

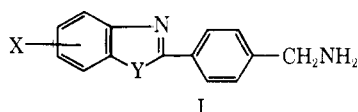
## Antimicrobials. 2. Substituted Benzothiazolybenzylamines and Related Compounds

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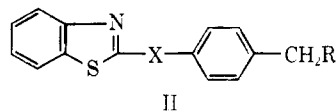
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Received June 22, 1971

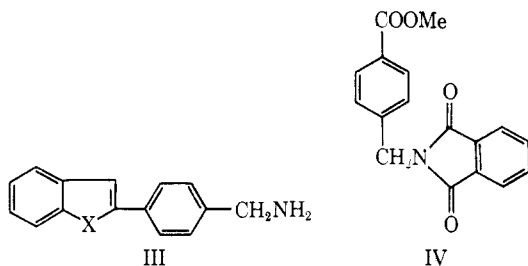
In a previous paper,<sup>1</sup> the antibacterial activity of 4-(2-benzothiazolyl)benzylamine (Ia) and related compounds was described. As part of a program aimed at studying structure-activity relationships in this series, we have modified Ia by benzene ring substitution (Ib-d) and by the introduction of bridging groups (IIa-c). 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 compounds.



- 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



- IIa, X = NH; R = NH<sub>2</sub>  
 b, X = O; R = NH<sub>2</sub>  
 c, X = CH=CH; R = NH<sub>2</sub>  
 d, X = NH; R = phthalimido  
 e, X = CH=CH(*trans*); R = H



IIIa, X = NH; b, X = O

**Chemistry.**—Gabriel reaction of methyl  $\alpha$ -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

IIc 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<sub>2</sub> 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<sup>2</sup> 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<sup>3</sup>

**Methyl  $\alpha$ -Phthalimido-*p*-toluate (1).**—Methyl  $\alpha$ -bromo-*p*-toluate (36.6 g) in DMF (300 ml) contg potassium phthalimide (32.6 g) was stirred 3 hr at 100°, coned *in vacuo*, and dild with H<sub>2</sub>O (500 ml). Extn with CHCl<sub>3</sub> gave a solid (40.4 g), mp 148–152°. The ester had mp 152.2–154° (CCl<sub>4</sub>). *Anal.* (C<sub>17</sub>H<sub>15</sub>NO<sub>4</sub>) C, H, N.

**2-Benzazolybenzyl 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<sub>2</sub>O. The resulting solid was collected, washed with H<sub>2</sub>O, EtOH, and Et<sub>2</sub>O, and dried. Compd prepd in this way are listed in Table I.

**Benzylamines.**—The phthalimide (1 part) and 98% NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O (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<sub>3</sub> 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<sub>3</sub> and extd with 2 N HCl. The aq layer was washed (CHCl<sub>3</sub>), basified, and extd with CHCl<sub>3</sub> to give a solid (3.1 g), mp 227–232°. Crystn (aq DMF) gave the expected phthalimide, mp 237–238°. *Anal.* (C<sub>22</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S) H, N; C: calcd 68.55; found, 67.9. The *N*-Ac deriv had mp 216–217° (CHCl<sub>3</sub>-hexane). *Anal.* (C<sub>24</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S) C, H, N. Decompn of either compd by the general method gave 13 (Table II).

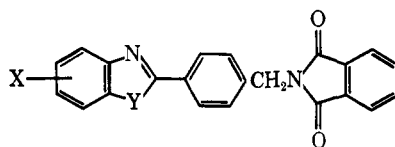
**4-(2-Benzothiazolyloxy)benzylamine (14).**—To NaH (3.6 g of 50% oil dispersion) in DMF (90 ml) at 0° was added *p*-hydroxybenzylamine·HCl (6.0 g) followed, after 5 min, by a soln of 2-chlorobenzothiazole (6.4 g) in DMF (20 ml). The mixt was stirred 1 hr at 0°, 1 hr at 25°, and then 1 hr at 60°, the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

(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  $\pm 0.4\%$  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.

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

TABLE I

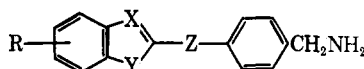


V

No.	X	Y	Time, hr	Yield, <sup>a</sup> %	Mp, °C	Cryst	Formula	Anal.
2	5-Me	S	0.5	88	222-224	CHCl <sub>3</sub> -EtOH	C <sub>23</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> S	C, H, N
3	6-Me	S	0.5	91	214.5-216	CHCl <sub>3</sub> -hexane	C <sub>23</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> S	C, H, N
4	5-Cl	S	0.5	94	255-256	CHCl <sub>3</sub> -EtOH	C <sub>22</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub> S	C, H, Cl, N
5	5-CF <sub>3</sub>	S	0.25	60 <sup>b</sup>	190-191	CHCl <sub>3</sub> -EtOH	C <sub>23</sub> H <sub>13</sub> F <sub>3</sub> N <sub>2</sub> O <sub>2</sub> S	C, H, N
6	H	O	1	90	315.5-317	DMF-EtOH <sup>c</sup>	C <sub>22</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	C, H, N; C <sup>e</sup>
7	H	NH	1	<i>d</i>				<i>d</i>

<sup>a</sup> Yields quoted are of crude products. <sup>b</sup> Product very crude; yield of pure product *ca.* 5%. <sup>c</sup> Anal. sample prep'd by sublimation at 220° (0.001 mm). C: calcd, 74.6; found, 74.0; <sup>d</sup> 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 <sup>f</sup>			Derivatives
										TB H37 Rv	EH	S. pyo	
8	5-Me	N	S	None	73	106-108	80-100° petr ether	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> S	C, H, N	12.5	10	1.6	
9	6-Me	N	S	None	85	138-141	80-100° petr ether	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> S	C, H, N	6.3	5	50	
10	5-Cl	N	S	None	95	132-133	80-100° petr ether	<i>a</i>		25	12.5	0.8	Picrate, mp 244-245° (MeOH); Anal. (C <sub>20</sub> H <sub>14</sub> ClN <sub>2</sub> O <sub>5</sub> S) C, H, Cl, N
11	H	N	O	None	86			<i>a</i>		50	12.5	1.6	HCl, mp 304-310° (H <sub>2</sub> O-EtOH); Anal. (C <sub>14</sub> H <sub>10</sub> ClN <sub>2</sub> O) C, H, Cl, N
12	H	N	NH	None	62 <sup>b</sup>	206-220		<i>a</i>		200	>200	25	Dipicrate, mp 247° dec (MeOH); Anal. (C <sub>25</sub> H <sub>19</sub> N <sub>9</sub> O <sub>14</sub> ) H, N; C <sup>e</sup>
13	H	N	S	NH	54	185-186	CHCl <sub>3</sub>	C <sub>14</sub> H <sub>13</sub> N <sub>2</sub> S	H, N; C <sup>d</sup>	50	25	6.3	
14	H	N	S	O	82	Oil				200	100	6.3	Citrate, mp 150-153° dec (MeOH-Et <sub>2</sub> O); Anal. (C <sub>28</sub> H <sub>20</sub> N <sub>2</sub> O <sub>8</sub> S) C, H, N
15	H	N	S	CH=CH (trans)	94			<i>e</i>		25	12.5	1.6	HCl, mp 305-306° dec (cond HCl); Anal. (C <sub>16</sub> H <sub>14</sub> ClN <sub>2</sub> S) C, H, Cl, N
16	H	CH	NH	None	73	189.5-191	MeCOEt	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub>	C, H, N	50	2.5	3.1	
17	H	CH	O	None	86	132-133		<i>a</i>		25	12.5	3.1	HCl, mp 287-289° dec (EtOH); Anal. (C <sub>15</sub> H <sub>14</sub> ClNO) C, H, N

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

**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<sub>2</sub>. The resulting product was basified with dil NaOH to give, by CHCl<sub>3</sub> extn, a solid (25.4 g), mp 115-123°. Cryst (hexane) gave **18**, mp 142.5-143.5°,  $\nu_{\max}$  951 (trans CH=CH) cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>13</sub>NS) C, H, N.

**trans-4-Aminomethyl-β-(2-benzothiazolyl)styrene·HCl (15).**—Compd **18** (5 g), NBS (3.9 g), and Bz<sub>2</sub>O<sub>2</sub> (10 mg) were refluxed 18 hr in CCl<sub>4</sub> (250 ml) under N<sub>2</sub> and with irradiation from a 100-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<sub>3</sub> (100 ml) was treated with hexamine (2.43 g) in CHCl<sub>3</sub> (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<sub>2</sub> (5.4 g) in EtOH (60 ml) contg AcOH (3 drops) were refluxed 3 hr, dild with H<sub>2</sub>O, and cooled to give the phenylhydrazone, (10.56 g), mp 163-164°. Anal. (C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>) C, H, N. The hydrazone (10 g) mixed with ZnCl<sub>2</sub> (5 g) was heated 5 min at 220°, the melt was cooled and extd with EtOAc. The oily solid (8.5 g) thus obt'd was chromatogd over Al<sub>2</sub>O<sub>3</sub> (150 g, neutral, activity III) using C<sub>6</sub>H<sub>6</sub>-EtOAc (1:1) as eluant to give a solid (2.58 g). Crystn from MeOH gave **19**, mp 194-195°. Anal. (C<sub>15</sub>-H<sub>10</sub>N<sub>2</sub>) C, H, N.

**4-(2-Indolyl)benzylamine (16).**—Compd **19** (2.0 g) was reduced with LAH (2.0 g) in Et<sub>2</sub>O (200 ml) for 15 min under reflux. The mixt was decomp'd with H<sub>2</sub>O (5 ml) and then 20% Rochelle salt soln (200 ml) was added. The Et<sub>2</sub>O layer was sep'd and evap'd to dryness, the residue was digested with 50% HCl (100

ml), and the soln was filtered. Neutraln of the filtrate with dil NH<sub>4</sub>OH and extn with Et<sub>2</sub>O gave **16** (Table II).

**α-Cyano-α-(2-methoxyphenyl)-4-cyanoacetophenone (20).**—To a refluxing soln of NaNH<sub>2</sub> (3.9 g) in C<sub>6</sub>H<sub>6</sub> (40 ml) contg anhyd MeOH (4.0 ml) was added methyl 4-cyanobenzoate (16.1 g) and *o*-methoxyphenylacetonitrile (14.7 g) in C<sub>6</sub>H<sub>6</sub> (60 ml). The soln was refluxed 2 hr, cooled, and dild with Et<sub>2</sub>O (500 ml). The yellow Na salt was collected, washed (Et<sub>2</sub>O), and dissolved in H<sub>2</sub>O, and the soln was acidified (2 N HCl). Ext'n with Et<sub>2</sub>O gave **20** (8.2 g), mp 130-133° (EtOAc). Anal. (C<sub>17</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>) 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<sub>2</sub>O. The ppt (5.7 g) crystd from MeOH to give **21**, mp 287-289°. Anal. (C<sub>15</sub>H<sub>10</sub>O<sub>3</sub>) C, H. Et<sub>2</sub>O-CH<sub>2</sub>N<sub>2</sub> gave **22**, mp 176.5-177° (MeOH). Anal. (C<sub>15</sub>H<sub>12</sub>O<sub>3</sub>) C, H.

**4-(2-Benzofuranyl)benzyl Alcohol (23).**—Compd **22** was reduced with LAH in Et<sub>2</sub>O in the usual way to give **23**, mp 174-175° (C<sub>6</sub>H<sub>6</sub>), in 62% yield. Anal. (C<sub>15</sub>H<sub>12</sub>O<sub>2</sub>) C, H.

**4-(2-Benzofuranyl)benzylamine·HCl (17).**—Compd **23** (2.24 g) in C<sub>6</sub>H<sub>6</sub> (25 ml) was refluxed with SOCl<sub>2</sub> (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 decomp'd in the usual way to give **17** (Table II).

**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.