Antimicrobials. 3. Benzothiazolylphenylalkylamines

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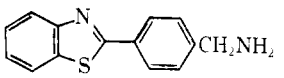
Received June 22, 1971

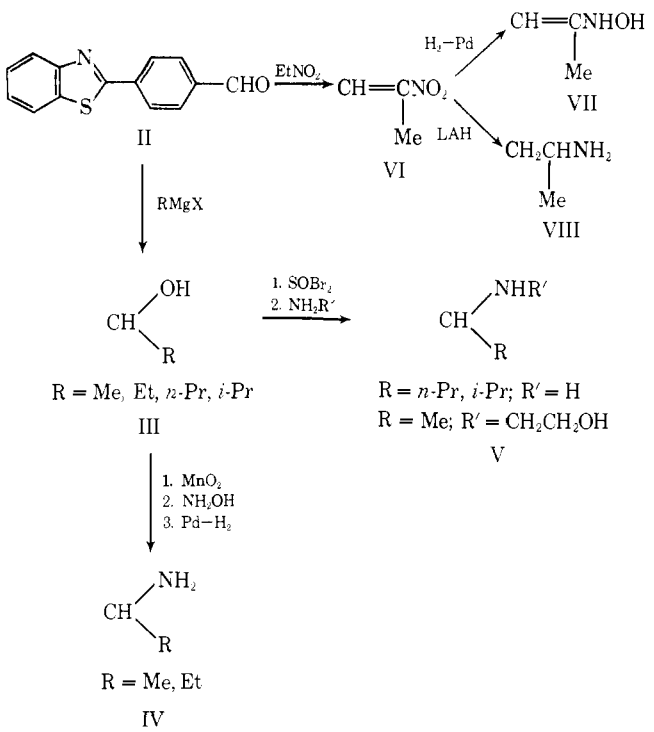
In a previous paper,[1] we described the preparation and antimicrobial properties of 4-(2-benzothiazolyl)-benzylamine (I) and related compounds. It was further shown[1,2] that by suitable structural modifications, the activity shown by I, particularly against *Streptococcus pyogenes*, could be considerably enhanced. In an effort to gain further information about structure–activity relationships within this series, and in the hope of producing compounds with useful antibacterial activity, a further series of compounds has been prepared. We were particularly interested in studying the effect on activity of substituents on the CH_2 group of I and of lengthening of the aliphatic chain, and the chemical and biological results of this investigation are reported here.



I

Chemistry.—Most of the compounds were prepared using the readily available[1] aldehyde (II; Scheme I) or

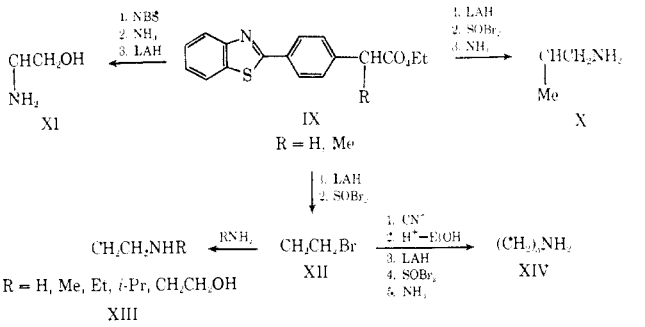
SCHEME I



the esters[3] (IX; Scheme II) as precursors.

The aldehyde II reacted with the appropriate Grignard reagent to afford the alcohols III. These were either converted *via* the Br compounds to the amines V or were oxidized to the corresponding ketones and these, as their oximes, reduced catalytically to afford the amines IV. Condensation of II with $EtNO_2$ produced the nitrostyrene VI which underwent partial reduction with Pd–H_2 to give the unsaturated hydroxylamine VII. With LAH, however, reduction was complete, and the required amine VIII was obtained. The analog X was prepared from the α-methyl ester IXb by the sequence shown. Compd IXb underwent smooth bromination with NBS and the resulting α-bromo ester was treated with NH_3 and then with LAH to yield XI. Similarly, reduction of IXa with LAH, followed by treatment with $SOBr_2$, gave XII which was treated with a series of amines to give compounds XIII. The nitrile, obtained in a conventional manner from XII, could not be reduced satisfactorily either by LAH or catalytically to give XIV. This amine was therefore prepared in the conventional manner using the longer route shown.

SCHEME II



Biological Results.—As is apparent from the results in Table I, the activity of the parent compound (I) against *Streptococcus pyogenes* can be improved considerably by substitution of the CH_2 with a suitable alkyl group (**1–4**). A similar increase in activity was obtained by lengthening of the side chain to 2 C atoms (**6**), but a further increase to a 3-C chain (**7**) did not lead to increased activity. Similarly, a combination of an α- or β-alkyl group in a 2-C chain (**5** or **8**) offered no advantages. None of the compds was significantly active *in vitro* against *Mycobacterium tuberculosis* or *Entamoeba histolytica*.

Experimental Section[4]

General Method for Amines (Table I).—The appropriate Br compound and amine were heated under the conditions given, and the products were isolated by acid extn. Except for **5** and **8**, yields were in excess of 50%.

General Methods for Alcohols (Table II). A.—Compds **17–20** were prepd from the appropriate Grignard reagent and 4-(2-benzothiazolyl)benzaldehyde[1] in Et_2O–C_6H_6 (1:1).

B.—Compds **21–23** were prepd by redn of the appropriate ester with LAH in Et_2O. Both methods gave yields in excess of 70%.

General Method for Bromo Compounds (Table III, 24–29).—The appropriate alcohol was refluxed for 1–2 hr in C_6H_6 with excess $SOBr_2$; dild with Et_2O, washing with $NaHCO_3$ soln and H_2O, and evapn gave the product. Yields were in excess of 60%.

4-(2-Benzothiazolyl)acetophenone (32) was prepd by oxidn of soln of **17** in EtOAc with activated MnO_2 (10 g/g) for 15 min at

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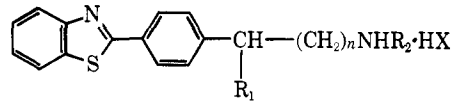
(1) P. J. Palmer, G. Hall, R. B. Trigg and J. V. Warrington, *J. Med. Chem.*, **14**, 1223 (1971).

(2) P. J. Palmer, R. J. Ward, and J. V. Warrington, *ibid.*, **14**, 1226 (1971).

(3) D. E. Evans, British Patent Application No. 1971/09483 (1971).

(4) Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Melting points were determined with a Büchi apparatus using open capillary tubes. Ir spectra were recorded on a Perkin-Elmer 237 spectrophotometer for Nujol mulls.

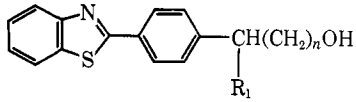
TABLE I



No.	R_1	R_2	n	X	Amine–Solvent	Time, hr, Temp (°C)	Mp, °C	Cryst	Formula	Analysis	MIC[k]
1	Me	H	0	Cl	See Experimental Section		284–286	EtOH	$C_{15}H_{15}ClN_2S \cdot H_2O$	C, H, Cl, N	0.8
2[a]	Et	H	0	Cl	See Experimental Section		303–304	EtOH–DMF	$C_{16}H_{17}ClN_2S$	C, H, Cl, N	1.6
3[b]	*n*-Pr	H	0	Cl	Liq NH_3–C_6H_6 (3:1)	24 (110)	290–291	2 *N* HCl	$C_{17}H_{19}ClN_2S$	C, H, Cl, N	1.6
4	*i*-Pr	H	0	[c]	Liq NH_3–C_6H_6 (3:1)	24 (110)	91–92	Hexane	$C_{17}H_{18}N_2S$	C, H, N	0.8
5[d]	Me	H	1	Br	Liq NH_3–C_6H_6 (3:1)	24 (110)	256–257.5	EtOH	$C_{16}H_{17}BrNS$	C, H, N	1.6
6	H	H	1	Cl	See Experimental Section		316–318	DMF	$C_{15}H_{15}ClN_2S$	C, H, Cl, N	0.4
7[e]	H	H	2	Br	Liq NH_3–C_6H_6 (3:1)	24 (110)	283.5–284.5	*i*-PrOH	$C_{16}H_{17}BrN_2S$	C, H, N	0.8
8[f]	H	Me	1	Br	33% $MeNH_2$–EtOH	24 (165)	268–269	H_2O	$C_{16}H_{17}BrN_2S$	C, H, Br, N	3.1
9	H	Et	1	Br	$EtNH_2$ (anhyd)	24 (165)	275–275.5	2 *N* HBr	$C_{17}H_{19}BrN_2S$	C, H, N; Br[g]	1.6
10	H	*i*-Pr	1	Cl	*i*-$PrNH_2$	24 (165)	286.5–288	[h]	$C_{18}H_{21}ClN_2S$	C, H, Cl, N	1.6
11	Me	CH_2CH_2OH	0	[c]	$HOCH_2CH_2NH_2$	3 (100)	111.5–112	C_6H_6	$C_{17}H_{18}N_2OS$	C, H, N	0.8
12[i]	CH_2OH	H	0	Cl	See Experimental Section		259–261	EtOH–Et_2O	$C_{16}H_{15}ClN_2OS$	C, H, N	12.5
13	H	CH_2CH_2OH	1	Cl	$HOCH_2CH_2NH_2$	6 (170)	262.5–263.5	Aq EtOH	$C_{17}H_{19}ClN_2OS$	C, H, Cl, N	0.4
14	CO_2Et	H	0	[c]	Satd NH_3–CH_2Cl_2	24 (25)	96.5–98	80–100° Petr ether	$C_{17}H_{16}N_2O_2S$	C, H, N	
15	CO_2H	H	0	[c]	0.880 NH_4OH	48 (25)	238–242	[i]	$C_{15}H_{12}N_2O_2S$	C, H, N	200
16	BTh–CH_2CHNH_2·HCl (Me)				See Experimental Section		305.5–306	MeOH–Et_2O	$C_{16}H_{17}ClN_2S$	C, H, N	1.6

[a] Free base, mp 107.5–109° (hexane). *Anal.* ($C_{16}H_{16}N_2S$) C, H, N. [b] Free base, mp 85–85.5° (hexane). *Anal.* ($C_{17}H_{18}N_2S$) C, H, N. [c] Free base. [d] Major product (74%) was 4-(2-benzothiazolyl)-α-methylstyrene, mp 128–129.5° (EtOH). *Anal.* ($C_{16}H_{13}NS$) C, H, N. [e] *N*-Ac compd, mp 153–153.5° (*i*-PrOH–hexane). *Anal.* ($C_{18}H_{16}N_2OS$) C, H, N. [f] *N,N*-Bis{2-[4-(2-benzothiazolyl)-phenyl]ethyl}methylamine (30%) also isolated: HCl, mp 288–289° dec (DMF–2 *N* HCl). *Anal.* ($C_{31}H_{26}ClN_3S_2$) C, H, N. [g] Br: calcd, 22.0; found, 22.5. [h] Purified by leaching with DMF. [i] Free base, mp 136–136.5° (C_6H_6). *Anal.* ($C_{15}H_{14}N_2OS$) C, H, N; *N,O*-Ac_2 deriv, mp 208–209° (MeOH). *Anal.* ($C_{19}H_{18}N_2O_3S$) C, H, N. [j] Purified by repptn from 1 *N* HCl with NH_4OH. [k] MIC in μg/ml against *S. pyogenes* detd by serial tube diln in nutrient broth medium (*cf.* ref 1).

TABLE II



No.	R_1	n	Method	Mp, °C	Cryst	Formula[a]
17	Me	0	A	166.5–167.5	EtOH	$C_{15}H_{13}NOS$
18	Et	0	A	182–183	C_6H_6	$C_{16}H_{15}NOS$
19	*n*-Pr	0	A	170–172	Me_2CO–*i*-Bu	$C_{17}H_{17}NOS$
20	*i*-Pr	0	A	177–177.5	Me_2CO–*i*-Bu	$C_{17}H_{17}NOS$
21	H	1	B	124–125	C_6H_6	$C_{15}H_{13}NOS$
22	Me	1	B	112.5–115	C_6H_6–hexane	$C_{16}H_{15}NOS$
23	H	2	B	97.5–98	C_6H_6–hexane	$C_{16}H_{15}NOS$

[a] All compds were analyzed for C, H, N.

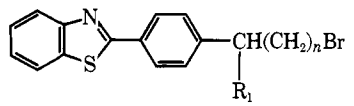
25°. **4-(2-Benzothiazolyl)propiophenone (33)** was prepd similarly from **18**.

The oximes (34, 35) were prepd by refluxing the appropriate ketone in EtOH contg $NH_2OH \cdot HCl$ (1.1 equiv) and 1 *N* NaOH (1.1 equiv); the reaction was followed by tlc.

Ethyl 4-(2-benzothiazolyl)-α-bromophenylacetate (30) was prepd in high yield by refluxing ethyl 4-(2-benzothiazolyl)phenylacetate (1 g), NBS (0.6 g), Bz_2O_2 (10 mg), and CCl_4 (30 ml) for 3 hr under W lamp illumination. Hydrolysis with const bp HBr for 0.5 hr gave the free acid **31**.

Hydrogenation of 34 and 35.—The oxime **34** (7.9 g) in Ac_2O (200 ml) contg Raney Ni (Tl, 1 g) and NaOAc (3.5 g) was hydrogenated at 3.5 kg/cm² and 50° for 6 hr, the mixt was poured into 2 *N* HCl (1 l.), stirred 12 hr, and filtered, and the product (6.79 g), mp 202.5–204.5°, was isolated. Crystn gave the *N*-Ac deriv of **1**, mp 208–209° (EtOH). *Anal.* ($C_{17}H_{16}N_2OS$) C, H, N. Hydrolysis in refluxing 6 *N* HCl for 16 hr gave 1 (81%) (Table I). Simi-

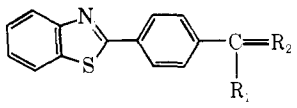
TABLE III



No.	R_1	n	Mp, °C	Cryst	Formula	Analysis
24	Me	0	107–109.5	EtOAc–60–80° petr ether	$C_{15}H_{12}BrNS$	H, Br, N; C[a]
25	*n*-Pr	0	111–113	Hexane	$C_{17}H_{16}BrNS$	H, N; C[b]
26	*i*-Pr	0	114.5–115.5	Hexane	$C_{17}H_{16}BrNS$	C, H, Br, N
27[c]	H	1	117–119	*i*-PrOH	$C_{15}H_{12}BrNS$	C, H, Br, N
28	Me	1	87–89	Hexane	$C_{16}H_{14}BrNS$	C, H, N
29	H	2	98.5–99	*i*-PrOH	$C_{16}H_{14}BrNS$	C, H, Br, N
30[d]	CO_2Et	0	119–120	*i*-PrOH	$C_{17}H_{14}BrNO_2S$	C, H, N
31[d]	CO_2H	0	203–203.5 dec	Me_2CO	$C_{15}H_{10}BrNO_2S$	C, H, N

[a] C: calcd, 56.6; found, 54.1. A satisfactory anal. for C could not be obtd despite repeated crystns and indicated purity by tlc. [b] C: calcd, 59.0; found, 58.3. [c] Cl analog prepd in CH_2Cl_2–$SOCl_2$ at room temp for 1 hr, mp 107–108° (*i*-PrOH). *Anal.* ($C_{15}H_{12}ClNS$) C, H, Cl, N. [d] see Experimental Section.

TABLE IV



No.	R_1	R_2	Mp, °C	Crystn	Formula[c]
32[a]	Me	O	179–181	EtOAc	$C_{15}H_{11}NOS$
33[b]	Et	O	159.5–161	EtOAc	$C_{16}H_{13}NOS$
34	Me	NOH	238.5–240	EtOH–H_2O (1:1)	$C_{15}H_{12}N_2OS$
35	Et	NOH	189–191	EtOH	$C_{16}H_{14}N_2OS$

[a] 2,4-DNP, mp 297.5–298.5 dec (DMF). *Anal.* ($C_{21}H_{15}N_5O_4S$) C, H, N. [b] 2,4-DNP, mp 246–248° dec (DMF). *Anal.* ($C_{22}H_{17}N_5O_4S$) C, H, N. [c] All compds were analyzed for C, H, N.

lar reduction of **35** gave the *N*-Ac deriv of **2**, mp 193–193.5° (C_6H_6) [*Anal.* ($C_{16}H_{16}N_2OS$) C, H, N], and the amine·HCl **2** (Table I).

Hydrogenation of 4-(2-benzothiazolyl)phenylacetonitrile.—Similar redns gave the *N*-Ac deriv of **6**, mp 172.5–174° (C_6H_6) [*Anal.* ($C_{17}H_{16}N_2OS$) C, H, N], and thence **6** (Table I).

4-(2-Benzothiazolyl)-α-hydroxymethylbenzylamine·HCl (**12**) was prepd by redn of **14** with LAH in Et_2O in the usual way (Table I).

3-[4-(2-Benzothiazolyl)phenyl]propionitrile was prepd from **27** by heating with NaCN (1.1 equiv) in DMSO at 95° for 2 hr. Dilh with H_2O, gave a solid (100%), mp 110–113°. The pure nitrile had mp 113–114° (*i*-PrOH). *Anal.* ($C_{16}H_{12}N_2S$) C, H, N.

Ethyl 3-[4-(2-benzothiazolyl)phenyl]propionate was prepd by refluxing the above compd (3.35 g) in EtOH (75 ml) contg H_2SO_4 (concd, 18 ml), for 7 hr, pouring onto ice, extg with Et_2O, and evapg to give 3.85 g (98%), mp 46–47°. The pure compd had mp 48–49° (hexane). *Anal.* ($C_{18}H_{17}NO_2S$) C, H, N. Alk hydrolysis gave the acid, mp 184–187° [subl 170° (0.01 mm)]. *Anal.* ($C_{16}H_{13}NO_2S$) H, N; C: calcd, 67.8, found, 67.3.

4-(2-Benzothiazolyl)-β-methyl-β-nitrostyrene.—4-(2-Benzothiazolyl)benzaldehyde (5 g), $MeNO_2$ (50 ml), and *n*-$BuNH_2$ (10 drops) were refluxed 3 hr and cooled, and the solid (4.25 g, 69%), mp 187–189°, was collected. The pure styrene had mp 188–190.5° ($MeNO_2$). *Anal.* ($C_{16}H_{12}N_2O_2S$) C, H, N.

4-(2-Benzothiazolyl)-β-hydroxyamino-β-methylstyrene was prepd by redn of the above in EtOH contg 2 *N* HCl and 10% Pd/C at 14.06 kg/cm² for 4 hr. Filtration, evapn, neutralization, and extn with Et_2O gave the styrene, mp 182.5–183° (C_6H_6–EtOH). *Anal.* ($C_{16}H_{14}N_2OS$) C, H, N.

2-Amino-1-[4-(2-benzothiazolyl)phenyl]propane (**16**) prepd (63%) by redn of the above compd with LAH in Et_2O, had mp 120–120.5° (EtOAc–hexane), [*Anal.* ($C_{16}H_{16}N_2S$) C, H, N], HCl, mp 305.5–306° (MeOH–Et_2O). *Anal.* ($C_{16}H_{17}ClN_2S$) C, H, N.

Acknowledgments.—The authors wish to thank Mr. W. K. Stevens and his staff for the biological results, and Mr. R. J. Clark for the microanalyses.

Synthesis and Norepinephrine-Depleting Activity of Some Esters of Metaraminol

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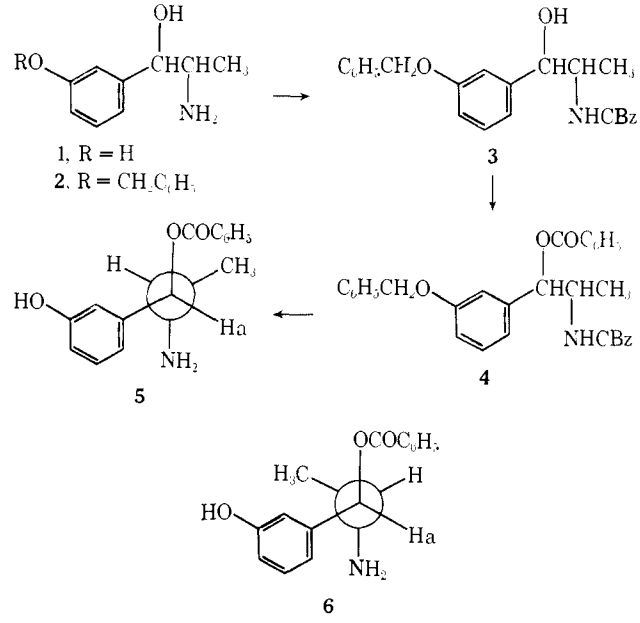
Received April 5, 1971

In a previous paper of this series,[2] it was reported that several ethers of the phenolic OH of metaraminol (**1**), (−)-erythro, were found to deplete the mouse heart of norepinephrine and to replace it with the substitute transmitter metaraminol.[3] Evidence was also presented showing that dealkylation of the ethers to metaraminol was necessary for norepinephrine depletion to occur. It was therefore of interest to consider other derivatives of metaraminol that would be susceptible to metabolic conversion to the phenethanolamine. In this report, we describe the synthesis and catecholamine-depleting activity of some esters of the side chain OH of metaraminol.

Chemistry.—Synthesis of the erythro benzoyl ester **5** uncontaminated by the threo isomer **6**[4] was accomplished by acylation of **3** in which the amino and phenolic OH functions of metaraminol were protected by the CBZ and benzyl ether blocking groups (Scheme I).

SCHEME I



Both protective groups were removed from **4** in one step by catalytic hydrogenation under acid conditions to give the (+)-erythro benzoyl ester **5**. The assignment of erythro stereochemistry to **5** was confirmed by nmr measurements which showed the expected erythro spin coupling constant of 4.0 Hz (at 6.20 ppm)[2,5] for the carbinol ester hydrogen H_a. Since this sequence of reactions would not be expected to affect the configuration at either of the 2 asymmetric centers in metaraminol, the (+)-erythro ester **5** has the same absolute configuration as metaraminol (*αR*, 1*S*).

The benzoyl ester **5** was also prepared by a method used for conversion of ephedrine to the corresponding benzoyl ester[8,9] (Scheme II). The (+)-threo halide[5]

(1) Deceased Oct 26, 1968.

(2) W. S. Saari, A. W. Raab, W. H. Staas, M. L. Torchiana, C. C. Porter, and C. A. Stone, *J. Med. Chem.*, **13**, 1057 (1970).

(3) For leading references to the substitute transmitter hypothesis, see: I. J. Kopin, *Annu. Rev. Pharmacol.*, **8**, 377 (1968); C. A. Stone and C. C. Porter, *Advan. Drug Res.*, **4**, 71 (1967); J. R. Crout, *Circ. Res.*, **18**, **19**, *Suppl.* **1**, 120 (1966).

(4) The threo isomers of **1** are considerably less active than metaraminol [(−)-erythro form of **1**] in depleting the mouse heart of norepinephrine.[5-7]

(5) W. S. Saari, A. W. Raab, and E. L. Engelhardt, *J. Med. Chem.*, **11**, 1115 (1968).

(6) M. L. Torchiana, C. C. Porter, and C. A. Stone, *Arch. Int. Pharmacodyn. Ther.*, **174**, 118 (1968).

(7) N. F. Albertson, F. C. McKay, A. E. Lape, J. O. Hoppe, W. H. Selberis, and A. Arnold, *J. Med. Chem.*, **13**, 132 (1970).

(8) L. H. Welsh, *J. Org. Chem.*, **32**, 119 (1967).

(9) H. Pfanz and H. Wieduwilt, *Arch. Pharm.*, **288**, 563 (1955).