiranyl)phenyl]trifluoromethanesulfonamide (12m).** A methanolic solution (100 mL) of crude bromohydrin **11m** (0.025 mol) was treated with aqueous 2 N sodium hydroxide (25 mL to pH 11), then diluted with water (200 mL), and extracted with ether (200 mL). The ether extracts on evaporation gave the crude product as an oil (8.0 g), which was chromatographed over Kieselgel (Merck 60H no. 7736, 200 g), developing and eluting with dichloromethane, collecting product at R_f ~0.75. Evaporation of the fractions containing product gave pure **12m** (4.0 g 45%), mp 36–40 °C. Anal. ($C_{16}H_{14}F_3NO_3S$) C, H, N.

***N*-Benzyl-*N*-[4-(2-oxiranyl)phenyl]trifluoromethanesulfonamide (12p).** Bromohydrin **11p** (3.6 g, 0.00826 mol) in methanol (30 mL) was treated with 4 N sodium hydroxide (4.3 mL) over 5 min, stirred for a further 5 min, and diluted with water (60 mL), and the mixture was extracted with petrol, bp 40–60 °C (4 × 20 mL), and ether (2 × 30 mL); the organic extracts on evaporation yielded product **12p** (an oil, 2.5 g, 85%) of high purity. Anal. ($C_{16}H_{14}F_3NO_3S$) H, N; C: calcd, 53.78; found, 53.30.

4,4′-Dimethoxybenzhydrylamine (15). From Chloride 17b. 4,4′-Dimethoxybenzhydrol (Aldrich; 7.33 g, 0.03 mol) in ether (100 mL) was saturated with hydrogen chloride. The mixture was evaporated to dryness, and the residue was redissolved in ether (80 mL), decanted from ~1 mL aqueous phase, and reevaporated to yield 4,4′-dimethoxybenzhydryl chloride (7.7 g, 98%) as an oil, which quickly solidified, mp 79–81 °C (lit.[21] 83–84 °C). This chloride (0.5 g, 0.00191 mol) in chloroform (5 mL) was added to chloroform (100 mL) saturated with ammonia gas (1.1 g) dropwise with stirring; the mixture was stirred for 2 h and then washed with water (2 × 20 mL); the chloroform layer on evaporation yielded product **15** (0.5 g, 100%) as a clear oil, which solidified (mp 50–54 °C): previously reported[22] as an oil.

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Supplementary Material Available: Biological data on series **7**, **14**, and **17** (1 page). Ordering information is given on any current masthead page.

Alkylating Angiotensin II Analogues:[1] Synthesis, Analysis, and Biological Activity of Angiotensin II Analogues Containing the Nitrogen Mustard Melphalan in Position 8

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Melphalan derivatives suitable for peptide synthesis, i.e., Boc-Mel and Mel-OBzl·HCl, have been prepared, and the integrity of their nitrogen mustard alkylating groups was examined by NMR, Volhard chlorine analysis, and colorimetric assay with 4-(*p*-nitrobenzyl)pyridine. By using the sensitive colorimetric assay, the stability of melphalan toward conditions commonly used for peptide synthesis, purification, and bioassay was evaluated. Further qualitative and quantitative assessment of the integrity of nitrogen mustard groups in angiotensin II was attempted in order to evaluate the significance of the observed biological results. [Ac-Asn[1],Mel[8]]angiotensin II was a potent competitive antagonist of angiotensin II in vitro (rat uterus) but a transient and reversible inhibitor in vivo.

Although a wide scope of effects has been shown for many peptide hormones, their clinical application has been fairly limited,[2] partially due to the rapid inactivation of these peptides in vivo. One approach to counter this lim-

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