

**827.** *Some Anti-microbial Compounds in the Heterocyclic Series. Part III.*<sup>1</sup> *Basic Ethers of the Benzothiazole and Benzoxazole Series.*

By H. D. COSSEY, C. J. SHARPE, and F. F. STEPHENS.

Some 2-*p*-dialkylaminoalkoxyphenyl-benzothiazoles and -benzoxazoles and related quaternary ammonium compounds are described. A synthesis of 2-phenylbenzothiazoles from *o*-aminobenzenethiols or 2,2'-diaminodiphenyl disulphides and aromatic aldehydes with nitrobenzene as a cyclising agent is described. The compounds are active against bacteria, fungi, and protozoa.

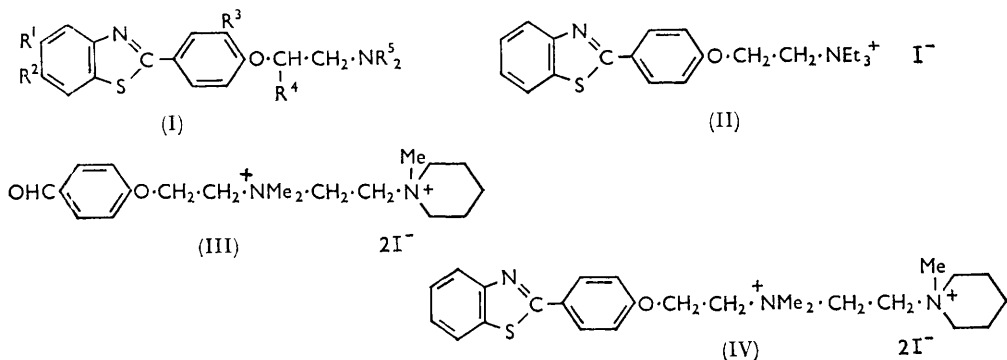
A SERIES of ethers of the 2-phenylbenzothiazole series (I; R<sup>1</sup> = H or Cl; R<sup>2</sup> = Cl, NMe<sub>2</sub>, or OEt; R<sup>3</sup> = H, OMe, or Br; R<sup>4</sup> = H or Me; R<sup>5</sup> = Me, Et, Bu<sup>n</sup>, or NR<sub>2</sub><sup>5</sup> = morpholino), together with quaternary ammonium compounds formally derived by alkylation of the terminal nitrogen atom (*e.g.*, II) have been prepared as part of a pharmacological study of choline ethers. The benzothiazole quaternary salt (II) was conceived as a heterocyclic analogue of the hypotensive drug Elvetil, *p*-CHPh:CH·C<sub>6</sub>H<sub>4</sub>·O·[CH<sub>2</sub>]<sub>2</sub>·NEt<sub>3</sub><sup>+</sup>Cl<sup>-</sup>.<sup>2</sup> Both quaternary and non-quaternary compounds in the new series were pharmacologically classified as non-specific spasmolytics but were found to possess interesting activity against fungi (dermatophytes) and bacteria. A study was therefore made of the relation between this anti-microbial activity and chemical structure by (*a*) preparation of 2-phenylbenzothiazoles bearing a basic ether group in the 2'-, 3'-, and 6-positions, (*b*) replacement of the basic ether by an amidinomethoxy-group, ·O·CH<sub>2</sub>·C(·NH)·NH<sub>2</sub>, (*c*) preparation of the 3-diethylaminopropoxy-homologue, (*d*) preparation of some benzoxazoles of the same general type, and (*e*) preparation of a phenanthridine analogue and its quaternary salts.

Many of the benzothiazoles were prepared by condensation of dialkylaminoalkoxybenzaldehydes with *o*-aminobenzenethiols. The basic alkoxybenzaldehydes were prepared

<sup>1</sup> Part II, Bower, Stephens, and Wibberley, *J.*, 1950, 3341.

<sup>2</sup> Cavallini, Mantegazza, Massarini, and Tomassini, *Il Farmaco (Pavia), Edn. Sci.*, 1953, **8**, 317; Zaimis, *J. Pharm. Pharmacol.*, 1955, **7**, 497.

as pale yellow oils by alkylation of hydroxybenzaldehydes with dialkylaminoalkyl chlorides. These and their quaternary salts were in some cases obtained in polymorphous forms. The *o*-aminobenzenethiols were prepared by reduction of 2,2'-dinitrodiphenyl disulphides with aqueous sodium sulphide in a modification of Hauser's method<sup>3</sup> or,



in three cases, by reaction of the amine with sulphur monochloride, followed by alkali (*i.e.*, the Herz reaction<sup>4,5</sup>). 2-(*p*-2-Diethylaminoethoxyphenyl)-6-dimethylaminobenzo-thiazole was prepared from 2-amino-5-dimethylaminobenzenethiosulphuric acid and *p*-2-diethylaminoethoxybenzaldehyde by the method described in Part I.<sup>5</sup>

Reaction of the ammonioalkoxybenzaldehydes with *o*-aminobenzenethiols (as zinc salts, hydrochlorides, or free bases) in refluxing ethanol<sup>6</sup> gave the quaternary 2-phenylbenzothiazoles in all cases. Under these conditions, however, the unquaternised benzaldehyde ethers failed to produce benzothiazoles, though they did so when the components were heated in acetic acid with ammonium acetate<sup>5</sup> (proof of thiazole ring closure was obtained with the preparation by this method of the known 2-phenylbenzothiazole from benzaldehyde and *o*-aminobenzenethiol). This ammonium acetate-acetic acid method gave only moderate yields of the basic benzothiazole ethers and these required extensive purification. When, however, an *o*-aminobenzenethiol hydrochloride and an equimolecular amount of dialkylaminoalkoxybenzaldehyde were heated at 180° in nitrobenzene the expected benzothiazole ether hydrochloride crystallised, on cooling, in good yield. Under these conditions the thiols would be expected to be first oxidised to their disulphides which, after Schiff's base formation, may undergo cleavage of the disulphide bond and ring closure; evidence for this was provided by showing that 2,2'-diaminodiphenyl disulphides could replace the *o*-aminobenzenethiols and in this manner *p*-anisaldehyde reacted with 2,2'-diamino-4,4'-dichlorodiphenyl disulphide (in nitrobenzene) to give 5-chloro-2-*p*-methoxyphenylbenzothiazole. Demethylation of the last-named compound with aluminium chloride or pyridine hydrochloride, followed by alkylation of the phenol with a dialkylaminoalkyl chloride, gave an alternative synthesis of the basic ethers.

Attempts to prepare benzothiazole diquaternary salts in which both terminal and heterocyclic nitrogen atoms were quaternised were unsuccessful although this was possible with the phenanthridine compound. Fusion of the iodide (II) with methyl toluene-*p*-sulphonate resulted only in an exchange of anion and when this iodide or its parent tertiary base was heated with an excess of ethyl iodide in dimethylformamide only the quaternary iodide was isolated. Some diquaternary salts of a different type were, however, prepared: reaction of 1-2'-chloroethylpiperidine with *p*-2-dimethylaminoethoxybenzaldehyde, followed by methylation, gave the diquaternary aldehyde di-iodide (III)

<sup>3</sup> Hauser, *Helv. Chim. Acta*, 1928, **11**, 198.

<sup>4</sup> Ast and Bogert, *Rec. Trav. chim.*, 1935, **54**, 917.

<sup>5</sup> Stephens and Wibberley, *J.*, 1950, 3336.

<sup>6</sup> Bogert and Taylor, *Coll. Czech. Chem. Comm.*, 1931, **3**, 480.

and this condensed with *o*-aminobenzenethiol to give the diquaternary benzothiazole derivative (IV).

2-*p*-Hydroxyphenylbenzoxazole was prepared by two routes: first, *p*-benzyloxybenzaldehyde was condensed with *o*-aminophenol to give the Schiff's base and this was cyclised<sup>7</sup> to 2-*p*-benzyloxyphenylbenzoxazole which, on hydrogenolysis, gave the required phenol; in the second route *p*-anisaldehyde was used in place of benzyloxybenzaldehyde, with demethylation in the last stage by hydriodic acid. Alkylation with 2-diethylaminoethyl chloride gave the desired 2-(*p*-2-diethylaminoethoxyphenyl)benzoxazole. From 2-amino-4- and -5-chlorophenol and *p*-anisaldehyde by a similar synthesis the corresponding basic ethers of 5- and 6-chlorobenzoxazole were prepared. The 5,6-dichloro-compound in this series was prepared because of the interesting anti-bacterial potentialities<sup>8,9</sup> in compounds derived from 2-amino-4,5-dichlorophenol. Although methods<sup>8,10</sup> exist for the preparation of this phenol an alternative and possibly more satisfactory method<sup>11</sup> is by chlorination of 5-chlorobenzoxazolone followed by ring-opening with alkali. Condensation of 2-amino-4,5-dichlorophenol with *p*-anisaldehyde and cyclisation of the resulting Schiff's base gave the benzoxazole from which the basic ether was obtained by methods outlined above.

The most active anti-bacterial and anti-fungal compounds were unquaternised basic 4'-ethers of the benzothiazole series and from this group 5-chloro-2-(*p*-2-diethylaminoethoxyphenyl)benzothiazole was chosen for clinical investigation.<sup>12</sup> This compound was also active *in vitro* against *M. tuberculosis*, *Trichomonas vaginalis*, and *Candida albicans*. In an effort to increase the antiprotozoal activity the compound was nitrated and gave a crystalline compound believed to be the 3',6'-dinitro-compound. The microbiological tests of these and other compounds will be published in detail elsewhere.

#### EXPERIMENTAL

*Dialkylaminoalkoxybenzaldehydes.*—(A) *Alkylation in ethanol.* The dialkylaminoalkyl chloride hydrochloride (0.11 mole) in the minimum quantity of cold water was made alkaline by 40% aqueous sodium hydroxide (to pH 11), the base extracted with benzene (3 × 10 ml.), and the benzene solution dried (MgSO<sub>4</sub>). The hydroxybenzaldehyde (0.1 mole) was added to a solution of sodium (2.3 g.) in ethanol (100 ml.), followed by the filtered benzene solution of base. The mixture was boiled under reflux for 6 hr., cooled, filtered from sodium chloride, and evaporated under reduced pressure. The residual oil was shaken with *n*-sodium hydroxide (50 ml.) and ether; the aqueous portion was twice extracted with chloroform and the combined, washed (water) organic portion was dried (over CaCl<sub>2</sub>) and evaporated, to give the crude basic aldehyde, usually as a brown oil, which was purified by distillation.

(B) *Alkylation in acetone.* The dialkylaminoalkyl chloride hydrochloride (0.1 mole) was converted into the free base and obtained as a solution in benzene as in (A). The hydroxybenzaldehyde (0.1 mole) was dissolved in acetone (100 ml.), anhydrous potassium carbonate (20 g.) was added, followed by the benzene solution, and the mixture was refluxed for 6 hr. Inorganic material was removed and the filtrate evaporated to give the crude aldehyde which was distilled.

(C) *Alkylation in toluene.* The dialkylaminoalkyl chloride hydrochloride (0.12 mole) was dissolved in water, the solution made alkaline with 40% aqueous sodium hydroxide, and the liberated base extracted with toluene (200 ml.). The toluene solution was dried by removal of the toluene-water azeotrope. Sodium (2.3 g.) was dissolved in ethanol (60 ml.), the hydroxybenzaldehyde (0.1 mol.) in ethanol (50 ml.) was added, and the mixture heated under reflux for 20 min. The ethanol was removed by evaporation, toluene (200 ml.) was added, and the final traces of ethanol were removed by azeotropic distillation. To this suspension of the sodium salt was added the toluene solution of dialkylaminoalkyl chloride, and the mixture

<sup>7</sup> Stephens and Bower, *J.*, 1949, 2971.

<sup>8</sup> Woolley and Pringle, *J. Biol. Chem.*, 1952, **194**, 729.

<sup>9</sup> Beaver, Roman, and Stoffel, *J. Amer. Chem. Soc.*, 1957, **79**, 1236.

<sup>10</sup> Acheson and Taylor, *J.*, 1956, 4731.

<sup>11</sup> Cf. U.S.P., 2,922,794.

<sup>12</sup> Thorne and Harvey, *Postgraduate Med. J.*, 1959, **35**, 696; Rubbo, Reich, and Dixon, *Oral Surgery and Oral Pathology*, 1958, **11**, 878.

heated under reflux for 24 hr. After cooling, the mixture was extracted with *N*-sodium hydroxide, then washed with water. Evaporation gave the crude basic aldehyde which was distilled.

The *aldehydes* in Table 1 were prepared by these methods. Their *derivatives*, prepared by conventional methods, are described in Table 2. Picrates generally gave unsatisfactory analyses: thiosemicarbazones were recrystallised from aqueous ethanol, citrates and the quaternary compounds from ethanol or ethanol-ether.

1-{2-[*N*-(2-*p*-formylphenoxyethyl)-*NN*-dimethylammonio]ethyl}-1-methylpiperidinium *Iodide* (III).—*p*-2-Dimethylaminoethoxybenzaldehyde (1 g.) and 1-2'-chloroethylpiperidine (1 g.) were heated together in a sealed tube at 100° for 16 hr. The contents of the tube were washed on to a filter with ether, and the solid residue was washed several times with ether. The residue was dissolved in ethanol and filtered, and the filtrate was evaporated to give a light brown oil (1.6 g.) which was redissolved in ethanol (3 ml.) and treated with methyl iodide (2 ml.). The pale yellow quaternary *aldehyde* (1.7 g.) separated and recrystallised from ethanol in needles, m. p. 199—200° (sometimes m. p. 135—136°) (Found: C, 39.7; H, 5.8. C<sub>19</sub>H<sub>32</sub>I<sub>2</sub>N<sub>2</sub>O<sub>2</sub> requires C, 39.7; H, 5.6%).

2-Amino-4-chlorobenzenethiol.—4,4'-Dichloro-2,2'-dinitrodiphenyl disulphide<sup>13</sup> (100 g.) was gradually added to sodium sulphide nonahydrate (218 g.) in boiling water (530 ml.), and the mixture boiled for 3 hr. Whilst the mixture was cooled in ice-water, carbon dioxide was passed into the vessel and the solution was brought to pH 6.5 by addition of concentrated hydrochloric acid (*ca.* 106 ml.). The mixture was extracted with chloroform (700 ml., in 3—4 portions), and the extract was filtered and immediately evaporated on a steam-bath (finally under reduced pressure) to give a brown oily residue. This was dissolved in 96% ethanol (200 ml.), concentrated hydrochloric acid (200 ml.) was added, and the mixture kept at 0° overnight. Pale yellow 2-amino-4-chlorobenzenethiol hydrochloride (85 g.), m. p. 195—198°, was removed and dried *in vacuo*. Evaporation of the aqueous-alcoholic mother-liquors gave a further quantity (12 g.; total 90%). Crystallisation from ethanolic hydrochloric acid gave yellow plates, m. p. 212—214° (decomp.) (Found: C, 37.0; H, 3.7. Calc. for C<sub>6</sub>H<sub>7</sub>Cl<sub>2</sub>NS: C, 36.8; H, 3.6%). The base was obtained as white crystals, m. p. 45°, from light petroleum (b. p. 60—80°).

2,2'-Diamino-4,4'-dichlorodiphenyl Disulphide.—96% Ethanol (100 ml.), 4,4'-dichloro-2,2'-dinitrodiphenyl disulphide (10 g.), and 98% hydrazine hydrate (10 ml.) were boiled for 3½ hr., the dark red solution becoming pale yellow. Addition of water (500 ml.) precipitated a pale yellow solid (8 g.), which crystallised from light petroleum (b. p. 60—80°) as pale brown crystals, m. p. 119—120° (Found: C, 45.4; H, 3.4; N, 8.5. Calc. for C<sub>12</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>2</sub>S<sub>2</sub>: C, 45.4; H, 3.2; N, 8.8%).

5-Chloro-2-(*p*-2-diethylaminoethoxyphenyl)benzothiazole.—(a) A mixture of *p*-2-diethylaminoethoxybenzaldehyde (26.4 g.) and 2-amino-4-chlorobenzenethiol hydrochloride (23 g.) in nitrobenzene (120 ml.) was heated under an air-condenser until the internal temperature reached 180—200° (15 min.), then allowed to cool overnight and filtered. The crystalline residue was pressed on the filter until 100 ml. of nitrobenzene filtrate had collected. The residue was washed with ether (25 ml., in 4 portions) to remove most of the colour and the excess of nitrobenzene, then with ethanol (50 ml.), and recrystallised from water, to give the white *benzothiazole hydrochloride* (38 g., 80%), m. p. 228°, λ<sub>max.</sub> 263, 312, and 325 mμ (ε 8100, 27,500, and 28,200 in EtOH) (Found: C, 57.7; H, 5.5. C<sub>19</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>2</sub>OS requires C, 57.4; H, 5.5%). The *base* was obtained by addition of ammonia to an aqueous solution of the hydrochloride and crystallised from ethanol in white plates, m. p. 93—94° (Found: C, 63.5; H, 5.9. C<sub>19</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>2</sub>S requires C, 63.2; H, 5.8%); it gave a *citrate*, needles (from water), m. p. 167° (Found: C, 54.9; H, 5.4. C<sub>25</sub>H<sub>30</sub>ClN<sub>2</sub>O<sub>3</sub>S requires C, 54.2; H, 5.4%).

(b) The *base* was also obtained by alkylation of 5-chloro-2-*p*-hydroxyphenylbenzothiazole with 2-diethylaminoethyl chloride.

2-[3-Bromo-4-(2-diethylaminoethoxy)phenyl]-5-chlorobenzothiazole *Hydrochloride*.—3-Bromo-4-(2-diethylaminoethoxy)benzaldehyde (1 g.) and 2-amino-4-chlorobenzenethiol hydrochloride (0.65 g.) under the same conditions (5 ml. of nitrobenzene at 180° for 1 hr.) gave the *bromophenylbenzothiazole hydrochloride* as white needles (from ethanol), m. p. 221—222° (Found: C, 47.9; H, 4.5. C<sub>19</sub>H<sub>21</sub>BrCl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S requires C, 47.9; H, 4.4%).

<sup>13</sup> Hodgson and Walker, *J.*, 1925, **127**, 443.

TABLE 1.  
Dialkylaminoalkoxybenzaldehydes, R·C<sub>6</sub>H<sub>4</sub>·CHO.

| Subst., R  | Method | Yield (%) | B. p./mm.                   | <i>n</i> <sub>D</sub> Temp. | Found (%) | Formula | Required (%) |
|--|--------|-----------|-----------------------------|-----------------------------|-----------|---------|--------------|
|  |        |           |                             |                             | C         | H       | C            |
| <i>o</i> -NEt <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O*                                     | A      | 45        | 164—166°/10; 119—122°/0.35  | 1.5261/20°                  | 71.1      | 8.5     | 70.6         |
| <i>m</i> -NEt <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O                                      | C      | 78        |                             |                             |           |         | 8.6          |
| <i>p</i> -NEt <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O                                      | A      | 75        | 174°/12; 109°/0.25          | 1.5242/21                   | 70.0      | 8.1     | 70.6         |
|  | A      | 18        | 171—173°/17; 101°/0.25      | 1.5477/23                   | 67.8      | 7.8     | 68.4         |
|  | C      | 33 †      |                             |                             |           |         |              |
| <i>p</i> -NEt <sub>2</sub> [CH <sub>2</sub> ] <sub>3</sub> ·O* †                                   | A      | 67        | 184—187°/20; 123—125°/0.8   | 1.5363/21                   | 70.5      | 8.9     | 70.6         |
|  | B      | 53        |                             |                             |           |         | 8.2          |
| <i>p</i> -NMe <sub>2</sub> ·CH <sub>2</sub> ·CHMe·O  | A      | 48        | 169—171°/17; 110—112°/0.25  | 1.5400/23                   | 69.1      | 8.3     | 69.5         |
| <i>p</i> -NBu <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O                                      | A      | 65        | 225—230°/20; 140—141°/0.25  | 1.5180/20                   | 73.5      | 9.8     | 73.6         |
| <i>p</i> -O<[CH <sub>2</sub> ·CH <sub>2</sub> ] <sub>2</sub> >N·[CH <sub>2</sub> ] <sub>2</sub> ·O | A      | 63        | 242—245°/21; 164°/0.35      | 1.5573/21                   | 66.4      | 7.5     | 66.4         |
| 3-Br-4-NEt <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O   | A      | 70        | 170°/19; 148°/0.3           | 1.5611/18                   | 53.1      | 6.6     | 52.0         |
| 3-MeO-4-NMe <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O  | C §    | 35        | 190—196°/19; 133—136°/0.4 ¶ | 1.5600/23                   | 64.3      | 7.2     | 64.6         |
| <i>p</i> -NEt <sub>2</sub> [CH <sub>2</sub> ] <sub>3</sub> ·O                                      | A      | 63        | 130—132°/0.07               | 1.5291/25                   | 71.2      | 9.2     | 71.4         |

\* Katz, Karger, Schroeder, and Cohen, *J. Org. Chem.*, 1953, 18, 1380. † 51% yield by slow addition of dimethylaminoethyl chloride hydrochloride to *p*-hydroxybenzaldehyde in toluene-K<sub>2</sub>CO<sub>3</sub>. ‡ Bernstein, Yale, Losee, Holsing, Martins, and Lott, *J. Amer. Chem. Soc.*, 1951, 73, 906. § 7 hours' boiling. ¶ Colourless plates, m. p. 49—50° (from ligroin).

TABLE 2.

Derivatives of dialkylaminoalkoxybenzaldehydes.

| Subst., R  | Derivative                      | M. p.                | Found (%)     | Formula     | Required (%) |
|--|---------------------------------|----------------------|---------------|-------------|--------------|
|  |                                 |                      | C             | H           | N            |
| <i>o</i> -NEt <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O †                                    | Thiosemicarbazone<br>Citrate    | 120—121°<br>113      | 57.4<br>54.8  | 7.5<br>6.4  | —            |
| <i>m</i> -NEt <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O                                      | Thiosemicarbazone<br>Citrate    | 115—116<br>108—109.5 | 57.1<br>55.0  | 7.3<br>6.4  | —            |
| <i>p</i> -NMe <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O                                      | Picrate                         | 128—129              | —             | —           | 12.8         |
|  | Thiosemicarbazone<br>Methiodide | 204—205<br>175—176   | 55.1<br>43.7  | 7.1<br>5.8  | 20.9<br>3.9  |
|  | Citrate                         | 112—113 †            | 52.8          | 5.9         | —            |
| <i>p</i> -NEt <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O* †                                   | Oxime<br>Picrate                | 89—90<br>135—136     | 66.5<br>—     | 8.5<br>—    | —            |
|  | Thiosemicarbazone*<br>Ethiodide | 145—146<br>120—121   | 57.4<br>47.3  | 7.5<br>6.1  | —            |
|  | Citrate                         | 125—126              | 55.1          | 6.5         | —            |
| <i>p</i> -NMe <sub>2</sub> ·CH <sub>2</sub> ·CHMe·O  | Picrate                         | 119—121              | —             | —           | 12.8         |
|  | Thiosemicarbazone<br>Methiodide | 160—162<br>128—130   | 56.1<br>44.8  | 7.0<br>5.6  | 20.0<br>—    |
|  | Thiosemicarbazone               | 115—116              | 61.1          | 8.5         | —            |
| <i>p</i> -O<[CH <sub>2</sub> ·CH <sub>2</sub> ] <sub>2</sub> >N·[CH <sub>2</sub> ] <sub>2</sub> ·O | Thiosemicarbazone               | 216—217              | 54.5          | 6.5         | —            |
| 3-Br-4-NEt <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O   | Thiosemicarbazone<br>Citrate    | 182—183<br>195—187 † | 45.3<br>46.2  | 5.9<br>5.5  | —            |
| 3-MeO-4-NMe <sub>2</sub> [CH <sub>2</sub> ] <sub>2</sub> ·O  | Thiosemicarbazone<br>Methiodide | 197—198<br>204—205   | 52.4<br>43.15 | 5.2<br>5.45 | —            |
| <i>p</i> -NEt <sub>2</sub> [CH <sub>2</sub> ] <sub>3</sub> ·O                                      | Picrate                         | 162—163              | 51.4          | 5.2         | —            |

\* Bernstein, Yale, Losee, Holsing, Martins, and Lott, *J. Amer. Chem. Soc.*, 1951, 73, 906. † With decomp.



TABLE 3.

2-Phenylbenzothiazole ethers,  $R \cdot C_6H_3 \begin{matrix} N \\ \diagdown \\ S \end{matrix} C_6H_4 \cdot O \cdot CHR' \cdot CH_2 \cdot NR''_2$ .(The ether group is in the *para*-position, except that in the first two compounds its position is *ortho* and in the third *meta*.)

| R     | R' | R''             | Compd. | M. p.      | Solvent for<br>crystn. | Found (%) |     | Formula   | Required (%) |     |
|-------|----|-----------------|--------|------------|------------------------|-----------|-----|---|--------------|-----|
|       |    |                 |        |            |                        | C         | H   |   | C            | H   |
| 5-Cl  | H  | Et              | Base   | 51—52°     | A                      | 62.2      | 5.6 | C <sub>19</sub> H <sub>21</sub> ClN <sub>2</sub> OS                             | 63.2         | 5.8 |
| 5-Cl  | H  | Et              | HCl    | 224—225    | B                      | 57.0      | 5.7 | C <sub>19</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>2</sub> OS               | 57.4         | 5.5 |
| 5-Cl  | H  | Et              | HCl    | 184—185    | C                      | 57.5      | 5.5 | C <sub>19</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>2</sub> OS               | 57.4         | 5.5 |
| H     | H  | Me              | MeI    | 261—262    | D                      | 49.2      | 4.8 | C <sub>18</sub> H <sub>21</sub> IN <sub>2</sub> OS                              | 49.15        | 4.8 |
| H     | H  | Et              | Base * | 37—39      | B                      | 69.3      | 6.9 | C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> OS                               | 69.9         | 6.8 |
| H     | H  | Et              | HCl    | 210—211    | D                      | 62.5      | 6.1 | C <sub>19</sub> H <sub>23</sub> ClN <sub>2</sub> OS                             | 62.9         | 6.4 |
| H     | Me | Me              | Base   | ¶          | B                      | 69.3      | 6.2 | C <sub>18</sub> H <sub>20</sub> N <sub>2</sub> OS                               | 69.2         | 6.4 |
| H     | Me | Me              | MeI    | 226—227    | D                      | 50.8      | 5.3 | C <sub>19</sub> H <sub>23</sub> IN <sub>2</sub> OS                              | 50.3         | 5.1 |
| 5-Cl  | H  | Me              | Base   | 121        | A                      | 60.9      | 5.1 | C <sub>17</sub> H <sub>17</sub> ClN <sub>2</sub> OS                             | 61.3         | 5.1 |
| 5-Cl  | H  | Me              | HCl    | 247—248    | D                      | 55.3      | 4.9 | C <sub>17</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>2</sub> OS               | 55.3         | 4.9 |
| 5-Cl  | H  | Me              | MeI    | 252—254    | D                      | 45.7      | 4.3 | C <sub>18</sub> H <sub>20</sub> ClIN <sub>2</sub> OS                            | 45.5         | 4.2 |
| 5-Cl  | H  | Et              | EtI    | 233        | D                      | 48.7      | 4.4 | C <sub>21</sub> H <sub>26</sub> ClIN <sub>2</sub> OS                            | 48.8         | 5.0 |
| 5-Cl  | H  | Et              | EtCl † | 220—222 ** | B-A                    | 57.0      | 7.0 | C <sub>21</sub> H <sub>26</sub> Cl <sub>2</sub> N <sub>2</sub> OS               | 56.9         | 6.4 |
| 5-Cl  | Me | Me              | Base   | 115—116    | B                      | 61.8      | 5.4 | C <sub>18</sub> H <sub>19</sub> ClN <sub>2</sub> OS                             | 62.3         | 5.5 |
| 5-Cl  | Me | Me              | HCl    | 204—205    | E                      | 56.5      | 5.0 | C <sub>18</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>2</sub> OS               | 56.4         | 5.2 |
| 5-Cl  | Me | Me              | MeI    | 234—235    | D                      | 46.5      | 4.4 | C <sub>19</sub> H <sub>22</sub> ClIN <sub>2</sub> OS                            | 46.7         | 4.5 |
| 5-Cl  | H  | Bu <sup>n</sup> | Base ‡ | 63—64      | A                      | 65.9      | 6.8 | C <sub>23</sub> H <sub>29</sub> ClN <sub>2</sub> OS                             | 66.3         | 7.0 |
| 5-Cl  | H  | M <sup>§</sup>  | Base   | 133—134    | B                      | 60.8      | 4.8 | C <sub>19</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>2</sub> S               | 60.9         | 5.1 |
| 5-Cl  | H  | M <sup>§</sup>  | HCl    | 252—254    | D                      | 55.3      | 4.7 | C <sub>19</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> S | 55.5         | 4.9 |
| 6-Cl  | H  | Et              | Base   | 116—117    | A                      | 62.7      | 5.5 | C <sub>19</sub> H <sub>21</sub> ClN <sub>2</sub> OS                             | 63.2         | 5.8 |
| 6-Cl  | H  | Et              | EtI    | 233—234    | D                      | 48.5      | 5.2 | C <sub>21</sub> H <sub>26</sub> ClIN <sub>2</sub> OS                            | 48.8         | 5.0 |
| 6-OEt | H  | Et              | Base   | 84—85      | A                      | 68.1      | 6.7 | C <sub>21</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub> S                 | 68.15        | 7.0 |
| 6-OEt | H  | Et              | HCl    | 192—193    | B                      | 61.7      | 6.3 | C <sub>21</sub> H <sub>27</sub> ClN <sub>2</sub> O <sub>2</sub> S               | 62.0         | 6.6 |

Solvents for crystallisation were: A, light petroleum (b. p. 60—80°); B, ethanol; C, methanol; D, water; E, propan-2-ol.

\* Picrate, m. p. 169—170°; base purified by distillation, b. p. 200°/0.25 mm. † Prep. from ethiodide by use of ion-exchange resin (De-acidite F.F.). ‡ The tartrate, m. p. 76—80°, showed maximum solubility in water at 60°. § Morpholino. ¶ Distilled, b. p. 219—221°/0.4 mm.; hydrochloride, m. p. 205—207°. \*\* With decomp.

5-Chloro-2-[4-(3-diethylaminopropoxy)phenyl]benzothiazole Hydrochloride.—2-Amino-4-chlorobenzenethiol hydrochloride (0.98 g.), 4-3'-diethylaminopropoxybenzaldehyde (1.2 g.) and nitrobenzene (5 ml.) under the same conditions gave the benzothiazole hydrochloride (1.27 g.), m. p. 197—198° (from propan-2-ol) as colourless plates,  $\lambda_{max}$  262, 312, and 325  $\mu$  ( $\epsilon$  8100, 27,500, and 27,800 in EtOH) (Found: C, 59.0; H, 6.2. C<sub>20</sub>H<sub>24</sub>ClN<sub>2</sub>OS requires C, 58.4; H, 5.9%).

2-(p-2-Dimethylaminoethoxyphenyl)benzothiazole.—o-Aminobenzenethiol hydrochloride (0.75 g.), p-2-dimethylaminoethoxybenzaldehyde (0.75 g.), glacial acetic acid (20 ml.), and ammonium acetate (10 g.) were boiled under reflux for 2 hr., then cooled and poured into water. The mixture was made alkaline with 10% aqueous sodium hydroxide, which precipitated an oil that solidified. Extraction with ether followed by evaporation gave the crude benzothiazole (1.15 g.) which was purified by chromatography in ether through alumina, followed by crystallisation from light petroleum (b. p. 60—80°) or ethanol, to give pale yellow plates, m. p. 74—75° (Found: C, 68.4; H, 6.1. C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>OS requires C, 68.5; H, 6.0%). The hydrochloride (from water) had m. p. 252—253° (Found: C, 60.5; H, 5.3. C<sub>17</sub>H<sub>19</sub>ClN<sub>2</sub>OS requires C, 61.0; H, 5.7%), and the picrate [from acetone-light petroleum (b. p. 40—60°)] m. p. 204—207°.

2-(p-Triethylammonioethoxyphenyl)benzothiazole Iodide.—o-Aminobenzenethiol hydrochloride (3.25 g.), NNN-triethyl-2-p-formylphenoxyethylammonium iodide (7.6 g.), and ethanol (150 ml.) were boiled for 2 hr., then the alcohol was removed by evaporation. The residual gum was dissolved in water; the quaternary benzothiazole (2.9 g.) crystallised. On recrystallisation from water it had m. p. 208—210° (2.1 g.) (Found: C, 52.0; H, 5.1; N, 5.6. C<sub>21</sub>H<sub>27</sub>IN<sub>2</sub>OS requires C, 52.2; H, 5.6; N, 5.8%).

2-[3-Methoxy-4-(2-trimethylammonioethoxy)phenyl]benzothiazole Iodide.—o-Aminobenzenethiol (1.25 g.; freshly distilled), NNN-triethyl-2-(4-formyl-3-methoxyphenoxyethyl)ammonium iodide (3.65 g.) and ethanol (50 ml.) were boiled for 2 hr., then allowed to cool. The yellow crystals (5 g.) were removed, washed with ether, and recrystallised from ethanol and then from

water, giving the quaternary *benzothiazole iodide* as white needles (3.5 g.), m. p. 210—211° (Found: C, 48.7; H, 5.6.  $C_{19}H_{23}IN_2O_2S$  requires C, 48.5; H, 4.9%).

The *benzothiazoles* recorded in Table 3 were prepared by the methods illustrated above. In general, the free bases were prepared by cyclisation (yields 40—50%) in ammonium acetate-acetic acid, and the hydrochlorides by cyclisation in nitrobenzene (yields 70—80%). Citrates and tartrates were prepared from the free bases by reaction with equimolecular quantities of the appropriate acid in 1:1 v/v acetone-ethanol (96%).

*2-(p-2-Diethylaminoethoxyphenyl)-6-dimethylaminobenzothiazole*.—*p*-2-Diethylaminoethoxybenzaldehyde (2.21 g.), 2-amino-5-dimethylaminobenzenethiosulphuric acid<sup>14</sup> (2.48 g.), glacial acetic acid (25 ml.), and ammonium acetate (12.5 g.) were boiled for 3 hr., then cooled and poured into water (100 ml.). After neutralisation with 40% aqueous sodium hydroxide, an oil was extracted with ether, and the dry ether solution was passed down an alumina column. Elution with ether gave a pale brown gum which crystallised. Three recrystallisations from light petroleum (b. p. 60—80°) gave yellow crystals, m. p. 63—64°, of the *benzothiazole derivative* (Found: C, 67.8; H, 7.3.  $C_{21}H_{27}N_3OS$  requires C, 68.3; H, 7.3%). The *tartrate* had m. p. 141—142° (from ethanol) (Found: C, 57.6; H, 6.2.  $C_{25}H_{33}N_3O_7S$  requires C, 57.8; H, 6.3%).

*1-[2-[N-(2-p-Benzothiazol-2'-yl)phenoxyethyl]-NN-dimethylammonio]ethyl]-1-methylpiperidinium Di-iodide* (IV).—*o*-Aminobenzenethiol (0.2 g.) and the di-iodide (III) (0.5 g.) in ethanol (20 ml.) were boiled for 1 hr., then cooled and diluted with ether. An amorphous yellow solid was removed. Crystallisation from water gave the *dimethiodide* (0.4 g.) as very pale yellow needles, m. p. 220—221° (decomp.) (Found: C, 44.2; H, 5.3; N, 6.0.  $C_{25}H_{35}I_2N_3OS$  requires C, 44.2; H, 5.2; N, 6.2%).

*5-Chloro-2-p-methoxyphenylbenzothiazole*.—(a) 2-Amino-4-chlorobenzenethiol hydrochloride (10.2 g.), *p*-anisaldehyde (7 g.), glacial acetic acid (100 ml.), and ammonium acetate (50 g.) were boiled under reflux for 3 hr., cooled, poured into water, and made alkaline with aqueous sodium hydroxide. A yellow solid separated and was collected, washed with water, and crystallised from ethanol, to give the *thiazole* (7.14 g., 50%), m. p. 149—151° (Found: C, 60.5; H, 4.0.  $C_{14}H_{10}ClNOS$  requires 61.0; H, 3.6%).

(b) 2,2'-Diamino-4,4'-dichlorodiphenyl disulphide (2 g.), *p*-anisaldehyde (1.7 g.), and nitrobenzene (10 ml.) were boiled under reflux for 15 min. then allowed to cool overnight. The product was removed by filtration and recrystallised from ethanol as white plates (2.8 g., 81%), m. p. 143—144°.

*5-Chloro-2-p-hydroxyphenylbenzothiazole*.—(a) 5-Chloro-2-*p*-methoxyphenylbenzothiazole (1.4 g.), chlorobenzene (10 ml.), and aluminium chloride (14 g.) were stirred at 60° for 7 hr., then treated with *n*-hydrochloric acid (330 ml.), steam-distilled to remove chlorobenzene, and filtered to remove a solid (1.35 g.). Crystallisation of this from aqueous ethanol gave pale brown needles (0.9 g.) of *5-chloro-2-p-hydroxyphenylbenzothiazole*, m. p. 255—259°,  $\lambda_{max}$  263, 315, and 327  $m\mu$  ( $\epsilon$  7200, 23,400, and 27,500 in EtOH) (Found: C, 60.5; H, 3.3.  $C_{13}H_8ClNOS$  requires C, 59.7; H, 3.1%).

(b) 5-Chloro-2-*p*-methoxyphenylbenzothiazole (2 g.) was added to pyridine hydrochloride (20 g.), and the mixture heated at 200° for 1 hr., then cooled and diluted with water. The precipitate (1.9 g.) was washed with water and dissolved in *n*-sodium hydroxide; after filtration it was reprecipitated with hydrochloric acid, washed, and crystallised from ethanol as white needles (1.45 g.), m. p. 257—258°, identical with the compound from (a). The compound becomes brown in the air.

*2-p-Chlorophenyl-6-methoxybenzothiazole*.—The zinc salt of 2-amino-5-methoxybenzenethiol (3.7 g.) was suspended in acetic acid (150 ml.), and *p*-chlorobenzoyl chloride (3.5 g.) was added. The mixture was boiled for 5 min., cooled, filtered, and diluted with water (500 ml.). The precipitate (4.4 g.) crystallised from ethanol, giving the pale yellow benzothiazole, m. p. 139—141° (Found: C, 60.7; H, 3.5. Calc. for  $C_{14}H_{10}ClNOS$ : C, 60.9; H, 3.6%).

*2-p-Chlorophenyl-6-hydroxybenzothiazole*.—This compound was prepared by demethylation of the preceding ether with aluminium chloride as described for the isomer. It was obtained as brown needles, m. p. 256—258°, from aqueous ethanol (Found: C, 59.7; H, 3.0.  $C_{13}H_8ClNOS$  requires C, 59.7; H, 3.1%).

*2-p-Chlorophenyl-6-2'-diethylaminoethoxybenzothiazole* was obtained as white plates, m. p. 72—74° (from light petroleum), by alkylation of the phenol with 2-diethylaminoethyl chloride

<sup>14</sup> Bogert and Updike, *J. Amer. Chem. Soc.*, 1927, **49**, 1373.

(Found: C, 63.25; H, 6.0.  $C_{19}H_{21}ClN_2OS$  requires C, 63.2; H, 5.8%). Its *hydrochloride* formed needles, m. p. 207—209°, from ethanol (Found: C, 56.9; H, 5.2.  $C_{19}H_{22}Cl_2N_2OS$  requires C, 57.4; H, 5.5%).

5-Chloro-2-p-(cyanomethoxy)phenylbenzothiazole. — 5-Chloro-2-p-hydroxyphenylbenzothiazole (5.2 g.), anhydrous potassium carbonate (6.0 g.), chloroacetonitrile (1.52 g.), and acetone (200 ml.) were boiled together under reflux for 24 hr. After cooling and filtration, the acetone was evaporated to give a pale yellow solid which was dissolved in chloroform and washed with *N*-sodium hydroxide, then water, and recovered. Crystallisation from benzene gave colourless prisms (4.7 g., 78%) of 5-chloro-2-p-(cyanomethoxy)phenylbenzothiazole, m. p. 165—166° (Found: C, 60.1; H, 3.5.  $C_{15}H_9ClN_2OS$  requires C, 59.9; H, 3.0%).

2-p-(Amidinomethoxy)phenyl-5-chlorobenzothiazole Hydrochloride.—Hydrogen chloride was passed into a solution of the above nitrile (1 g.) in dioxan (50 ml.) and absolute ethanol (5 ml.) for 5 hr., at 0°. The solution was left for 4 days at room temperature, a colourless solid separating. After addition of ether to complete the precipitation, the solid was removed, washed with ether, and then added to saturated ethanolic ammonia (15 ml.). This mixture was set aside for 4 hr. at room temperature, then heated to 75°. Addition of ether to the cooled solution precipitated the *amidine hydrochloride* (1.4 g.), which, crystallised from 50% aqueous ethanol, had m. p. 270° (decomp.) (0.65 g.),  $\lambda_{max.}$  (in EtOH) 262, 306, and 322  $m\mu$  ( $\epsilon$  9800, 22,900, and 22,400),  $\lambda_{infr.}$  238—240  $m\mu$  ( $\epsilon$  19,500) (Found: C, 51.0; H, 4.4.  $C_{15}H_{13}Cl_2N_3OS$  requires C, 50.8; H, 3.8%).

Nitration of 5-Chloro-2-(p-2-diethylaminoethoxyphenyl)benzothiazole.—The benzothiazole (3.6 g.) in sulphuric acid (15 ml.; *d* 1.84) was treated with a mixture of nitric acid (2.3 g.; *d* 1.5) and sulphuric acid (5 ml.; *d* 1.84) in 35 min. with stirring at 5—10°. The solution was stirred at room temperature for a further hour, then poured on ice and 40% sodium hydroxide solution. The orange precipitate (4.5 g.), m. p. 138—142°, was removed and dissolved in hot benzene, and the solution was allowed to cool and filtered to remove a red solid (0.25 g.). The filtrate was heated to the b. p. and light petroleum (b. p. 60—80°) was added to turbidity; on cooling, yellow needles (2.95 g.), m. p. 153—155°, separated and recrystallised from benzene—light petroleum (b. p. 60—80°) to give pale yellow needles of the *dinitro-compound* (2.4 g.), m. p. 155—156° (Found: C, 50.4; H, 4.1.  $C_{19}H_{18}ClN_5O_7S$  requires C, 50.6; H, 4.2%). This gave a *hydrochloride*, m. p. 198.5—199° (from ethanol),  $\lambda_{max.}$  232, 296, 310, and 322  $m\mu$  ( $\epsilon$  27,700, 21,400, 24,000, and 24,000 in EtOH) (Found: C, 46.8; H, 4.9.  $C_{19}H_{20}Cl_2N_4O_5S_2C_2H_5\cdot OH$  requires C, 47.3; H, 4.9%), and a *tartrate*, m. p. 167—169° (from 50% ethanol) (Found: C, 44.7; H, 4.5.  $C_{23}H_{25}ClN_4O_{11}S_2H_2O$  requires C, 44.6; H, 4.4%).

2-p-Hydroxyphenylbenzoxazole.—(a) 2-p-Methoxyphenylbenzoxazole<sup>7</sup> (2 g.), hydriodic acid (10 ml.; *d* 1.94), and red phosphorus (0.2 g.) were heated together under reflux at 125—130° for 1 hr., then cooled, diluted with water (25 ml.), and neutralised with ammonia. The precipitate was removed, washed with water, and crystallised from ethanol to give 2-p-hydroxyphenylbenzoxazole (1.8 g.), m. p. 252—253° (Found: C, 74.3; H, 4.4.  $C_{13}H_9NO_2$  requires C, 74.0; H, 4.3%).

(b) p-Benzoyloxybenzaldehyde (2.12 g.) with *o*-aminophenol (1.09 g.) in hot ethanol (50 ml.) gave 2-(4-benzoyloxybenzylideneamino)phenol (2.38 g.), m. p. 109—110° (Found: C, 78.7; H, 5.8.  $C_{20}H_{17}NO_2$  requires C, 79.2; H, 5.7%), which was cyclised with lead tetra-acetate<sup>7</sup> (3.48 g.) in benzene (20 ml.) to give 2-p-benzoyloxyphenylbenzoxazole (1.5 g.), m. p. 144—145° (from cyclohexane) (Found: C, 79.9; H, 5.4.  $C_{20}H_{15}NO_2$  requires C, 79.7; H, 5.0%). Hydrogenolysis with 5% palladium-charcoal in ethyl acetate at room temperature and pressure then gave a solid identical with that obtained as in (a).

2-(p-2-Diethylaminoethoxyphenyl)benzoxazole.—2-p-Hydroxyphenylbenzoxazole (2.1 g.) and 2-diethylaminoethyl chloride hydrochloride (1.7 g.) were added to a solution from sodium (0.5 g.) in ethanol (25 ml.) and the mixture boiled for 5 hr., filtered, and evaporated, and the residue was shaken with *N*-sodium hydroxide and ether. Evaporation of the washed and dried ether gave an oil (2.2 g.) which crystallised. Recrystallisation from light petroleum (b. p. 40—60°) gave yellow plates, m. p. 59—60°, of the ether,  $\lambda_{max.}$  276 and 312  $m\mu$  ( $\epsilon$  17,800 and 38,000 in EtOH) [*hydrochloride*, m. p. 190—191° (Found: C, 65.3; H, 7.1.  $C_{19}H_{23}ClN_2O_2$  requires C, 65.8; H, 6.6%)].

5,6-Dichlorobenzoxazolone.—5-Chlorobenzoxazolone (5.85 g.),<sup>15</sup> suspended in glacial acetic

<sup>15</sup> Beilstein's "Handbuch der Organischen Chemie," 4th edn., Vol. XXVII, p. 179 but method of MacDonal and Chechak, *Canad. J. Research*, 1948, **26**, B, 432.



acid (50 ml.), was stirred and cooled in ice-water during dropwise addition of sulphuryl chloride (3.8 ml.). After 2 hr., the mixture was set aside at room temperature overnight then heated on a steam-bath for 1 hr., cooled, and poured into water. The solid obtained, when crystallised from ethanol, was pale pink (6.1 g.), m. p. 202—203°. <sup>11</sup>

*2-Amino-4,5-dichlorophenol.*—5,6-Dichlorobenzoxazolone (7.3 g.) and 10% sodium hydroxide solution (100 ml.) were boiled for 1 hr., then cooled and made faintly acid by acetic acid, and the precipitate was crystallised from water, to give the yellow amine (4.25 g.), m. p. ca. 170° (decomp. on rapid heating) (Found: C, 41.0; H, 3.1; N, 7.9; Cl, 40.1. Calc. for C<sub>8</sub>H<sub>5</sub>Cl<sub>2</sub>NO: C, 40.5; H, 2.8; N, 7.9; Cl, 39.9%).

The following compounds were similarly prepared in moderate to good yields by the route, Schiff's base → *p*-methoxyphenylbenzoxazole → *p*-hydroxyphenylbenzoxazole → 2-(*p*-2-diethylaminoethoxyphenyl)benzoxazole: 4-chloro-2-(4-methoxybenzylideneamino)phenol, pale yellow needles [from light petroleum, (b. p. 60—80°)], m. p. 89° (Found: C, 64.5; H, 4.7. C<sub>14</sub>H<sub>12</sub>ClNO<sub>2</sub> requires C, 64.2; H, 4.6%); 4,5-dichloro-2-(4-methoxybenzylideneamino)phenol, yellow needles (from ligroin), m. p. 134—134.5° (Found: C, 57.0; H, 3.7. C<sub>14</sub>H<sub>11</sub>Cl<sub>2</sub>NO<sub>2</sub> requires C, 57.0; H, 3.8%); 5-chloro-2-*p*-methoxyphenylbenzoxazole, pink plates (from ethanol), m. p. 153—154° (Found: C, 64.5; H, 4.3. C<sub>14</sub>H<sub>10</sub>ClNO<sub>2</sub> requires C, 64.7; H, 3.85%); 5,6-dichloro-2-*p*-methoxyphenylbenzoxazole, m. p. 152—153° (from ethanol) (Found: C, 57.7; H, 3.7. C<sub>14</sub>H<sub>9</sub>Cl<sub>2</sub>NO<sub>2</sub> requires C, 57.1; H, 3.1%); 5-chloro-2-*p*-hydroxyphenylbenzoxazole (from ethanol), m. p. 263—264° (Found: C, 64.1; H, 3.6. C<sub>13</sub>H<sub>9</sub>ClNO<sub>2</sub> requires C, 63.5; H, 3.3%); 5,6-dichloro-2-*p*-hydroxyphenylbenzoxazole (from ethanol), m. p. 237—238° (Found: C, 56.0; H, 3.0. C<sub>13</sub>H<sub>7</sub>Cl<sub>2</sub>NO<sub>2</sub> requires C, 55.7; H, 2.5%); 5-chloro-2-(*p*-2-diethylaminoethoxyphenyl)benzoxazole, needles (from aqueous ethanol), m. p. 94° (Found: C, 66.7; H, 6.7. C<sub>19</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>2</sub> requires C, 66.2; H, 6.15%) [hydrochloride, m. p. 226—227° (from aqueous hydrochloric acid)]; 5,6-dichloro-2-(*p*-2-diethylaminoethoxyphenyl)benzoxazole hydrochloride, m. p. 260—262° (from ethanol) (Found: C, 55.0; H, 5.4; N, 7.1; Cl, 25.1. C<sub>19</sub>H<sub>21</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>2</sub> requires C, 54.8; H, 5.1; N, 6.8; Cl, 25.3%).

*6-p-Hydroxyphenylphenanthridine.*—6-*p*-Methoxyphenylphenanthridine <sup>16</sup> (3 g.) and pyridine hydrochloride (20 g.) were heated to 200° for 1 hr., cooled, and triturated with water. The insoluble solid was collected, washed with water, and extracted with boiling *n*-sodium hydroxide (100 ml.). After filtration, the alkaline solution was acidified with acetic acid, and the precipitate (2.5 g.) crystallised from ethanol to give 6-*p*-hydroxyphenylphenanthridine as colourless prisms (1.85 g.), m. p. 257—257.5° (lit., <sup>16</sup> 237°) (Found: C, 84.3; H, 4.8. Calc. for C<sub>19</sub>H<sub>13</sub>NO: C, 84.4; H, 4.8%).

*6-(p-2-Diethylaminoethoxyphenyl)phenanthridine.*—The preceding phenol was boiled in acetone for 24 hr. with potassium carbonate and 2-diethylaminoethyl chloride hydrochloride, and the crude ether treated with citric acid to give the *ether citrate* as colourless needles, m. p. 142—143° (decomp.) (from ethanol-ether), λ<sub>max.</sub> 250, 305, 336, and 352 mμ (ε 40,700, 10,700, 5400, and 4500 in EtOH) (Found: C, 66.0; H, 6.15. C<sub>31</sub>H<sub>34</sub>N<sub>2</sub>O<sub>8</sub> requires C, 66.1; H, 6.1%). The *ethobromide* formed pale yellow prisms, m. p. 146—147° (decomp.), from ethanol-ether (Found: C, 66.6; H, 6.9. C<sub>27</sub>H<sub>31</sub>BrN<sub>2</sub>O<sub>2</sub>C<sub>2</sub>H<sub>5</sub>·OH requires C, 66.3; H, 7.1%).

*6-(p-2-Diethylaminoethoxyphenyl)phenanthridine Dimethiodide.*—6-(*p*'-2-Diethylaminoethoxyphenyl)phenanthridine citrate (1.12 g.) was decomposed with *n*-sodium hydroxide, and the free base taken into benzene. After drying (MgSO<sub>4</sub>) and evaporation of the benzene the residual oil was heated in nitrobenzene with dimethyl sulphate (1 ml.) at 150° for ½ hr. The nitrobenzene was removed in steam, and the aqueous residue evaporated to dryness. The solid residue was dissolved in water (10 ml.), and saturated aqueous sodium iodide (5 ml.) was added. The yellow precipitate produced was collected and crystallised from ethanol, to give orange needles of the *dimethiodide* (360 mg.), m. p. 215—216° (decomp.) (Found: C, 49.2; H, 4.93. C<sub>27</sub>H<sub>32</sub>I<sub>2</sub>N<sub>2</sub>O requires C, 49.6; H, 4.9%).

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RESEARCH DEPARTMENT, THE CROOKES LABORATORIES LTD.,  
PARK ROYAL, LONDON, N.W.10.

[Present address: TWYFORD LABORATORIES LTD.,  
TWYFORD ABBEY ROAD, LONDON, N.W.10.]

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