Antimicrobials. 2. Substituted Benzothiazolylbenzylamines and Related Compounds

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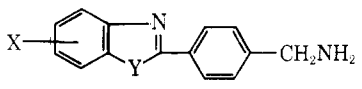
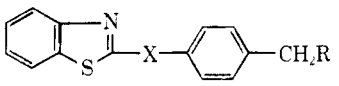
In a previous paper,[1] the antibacterial activity of 4-(2-benzothiazolyl)benzylamine (Ia) and related compounds was described. As part of a program aimed at studying structure–activity relationships in this series, we have modified Ia by benzene ring substitution (Ib–d) and by the introduction of bridging groups (IIa–e). We have also investigated the importance or otherwise of the benzothiazole moiety of Ia by the preparation of the benzoxazole and benzimidazole analogs Ie and If, together with the indole IIIa and benzofuran IIIb compds.



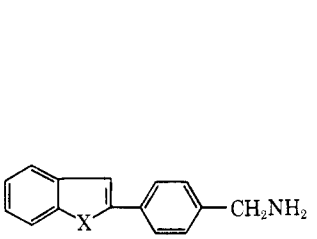
I

Ia, X = H; Y = S
b, X = 5-Me; Y = S
c, X = 6-Me; Y = S
d, X = 5-Cl; Y = S
e, X = H; Y = O
f, X = H; Y = NH

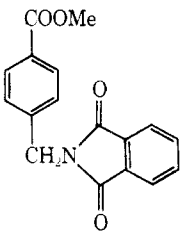


II

IIa, X = NH; R = NH_2
b, X = O; R = NH_2
c, X = CH=CH; R = NH_2
d, X = NH; R = phthalimido
e, X = CH=CH(*trans*); R = H



III



IV

IIIa, X = NH; b, X = O

Chemistry.—Gabriel reaction of methyl α-bromo-*p*-toluate afforded *p*-methoxycarbonylbenzyl phthalimide (IV) in high yield. Condensation of IV with a variety of benzene-substituted *o*-aminothiophenols, with *o*-aminophenol, and with *o*-phenylenediamine in polyphosphoric acid afforded the phthalimides V (Table I), which by hydrazine fission gave Ib–f. 2-Chlorobenzothiazole reacted smoothly with *p*-hydroxybenzylamine to give IIb and with *p*-aminobenzylphthalimide to give IId and thence the required amine IIa. Condensation of 2-methylbenzothiazole with *p*-tolualdehyde yielded the stilbene derivative IIe, which by NBS bromination and subsequent Gabriel reaction was transformed into the amine IIc. 2-*p*-Cyanophenylindole, prepared by Fischer indole synthesis from *p*-cyanoacetophenone phenylhydrazone, was reduced with LAH to give IIIa. The benzofuran derivative IIIb was obtained from methyl 4-(2-benzofuranyl)benzoate by LAH reduction, followed by $SOCl_2$ treatment and then a Gabriel reaction.

Biological Activity.—All the compounds were screened against a range of Gram-positive and Gram-negative bacteria, *Mycobacterium tuberculosis*, *Entamoeba histolytica*, and the common dermatophytes. None of the compounds had sufficient *in vitro* antituberculous activity to be tested *in vivo*. The 6-methylbenzothiazole derivative **9** and the indole **16** had reasonable *in vitro* activity against *E. histolytica*, but were not sufficiently active in the Jones' weanling rat test[2] to be of interest. None of the compounds showed significant activity against fungi or Gram-negative bacteria, but all of them, with the exception of the substituted benzothiazole **9** and the benzimidazole derivative **12**, were more active against the Gram-positive *Streptococcus pyogenes* than the parent compound Ia.

Experimental Section[3]

Methyl α-Phthalimido-*p*-toluate (1).—Methyl α-bromo-*p*-toluate (36.6 g) in DMF (300 ml) contg potassium phthalimide (32.6 g) was stirred 3 hr at 100°, concd *in vacuo*, and dild with H_2O (500 ml). Extn with $CHCl_3$ gave a solid (40.4 g), mp 148–152°. The ester had mp 152.2–154° (CCl_4). *Anal.* ($C_{17}H_{13}NO_4$) C, H, N.

2-Benzazolylbenzyl Phthalimides.—To a stirred mixt of **1** (1 part by wt) in polyphosphoric acid (5–10 parts by vol) at 120–140° was added the theoretical quantity of the appropriate *o*-aminophenol, *o*-phenylenediamine, or *o*-aminobenzenethiol. (In the latter case, either the free thiol or the corresponding disulfide can be used; also, the *o*-aminobenzenethiol could be used either as the free base or as the hydrochloride.) The temp of the mixt was raised to 180° and maintd thus for 0.25–1 hr before cautiously pouring the mixt into H_2O. The resulting solid was collected, washed with H_2O, EtOH, and Et_2O, and dried. Compds prepd in this way are listed in Table I.

Benzylamines.—The phthalimide (1 part) and 98% $NH_2NH_2 \cdot H_2O$ (2 parts) in EtOH (30 parts) were refluxed 1 hr, the solvent was evapd, and the residue was warmed with 2 *N* NaOH (20 parts). Extn with $CHCl_3$ gave the amine (see Table II).

4-(2-Benzothiazolylamino)benzylamine (13).—4-Aminobenzylphthalimide (2.9 g) and 2-chlorobenzothiazole (1.96 g) in tetrachloroethane (40 ml) were refluxed 46 hr, and the cooled mixt was dild with $CHCl_3$ and extd with 2 *N* HCl. The aq layer was washed ($CHCl_3$), basified, and extd with $CHCl_3$ to give a solid (3.1 g), mp 227–232°. Crystn (aq DMF) gave the expected phthalimide, mp 237–238°. *Anal.* ($C_{22}H_{15}N_3O_2S$) H, N; C: calcd 68.55; found, 67.9. The *N*-Ac deriv had mp 216–217° ($CHCl_3$–hexane). *Anal.* ($C_{24}H_{17}N_3O_3S$) C, H, N. Decompn of either compd by the general method gave **13** (Table II).

4-(2-Benzothiazolyloxy)benzylamine (14).—To NaH (3.6 g of 50% oil dispersion) in DMF (90 ml) at 0° was added *p*-hydroxybenzylamine·HCl (6.0 g) followed, after 5 min, by a soln of 2-chlorobenzothiazole (6.4 g) in DMF (20 ml). The mixt was stirred 1 hr at 0°, 1 hr at 25°, and then 1 hr at 60°, the solvent was evapd, and the residue was basified to give the amine (Table II).

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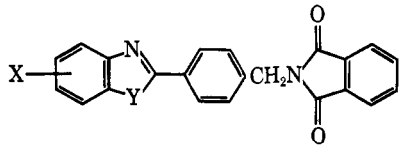
(1) P. J. Palmer, G. Hall, R. B. Trigg, and J. V. Warrington, *J. Med. Chem.*, **14**, 1223 (1971).

(2) W. R. Jones, *Ann. Trop. Med. Parasitol.*, **40**, 130 (1946).

(3) Where analyses are indicated only by symbols of the elements, analytical results obtained for those 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

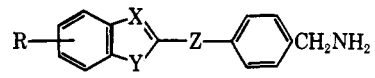


V

No.	X	Y	Time, hr	Yield,[a] %	Mp, °C	Cryst	Formula	Anal.
2	5-Me	S	0.5	88	222–224	$CHCl_3$–EtOH	$C_{23}H_{16}N_2O_2S$	C, H, N
3	6-Me	S	0.5	91	214.5–216	$CHCl_3$–hexane	$C_{23}H_{16}N_2O_2S$	C, H, N
4	5-Cl	S	0.5	94	255–256	$CHCl_3$–EtOH	$C_{22}H_{13}ClN_2O_2S$	C, H, Cl, N
5	5-CF_3	S	0.25	60[b]	190–191	$CHCl_3$–EtOH	$C_{23}H_{13}F_3N_2O_2S$	C, H, N
6	H	O	1	90	315.5–317	DMF–EtOH[c]	$C_{22}H_{14}N_2O_3$	H, N; C[c]
7	H	NH	1	*d*				*d*

[a] Yields quoted are of crude products. [b] Product very crude; yield of pure product *ca.* 5%. [c] Anal. sample prepd by sublimation at 220° (0.001 mm). C: calcd, 74.6; found, 74.0; [d] Product was a phosphate complex which was used as such in the next stage.

TABLE II



No.	R	X	Y	Z	Yield, %	Mp, °C	Cryst	Formula	Analysis	MIC[f] *TB* H37 Rv	MIC[f] *EH*	MIC[f] *S. pyo*	Derivatives
8	5-Me	N	S	None	73	106–108	80–100° petr ether	$C_{15}H_{14}N_2S$	C, H, N	12.5	10	1.6	
9	6-Me	N	S	None	85	138–141	80–100° petr ether	$C_{15}H_{14}N_2S$	C, H, N	6.3	5	50	
10	5-Cl	N	S	None	95	132–133	80–100° petr ether	*a*		25	12.5	0.8	Picrate, mp 244–245° (MeOH); *Anal.* ($C_{20}H_{14}ClN_5O_7S$) C, H, Cl, N
11	H	N	O	None	86			*a*		50	12.5	1.6	HCl, mp 304–310° (H_2O–EtOH); *Anal.* ($C_{14}H_{13}ClN_2O$) C, H, Cl, N
12	H	N	NH	None	62[b]	206–220		*a*		200	>200	25	Dipicrate, mp 247° dec (MeOH); *Anal.* ($C_{26}H_{19}N_9O_{14}$) H, N; C[c]
13	H	N	S	NH	54	185–186	$CHCl_3$	$C_{14}H_{13}N_3S$	H, N; C[d]	50	25	6.3	
14	H	N	S	O	82	Oil				200	100	6.3	Citrate, mp 150–153° dec (MeOH–Et_2O); *Anal.* ($C_{20}H_{20}N_2O_8S$) C, H, N
15	H	N	S	CH=CH (trans)	94			*e*		25	12.5	1.6	HCl, mp 305–306° dec (concd HCl); *Anal.* ($C_{16}H_{13}ClN_2S$) C, H, Cl, N
16	H	CH	NH	None	73	189.5–191	MeCOEt	$C_{15}H_{14}N_2$	C, H, N	50	2.5	3.1	
17	H	CH	O	None	86	132–133		*a*		25	12.5	3.1	HCl, mp 287–289° dec (EtOH); *Anal.* ($C_{15}H_{14}ClNO$) C, H, N

[a] Compd carbonates rapidly; characterized as suitable salt. [b] Yield based on *o*-phenylenediamine. [c] C: calcd, 45.8; found, 46.4. [d] C: calcd, 65.9; found, 66.4. [e] Product isolated directly as HCl salt. [f] MIC values detd as described previously.[1]

***trans*-β-(2-Benzothiazolyl)-4-methylstyrene (18).**—2-Methylbenzothiazole (14.9 g), *p*-tolualdehyde (12.0 g), and concd HCl (15 ml) were stirred vigorously for 26 hr at 160–180° under N_2. The resulting product was basified with dil NaOH to give, by $CHCl_3$ extn, a solid (25.4 g), mp 115–123°. Cryst (hexane) gave **18**, mp 142.5–143.5°, ν_{max} 951 (trans CH=CH) cm^{-1}. *Anal.* ($C_{16}H_{13}NS$) C, H, N.

***trans*-4-Aminomethyl-β-(2-benzothiazolyl)styrene·HCl (15).**—Compd **18** (5 g), NBS (3.9 g), and Bz_2O_2 (10 mg) were refluxed 18 hr in CCl_4 (250 ml) under N_2 and with irradiation from a 100-W W lamp. Evapn of the solvent gave a product–succinimide complex (8.86 g), mp 151.5–155°. A hot soln of this solid (7.47 g) in $CHCl_3$ (100 ml) was treated with hexamine (2.43 g) in $CHCl_3$ (80 ml), the mixt was refluxed 5 min and cooled, and the salt (5.0 g), mp 213-214°, was collected. Decompn with boiling 2 *N* HCl (50 ml) for 1 hr gave **15** (Table II).

2-(4-Cyanophenyl)indole (19).–*p*-Cyanoacetophenone (7.25 g) and $PhNHNH_2$ (5.4 g) in EtOH (60 ml) contg AcOH (3 drops) were refluxed 3 hr, dild with H_2O, and cooled to give the phenylhydrazone, (10.56 g), mp 163–164°. *Anal.* ($C_{15}H_{13}N_3$) C, H, N. The hydrazone (10 g) mixed with $ZnCl_2$ (5 g) was heated 5 min at 220°, the melt was cooled and extd with EtOAc. The oily solid (8.5 g) thus obtd was chromatogd over Al_2O_3 (150 g, neutral, activity III) using C_6H_6–EtOAc (1:1) as eluant to give a solid (2.58 g). Crystn from MeOH gave **19**, mp 194–195°. *Anal.* ($C_{15}H_{10}N_2$) C, H, N.

4-(2-Indolyl)benzylamine (16).—Compd **19** (2.0 g) was reduced with LAH (2.0 g) in Et_2O (200 ml) for 15 min under reflux. The mixt was decompd with H_2O (5 ml) and then 20% Rochelle salt soln (200 ml) was added. The Et_2O layer was sepd and evapd to dryness, the residue was digested with 50% HCl (100 ml), and the soln was filtered. Neutraln of the filtrate with dil NH_4OH and extn with Et_2O gave **16** (Table II).

α-Cyano-α-(2-methoxyphenyl)-4-cyanoacetophenone (20).—To a refluxing soln of $NaNH_2$ (3.9 g) in C_6H_6 (40 ml) contg anhyd MeOH (4.0 ml) was added methyl 4-cyanobenzoate (16.1 g) and *o*-methoxyphenylacetonitrile (14.7 g) in C_6H_6 (60 ml). The soln was refluxed 2 hr, cooled, and dild with Et_2O (500 ml). The yellow Na salt was collected, washed (Et_2O), and dissolved in H_2O, and the soln was acidified (2 *N* HCl). Extn with Et_2O gave **20** (8.2 g), mp 130–133° (EtOAc). *Anal.* ($C_{17}H_{12}N_2O_2$) C, H, N.

4-(2-Benzofuranyl)benzoic Acid (21) and Me Ester (22).—Compd **20** (5.6 g) in AcOH–48% aq HBr (1:1; 140 ml) was heated 3 hr at 140–160°; the soln was cooled and poured into H_2O. The ppt (5.7 g) crystd from MeOH to give **21**, mp 287–289°. *Anal.* ($C_{15}H_{10}O_3$) C, H. Et_2O–CH_2N_2 gave **22**, mp 176.5–177° (MeOH). *Anal.* ($C_{16}H_{12}O_3$) C, H.

4-(2-Benzofuranyl)benzyl Alcohol (23).—Compd **22** was reduced with LAH in Et_2O in the usual way to give **23**, mp 174–175° (C_6H_6), in 62% yield. *Anal.* ($C_{15}H_{12}O_2$) C, H.

4-(2-Benzofuranyl)benzylamine·HCl (17).—Compd **23** (2.24 g) in C_6H_6 (25 ml) was refluxed with $SOCl_2$ (1.5 ml) for 1 hr to give the Cl compd (2.34 g). This was dissolved in DMF (12 ml,) potassium phthalimide (1.79 g) was added, and the mixt was stirred 0.5 hr at 95°. The resulting phthalimide (2.3 g) was decompd in the usual way to give **17** (Table II).

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