174. *Some Anti-microbial Compounds in the Heterocyclic Series. Part IV.*[1] *Non-photosensitizing Basic Ethers in the Benzothiazole Series.*

By H. D. Cossey, J. Judd, and F. F. Stephens.

Basic ethers of phenylbenzothiazoles in which the nuclei are joined in the 2-position by CH_2, S, NH, O, $CH_2{\cdot}CH_2$, $S{\cdot}CH_2$, $CH_2{\cdot}S$, $NH{\cdot}CH_2$, $CH_2{\cdot}NH$, $CH_2{\cdot}O$, and CH:CH, or in which the benzothiazole nucleus is reduced, are described. The compounds were prepared as non-photosensitizing anti-microbial agents and the relationships between structure and these properties are discussed. 2-Benzylthiobenzothiazole basic ethers show greater activity against bacteria, fungi, and protozoa than the compounds described previously.

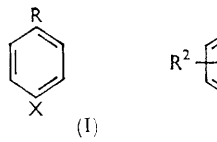
In Part III [1] the preparation of some 2-phenylbenzothiazole basic ethers was described and from these 5-chloro-2-(*p*-2-diethylaminoethoxyphenyl)benzothiazole was chosen for clinical investigation. This substance proved to be an effective topical fungicide but was found to possess biological photosensitizing properties (see Discussion). A study was therefore made of the relationships between structure, photosensitizing properties, and anti-microbial activity with the object of devising new non-irritant antifungal agents. This report deals with the chemistry and ultraviolet absorption spectra of 2-substituted benzothiazole basic ethers differing from those described in Part III in that the phenyl and benzothiazole nuclei are not directly linked, or in which the benzothiazole nucleus is reduced.

The photosensitizing 2-phenyl-compounds previously described [1] have absorption peaks in the 315—330 mμ region and, although in general such photosensitization results from the absorption of a wide spectrum of radiation, the effects produced by these compounds may be related, as in the case of the furocoumarins,[2] to a specific range of wavelengths. In the case of the related 2-methylbenzothiazoles there is no photosensitization and absorption only occurs below 300 mμ. Since the lower limit of solar ultraviolet radiation is in the region of 290 mμ [3] it is probable that compounds whose principal absorption maxima are below this limit will not cause photosensitization. The problem of overcoming photosensitivity could therefore be approached by reducing the conjugation in the 2-phenylbenzothiazole system so that light absorption occurred at lower wavelengths and for this reason compounds of type (III), in which the conjugation between phenyl and benzothiazole rings is broken, were prepared.

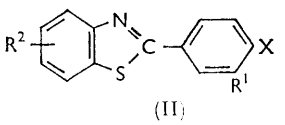
In a first group of compounds a single atom separated the two rings (III; Y = CH_2, S, NH, or O) and these compounds had absorption peaks at wavelengths lower than that shown by 5-chloro-2-(*p*-2-diethylaminoethoxyphenyl)benzothiazole. The compounds were not photosensitizers but possessed no significant anti-microbial activity. In a second group, a two-atom chain was introduced between the rings (III; Y = $CH_2{\cdot}CH_2$, $S{\cdot}CH_2$, $CH_2{\cdot}S$, $NH{\cdot}CH_2$, $CH_2{\cdot}NH$, or $CH_2{\cdot}O$) and two benzylthiobenzoxazoles were also prepared. The compounds again had maximum absorption at lower wavelengths and were not photosensitizers but, in the case of phenethyl- and benzylthio-compounds, antifungal activity comparable with that shown by the compounds described in Part III [1] was obtained. The relationship between structure and anti-microbial activity in these two series was therefore more closely investigated by the preparation of compounds in which the benzene and phenyl rings were substituted with halogen, acetyl, methoxyl, methyl, amino-, acetamido-, and nitro-groups, in which the bridging element carried methyl groups and in which the benzo-ring was reduced.

[1] Part III, Cossey, Sharpe, and Stephens, *J.*, 1963, 4322.
[2] Pathak and Fellman, *Nature*, 1960, **185**, 382.
[3] Blum, *Physiol. Rev.*, 1945, **25**, 483.

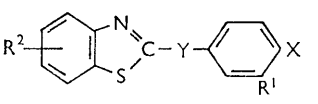
An alternative method of reducing the conjugation is by synthesis of benzothiazoline analogues (IV). 2-(*p*-2-Diethylaminoethoxyphenyl)-3-methylbenzothiazoline showed no absorption in the 325 mμ region and was not a photosensitizer, but possessed no antifungal activity. The alternative approach, by increasing the maximum absorption wavelength, which incidentally has a practical limitation since the compounds may become coloured and therefore clinically undesirable, was investigated by the preparation of 5-chloro-2-(*p*-2-diethylaminoethoxystyryl)benzothiazole (IIId; $R^1 = H$, $R^2 = 5\text{-Cl}$, Y = CH:CH). The hydrochloride of this had an absorption maximum at 356 mμ but was optically unstable; thus, on standing in daylight or on irradiation with an ultraviolet lamp, the maximum changed to 320 mμ characteristic of the *cis-trans* isomerism and dimerization shown by amidinostilbenes.[4] The compound was a non-photosensitizer and possessed anti-microbial activity.



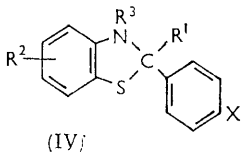
(I)



(II)



(III)



(IV)

a: X = H
b: X = OH
c: X = OMe
d: X = O·$[CH_2]_2$·NEt_2
e: X = O·$[CH_2]_2$·NMe_2
f: X = O·$[CH_2]_3$·NEt_2

g: X = O·CH(Me)·CH_2·NEt_2
h: X = O·CH_2·CH(Me)·CH_2·NMe_2
i: X = O·$[CH_2]_2$·NBu^n_2
j: X = O·$[CH_2]$·N⟨O⟩
k: X = O·CH_2·$C(NH_2)$:NH

2-Benzylbenzothiazoles (III; Y = CH_2) were prepared by condensation [5] of methoxyphenylacetyl chlorides with *o*-aminobenzenethiols in dimethylaniline (when the corresponding disulphide dihydrochloride was used, much lower yields resulted). The resulting methoxybenzylbenzothiazoles were demethylated with pyridine hydrochloride and the phenols alkylated with dialkylaminoalkyl chlorides. Synthesis of 2-(*p*-2-diethylaminoethoxyphenylthio)benzothiazole (IIId; $R^1 = R^2 = H$, Y = S) by alkylation of benzothiazole-2-thiol with *p*-2-diethylaminoethoxychlorobenzene [6] was unsuccessful but reaction did occur with *p*-nitrochlorobenzene in ethanolic sodium ethoxide on heating under reflux for 20 days. Stannous chloride reduction of the nitrophenylthio-compound, followed by conversion of the resulting amine into the phenol by diazotization, and alkylation of this gave the required compound. Reaction [7] of 2-chlorobenzothiazole with *p*-anisidine gave 2-(*p*-methoxyanilino)benzothiazole which was demethylated with hydrobromic acid and the phenol alkylated as before to give compound (IIId; $R^1 = R^2 = H$, Y = NH). Alkylation of *p*-2-diethylaminoethoxyphenol with 2-chlorobenzothiazole gave very low yields of the 2-(*p*-2-diethylaminoethoxyphenoxy)benzothiazole (IIId; $R^1 = R^2 = H$, Y = O); this compound was therefore prepared by treating 2-chlorobenzothiazole with an excess of hydroquinone to give a mixture of mono- and di-ethers from which the monoether could be separated then alkylated with 2-diethylaminoethyl chloride.

2-Phenethylbenzothiazoles (III; Y = CH_2·CH_2) were prepared by condensation of *o*-aminobenzenethiols with β-phenylpropionyl chlorides as for the 2-benzylbenzothiazoles. The 2-benzylthiobenzothiazoles (III; Y = S·CH_2) were prepared by reaction of dialkylaminoalkoxybenzyl chlorides (as hydrochlorides) with benzothiazole-2-thiols. That the desired compounds and not the isomeric 3-benzylbenzothiazole-2-thiones were obtained was shown by spectroscopy,[8] although when 4-acetoxybenzyl bromide was used a mixture

[4] Fulton and Goodwin, *Brit. J. Pharmacol.*, 1946, **1**, 234; Henry, *J.*, 1946, 1156; Fulton and Dunitz, *Nature*, 1947, **160**, 161.
[5] Lankelma and Knauf, *J. Amer. Chem. Soc.*, 1931, **53**, 309.
[6] Drain, Peak, and Whitmont, *J.*, 1949, 2680.
[7] D'Amico, Tung, and Walker, *J. Amer. Chem. Soc.*, 1959, **81**, 5957.
[8] Morgan, *J.*, 1958, 854.

of these isomers was obtained in one case. The benzyl chlorides so required were obtained from the corresponding aldehydes (see Part III [1]) by Cannizzaro reaction with formaldehyde and alkali or by catalytic hydrogenation to the alcohol followed by reaction with thionyl chloride. *p*-Hydroxyphenylmercaptoacetic acid [9] was prepared from the corresponding nitro-compound by reduction followed by diazotization, and reacted with 2-amino-4-chlorobenzenethiol to give 5-chloro-2-(*p*-hydroxyphenylthiomethyl)benzothiazole in low yield. Alkylation of this in the usual manner gave the required basic ether (IIId; $R^1 = H$, $R^2 = 5\text{-Cl}$, $Y = CH_2{\cdot}S$). Neither *p*-nitrophenyl- nor *p*-aminophenyl-mercaptoacetic acid would condense with *o*-aminobenzenethiol itself. In contrast, *p*-hydroxyphenoxyacetic acid condensed in good yield with 2-amino-4-chlorobenzenethiol to give 5-chloro-2-(*p*-hydroxyphenoxymethyl)benzothiazole from which the system (III; $Y = CH_2{\cdot}O$) could be prepared. 2-(*p*-2-Diethylaminoethoxybenzylamino)benzothiazole (IIId; $R^1 = R^2 = H$, $Y = NH{\cdot}CH_2$) was prepared by condensation of 2-chlorobenzothiazole with *p*-2-diethylaminoethoxybenzylamine, the last-named compound being obtained from the corresponding benzyl chloride by the phthalimide–hydrazine route. The toluene-*p*-sulphonate of 5-chloro-2-hydroxymethylbenzothiazole condensed with *p*-2-diethylaminoethoxyaniline to give 5-chloro-2-(*p*-2-diethylaminoethoxyanilinomethyl)benzothiazole (IIId; $R^1 = H$, $R^2 = Cl$, $Y = CH_2{\cdot}NH$).

Several methods [10] exist for the preparation of benzothiazolines from ketones and *o*-aminobenzenethiols but neither Kiprianov's nor Elderfield's methods succeeded in giving pure compounds when attempts were made to prepare 2-(*p*-2-diethylaminoethoxyphenyl)-2-methylbenzothiazoline. The synthesis [11] of benzothiazolines from aldehydes and *o*-alkylaminobenzenethiols proceeds with greater ease and 2-(*p*-2-diethylaminoethoxyphenyl)-3-methylbenzothiazoline was so prepared from o-methylaminobenzenthiol and *p*-2-diethylaminoethoxybenzaldehyde. The 5-chloro-derivative was also prepared. The method of Baker and Fierz-David [11] was also used to prepare 3-(*p*-chlorobenzyl)-2-(*p*-2-diethylaminoethoxyphenyl)benzothiazoline, the *o*-(*p*-chlorobenzylamino)benzenethiol intermediate being obtained by alkylation of benzothiazolone with *p*-chlorobenzyl chloride followed by hydrolysis.

The styrylbenzothiazoles (III; $Y = CH{:}CH$) were obtained by a modification of Brown and Kon's [12] method. In the reaction of anisaldehyde with 5-chloro-2-methylbenzothiazole by this method a small yield of a substance analysing as the addition compound, 5-chloro-2-(β-hydroxy-β-*p*-methoxyphenyl)ethylbenzothiazole, was also isolated. Reduction of styrylbenzothiazoles having basic ether groups with zinc and acetic acid gave the phenethylbenzothiazoles (III; $Y = CH_2{\cdot}CH_2$) in low yield, but catalytic hydrogenation (palladium–charcoal, platinum oxide, or Raney nickel) was unsuccessful.

The preparation of the numerous halogenated hydroxybenzaldehydes and other intermediates required in this work was generally by existing methods or modification of these. Bromination of 3-chloro-4-hydroxybenzaldehyde in acetic acid gave the 3-bromo-5-chloro-derivative, and a more convenient synthesis of 3-chloroanisaldehyde than those reported [13,14] was by means of sulphuryl chloride. 4-(2-Diethylaminoethoxy)-α-methylbenzyl alcohol was obtained by Grignard reaction from methylmagnesium iodide and *p*-2-diethylaminoethoxybenzaldehyde and was converted into the chloride with thionyl chloride. 2-(*p*-2-Diethylaminoethoxyphenyl)propan-2-ol was prepared in a similar manner from the acetophenone. β-(*p*-Methoxyphenyl)butyric acid and β-(3-chloro-4-methoxyphenyl)propionic acid were prepared by catalytic reduction of the corresponding cinnamic acids. β-(3-Bromo-4-methoxyphenyl)propionic acid was obtained by direct

[9] Oksengendler and Gerasimenko, *Zhur. obshchei Khim.*, 1957, **27**, 3214.
[10] Kiprianov and Portnyagina, *J. Gen. Chem.* (*U.S.S.R.*), 1955, **25**, 2223; Teuber and Waider, *Chem. Ber.*, 1958, **91**, 2341; Pazenko, *Ukrain. khim. Zhur.*, 1959, **25**, 348; Elderfield and McClenachan, *J. Amer. Chem. Soc.*, 1960, **82**, 1982.
[11] Baker and Fierz-David, *Helv. Chim. Acta*, 1950, **33**, 2011.
[12] Brown and Kon, *J.*, 1948, 2147.
[13] Gray, Jones, and Marson, *J.*, 1956, 1417.
[14] Ginsburg, *J. Amer. Chem. Soc.*, 1951, **73**, 702.

bromination of β-*p*-methoxyphenylpropionic acid in chloroform. The benzothiazole-2-thiols were obtained by five general methods: (*a*) by reduction of *o*-nitrochlorobenzenes with sodium disulphide in the presence of carbon disulphide, (*b*) by hydrolysis of thiazathionium salts (formed in Herz [1] reactions) to *o*-aminobenzenethiols which then undergo ring closure with carbon disulphide, (*c*) from 2-aminobenzothiazoles by diazonium reaction [15] to the 2-bromo-compound followed by reaction with thiourea,[16] (d) by ring closure of phenylthioureas with sulphur [17] and (*e*) by nitration of 2,2′-bisbenzothiazolyl disulphides followed by reduction of the disulphide bond with sodium sulphite and conversion of the nitrobenzothiazolethiols so obtained to amines, followed by Sandmeyer reaction to halogenobenzothiazole-2-thiols [18] (the last stage of this sequence failed when applied to 6-amino-5-chlorobenzothiazole-2-thiol).

Discussion

Microbiological Results.—Full details of the microbiological investigation and a discussion of the results will be published elsewhere. Compounds of type (III) with a single atom bridging the phenyl and benzothiazole nuclei (Y = CH_2, S, NH, or O) show no significant activity against fungi and only slight activity against *Streptococcus pyrogenes*. Activity comparable with that shown by the best compounds described in Part III appears when Y is CH:CH, CH_2·CH_2, S·CH_2, S·CH(Me), CH_2·CH(Me), or CH(Me)·CH_2. With the bridging group Y = CH_2·S, NH·CH_2, CH_2·NH, or CH_2·O there is no significant activity against fungi and only moderate activity against Gram-positive bacteria. Within the series of benzylthiobenzothiazoles (III; Y = S·CH_2) (which was most thoroughly investigated) greatest activity was found with a 2-diethylaminoethoxy-side-chain in the 4′-position. In the 2-(*p*-2-diethylaminoethoxybenzylthio)benzothiazole series, substitution of halogen (principally chlorine) is specifically related to activity and greatest activity is found with 2-[3-bromo-4-(2-diethylminoethoxy)benzylthio]-6-chlorobenzothiazole citrate (minimum inhibitory concentrations in μg./ml.: *Trichophyton mentagrophytes* = 0·5, *Epidermophyton floccosum* = 0·5, *Candida albicans* = 30, *S. pyogenes* = 3). The compounds were not active against Gram-negative organisms but selected compounds were found to be highly active (<1 μg./ml.) against *Mycobacterium tuberculosis*. A study of the stereochemistry of active and inactive compounds with the aid of Courtauld molecular models initially suggested that, as in the case of anilino-*s*-triazines,[19] fungitoxicity was related to coplanarity of the phenyl and benzothiazole nuclei and to freedom of rotation about the axis joining these nuclei; thus, in the inactive series (III; Y = CH_2, S, NH, or O), the nuclei are not coplanar and rotation about the linking axis is not possible, and in the other inactive series (III; Y = CH_2·S, NH·CH_2, CH_2·NH, or CH_2·O) although a coplanar state is possible, free rotation is not. In the active series (III; Y = S·CH_2 or CH_2·CH_2) coplanarity and free rotation are possible. These dual requirements, however, do not hold for the active series [III; Y = CH(Me)·CH_2, CH_2·CH(Me), or S·CH(Me)] where free rotation is not possible.

Pharmacology.—Normal intact skin treated topically with dilute alcoholic solutions of 5-chloro-2-(*p*-2-diethylaminoethoxyphenyl)benzothiazole hydrochloride and subsequently exposed to sunlight displays a photosensitive reaction consisting of erythema, swelling, and pain. Increase in capillary permeability can be followed by use of an intravenous injection of a vital dye (Evans Blue) which stains surrounding tissue when capillaries become permeable to protein. The rapidity with which photosensitized skin reacts is striking and suggests that in some way the effect results from an immediate action on the

[15] Elderfield and Short, *J. Org. Chem.*, 1953, **18**, 1092.
[16] Mackie and Misra, *J.*, 1955, 1030.
[17] Sebrell and Boord, *J. Amer. Chem. Soc.*, 1923, **45**, 2390.
[18] Cutter and Golden, *J. Amer. Chem. Soc.*, 1947, **69**, 831; Teppema and Sebrell, *ibid.*, 1927, **49**, 1779; Drozdov and Stavrovskyaya, *Zhur. obshchei Khim.*, 1937, **7**, 2813.
[19] Burchfield and Storrs, *Nature*, 1960, **187**, 593.

TABLE 1.

Ultraviolet absorption spectra ($\lambda_{max.}$ in mμ, log ε in parentheses) and photosensitivity of benzothiazoles and related compounds.

Compound	Solvent *	$\lambda_{max.}$	Photosensitivity
5-Chloro-2-methylbenzothiazole	A	222 (4·46), 254 (3·78), 290 (3·22), 300 (3·20)	−
(IIa: R^1 = H, R^2 = 5-Cl)	B	222 (4·29), 238 (4·41), 260 (3·97), 289 (4·26), 298—300 † (4·23)	+
(IIb; R^1 = H, R^2 = 5-Cl)	B	263 (3·86), 315 (4·37), 327 (4·44)	+
(IId; R^1 = H, R^2 = 5-Cl ‡	B	263 (3·90), 312 (4·39), 325 (4·50)	+
,, §	A	218 (4·64), 270 (3·93), 311 (4·36), 324 (4·37)	−
5-Chloro-2-(*p*-2-diethylaminoethoxyphenyl)benzoxazole	B	276 (4·25), 312 (4·58)	+
(IIf; R^1 = H; R^2 = 5-Cl) ‡	B	262 (3·91), 312 (4·40), 325 (4·44)	+
(IIk; R^1 = H; R^2 = 5-Cl) ‡	B	238—240 † (4·29), 262 (3·99), 306 (4·36), 322 (4·35)	+
(IIId; R^1 = H, R^2 = 5-Cl, Y = CH_2·) ¶	B	227 (4·61), 256 (4·06), 292 (3·62)	−
(IIId; R^1 = R^2 = H, Y = S) ¶	A	230 (4·48), 280 (4·25), 286—288 † (4·22), 300 (4·12)	−
(IIId; R^1 = R^2 = H, Y = NH)	A	218 (4·43), 298 (4·37)	−
(IIId; R^1 = R^2 = H, Y = O) ‡	A	220 (4·54), 250 (4·09), 305 (2·72)	−
(IIIa; R^1 = H, R^2 = 5-Cl, Y = CH_2·CH_2)	A	223 (4·55), 255 (3·95), 290 (3·42)	−
(IIId; R^1 = H, R^2 = 5-Cl, Y = CH_2·CH_2) ‡	A	225 (4·59), 258 (3·92), 290 (3·38)	−
(IIId; R^1 = Br, R^2 = 5-Cl, Y = CH_2·CH_2) ‡	A	224 (4·64), 256 (3·88), 280 (3·50), 303 (3·42)	−
(IIId; R^1 = R^2 = H, Y = S·CH_2) ¶	B	227 (4·35), 282 (4·03), 300 (3·89)	−
(IIId; R^1 = Cl, R^2 = H, Y = S·CH_2) ¶	B	223 (4·52), 283 (4·22), 290 (4·19)	−
(IIId; R^1 = H, R^2 = 5-Cl, Y = CH_2·S) ¶	B	226 (4·55), 292 (3·75)	−
(IIId; R^1 = R^2 = H, Y = NH·CH_2)	A	226 (4·64), 269 (3·98)	− ¶
(IIId; R^1 = H, R^2 = 5-Cl, Y = CH_2·NH)	B	224 (4·57), 240 † (4·43), 293 (3·68), 302 (3·71)	− ‖
(IIId; R^1 = H, R^2 = 5-Cl, Y = CH_2·O) ¶	B	226 (4·62), 256 (3·96), 290 (3·67)	−
(IVd; R^1 = R^2 = H, R^3 = Me)	A	230 (4·57), 312 (3·65)	− ‡
(IIId; R^1 = H, R^2 = 5-Cl, Y = CH:CH) ‡	A	230 (4·42), 355 (4·60)	−
6-(*p*-2-Diethylaminoethoxyphenyl)phenanthridine ¶	A	232 (4·52), 320 (4·12) **	
	B	250 (4·61), 305 (4·03), 336 (3·73), 352 (3·65)	−

* A, 50% aqueous ethanol; B, ethanol. † Inflection. ‡ Hydrochloride. § Ethiodide. ¶ Citrate. ‖ Dihydrochloride. ** After irradiation for 15 min. with the ultraviolet lamp.

blood vessels (possibly by release of existing chemical substances). Pretreatment of animals with either reserpine, dextran, or ergotoxine will block the increase in capillary permeability and topically applied cysteine will retard the photosensitizing action. By the use of filters it was shown that the wavelengths responsible for photosensitizing action with 5-chloro-2-(*p*-2-diethylaminoethoxyphenyl)benzothiazole hydrochloride lie between 310 and 390 mμ.

In Table 1 the ultraviolet absorption data and photosensitizing action of some of the compounds described in this report are presented. Photosensitizers in all cases except one have prominent absorption in the 320—330 mμ region and absorption in this region is absent in the non-photosensitizers. An exception in the case of the non-photosensitizing 5-chloro-2-(*p*-2-diethylaminoethoxyphenyl)benzothiazole ethiodide (absorbing at 324 mμ) is probably because the substance does not penetrate the skin, which is electrically polarized, generally impermeable to electrolytes, and highly selective in allowing substances to pass through it. That 5-chloro-2-(*p*-2-diethylaminoethoxyphenyl)benzothiazole is absorbed through the skin and into the systemic circulation is shown by the appearance of light-induced capillary permeability in an area remote from a topical application of this substance. These facts suggest that the photosensitizing compounds reach a layer (stratum corneum) where the molecule is fixed in a viscous medium such that, on irradiation, it becomes excited (triplet state) [20] and the resulting energy transfer leads to local disturbance of skin biochemistry with the development of inflammation.

Experimental

Benzothiazoles (III; Y = S, NH, O).—2-(p-*Aminophenylthio)benzothiazole.* A suspension of 2-(*p*-nitrophenylthio)benzothiazole (16·8 g.) in concentrate hydrochloric acid (100 ml.) was heated on a water-bath and a solution of stannous chloride dihydrate (40·8 g.) added with stirring during 15 min. The stirring and heating were continued for a further 1 hr., the mixture was cooled and poured into an excess of 40% sodium hydroxide solution. The oily precipitate was extracted with ether, the ether dried ($MgSO_4$) and evaporated to leave a colourless solid (13 g.). Crystallization from benzene–light petroleum (b. p. 60—80°) gave colourless needles of 2-(*p*-aminophenylthio)benzothiazole (10·0 g.), m. p. 122—123° (lit.,[21] 123°).

2-(p-*Hydroxyphenylthio)benzothiazole.* Finely ground 2-(*p*-aminophenylthio)benzothiazole (18 g.) was heated on a water-bath for 1 hr. with 2N-sulphuric acid (300 ml.). The stirred suspension of the sulphate was cooled to 0°, sodium nitrite (4·6 g.) in water (25 ml.) added over 30 min., and the mixture kept at 0° for a further 30 min. The solution was filtered from unreacted sulphate (1 g.) and added with stirring over 1 hr. to a solution of copper sulphate (18 g.) in water (1 l.) at 60—70° then kept at 85—90° for 2 hr. The mixture was cooled, extracted with chloroform, and the chloroform extracted with N-sodium hydroxide. Acidification with N-hydrochloric acid, extraction with chloroform and evaporation gave a brown oil. Crystallization from benzene–light petroleum (b. p. 60—80°) gave a brown solid (6·5 g.) which was recrystallized from aqueous ethanol to give colourless needles of 2-(p-*hydroxyphenylthio)benzothiazole* (5·4 g.), m. p. 178—179° (Found: C, 60·5; H, 4·0. $C_{13}H_9NOS_2$ requires C, 60·2; H, 3·5%). A further quantity (1·15 g.) was obtained from the mother-liquors.

2-(p-2-*Diethylaminoethoxyphenylthio)benzothiazole citrate.* 2-(*p*-Hydroxyphenylthio)benzothiazole (2 g.) was alkylated with 2-diethylaminoethyl chloride hydrochloride in acetone–potassium carbonate [1] to give an oil (2 g.) which was dissolved in methanol, citric acid (1·2 g.) added, and the solution refluxed for 15 min. The colourless solid (3·0 g.) which separated on the addition of ether was recrystallized from acetone to give colourless needles of the *citrate* (1·4 g.), m. p. 96—98° (Found: C, 54·7; H, 6·1. $C_{25}H_{30}N_2O_8S_2$ requires C, 54·5; H, 5·45%).

2-p-*Methoxyanilinobenzothiazole.*—*p*-Anisidine (20 g.) was heated to 80—100°, 2-chlorobenzothiazole (13·6 g.) added with stirring over 15 min., and the temperature then raised to 150° for 6 hr. The mixture was cooled to 90°, water (100 ml.) added, and the mixture stirred

[20] Reid, "Excited States in Chemistry and Biology," Butterworth, London, 1957.
[21] Itai and Yamamoto, *J. Pharm. Soc. Japan*, 1948, **68**, 128.

for ½ hr. The solid was filtered off, washed with water, and recrystallized from ethanol (charcoal) to give 2-*p*-methoxyanilinobenzothiazole (15·3 g.), m. p. 158—159° (lit.,[22] 158—159°).

2-p-*Hydroxyanilinobenzothiazole.* A solution of 2-*p*-methoxyanilinobenzothiazole (6·0 g.) in 44% w/w hydrobromic acid (50 ml.) was heated under reflux for 3 hr. The solid which separated on cooling was filtered off, dissolved in boiling water, and precipitated with concentrated ammonia solution to give a colourless solid (5·04 g.). Crystallization from ethyl acetate–light petroleum (b. p. 60—80°) gave the *phenol* as colourless needles (3·85 g.), m. p. 203—204° (Found: C, 64·4; H, 4·5. $C_{13}H_{10}N_2OS$ requires C, 64·45; H, 4·2%).

2-(p-2-*Diethylaminoethoxyanilino*)*benzothiazole.* The above phenol (3·85 g.) was alkylated as described above to give the *basic ether* (1·5 g.), m. p. 83—84° (Found: C, 66·7; H, 7·3. $C_{19}H_{23}N_3OS$ requires C, 66·8; H, 6·8%).

2-p-*Hydroxyphenoxybenzothiazole.* Hydroquinone (13·2 g.) was dissolved in a solution from sodium (1·38 g.) in absolute ethanol (150 ml.), 2-chlorobenzothiazole (10·2 g.) was added, and the solution was heated under reflux for 24 hr. The precipitated sodium chloride (3·05 g.) was filtered from the hot solution and washed with ethanol. Colourless needles crystallized in the filter and these (0·1 g.) were separated from salt by washing with water. The cooled filtrate deposited colourless needles (2·88 g.) which were combined with the needles obtained above and recrystallized from ethanol to give 1,4-*di*-(2-*benzothiazolyloxy*)*benzene* (1·5 g.), m. p. 171—172° (Found: C, 64·0; H, 3·5. $C_{20}H_{12}N_2O_2S_2$ requires C, 63·8; H, 3·2%). The ethanolic filtrate and washings were evaporated and the brown oily residue triturated with N-hydrochloric acid (200 ml.). The mixture was cooled, the brown solid (10·2 g.), m. p. 110—145°, removed and crystallized from aqueous ethanol to give 2-p-*hydroxyphenoxybenzothiazole* as colourless plates (6·52 g.), m. p. 168—169° (Found: C, 64·4; H, 4·3. $C_{13}H_9NO_2S$ requires C, 64·2; H, 3·7%).

2-(p-2-*Diethylaminoethoxyphenoxy*)*benzothiazole hydrochloride.* (*a*) Sodium (0·23 g.) was dissolved in absolute ethanol (25 ml.), *p*-(2-diethylaminoethoxy)phenol (2·1 g.) was added, followed by 2-chlorobenzothiazole (1·7 g.), and the solution heated under reflux for 4 hr. The precipitated sodium chloride (0·48 g.) was filtered from the cooled mixture, washed with ethanol, and the filtrate and washings were evaporated. The residue was treated with 40% sodium hydroxide solution and ether, the ethereal layer was extracted with N-hydrochloric acid which was then made alkaline, extracted with ether, dried ($MgSO_4$), and evaporated. The oily residue was dissolved in sodium-dried ether and hydrogen chloride passed into the solution. The precipitated solid (0·75 g.) was recrystallized from acetone to give colourless prisms of the *hydrochloride* (0·33 g.), m. p. 170—172° (Found: C, 60·0; H, 6·3. $C_{19}H_{23}ClN_2O_2S$ requires C, 60·2; H, 6·1%).

(*b*) 2-*p*-Hydroxyphenoxybenzothiazole (4·0 g.) was dissolved in a solution from sodium (0·76 g.) in absolute ethanol (75 ml.) and 2-diethylaminoethyl chloride hydrochloride (2·9 g.) added. After heating under reflux for 4 hr. the solution was cooled and the precipitated sodium chloride (1·9 g.) removed and washed with ethanol. The filtrate and washings were evaporated, the oily residue was dissolved in ether, and the ether was extracted with N-sodium hydroxide solution, dried ($MgSO_4$), and evaporated to give a brown oil (2·38 g.). The hydrochloride was prepared as in (*a*) to give colourless prisms (1·35 g.), m. p. 171—172° (from ethanol–ether) identical with those previously obtained. The sodium hydroxide extract gave starting material (1·87 g.) on acidification.

Phenylalkylbenzothiazoles (III; Y = CH_2, $CH_2{\cdot}CH_2$, $CH_2{\cdot}CH(Me)$, $CH(Me)CH_2$).—β-(3-*Bromo*-4-*methoxyphenyl*)*propionic acid.* Bromine (8·0 g.) was added to a stirred solution of β-*p*-methoxyphenylpropionic acid (9·0 g.) in chloroform (50 ml.) over ½ hr. and the stirring continued for 1 hr. The chloroform was evaporated and the residue recrystallized from benzene–light petroleum (b. p. 60—80°) to give the *acid* as colourless plates (6·18 g.), m. p. 96—97° (Found: C, 46·2; H, 4·2. $C_{10}H_{11}BrO_3$ requires C, 46·35; H, 4·3%).

β-p-*Methoxyphenylbutyric acid.* 3-*p*-Methoxyphenylbut-2-enoic acid (5 g.) was partly dissolved in ethyl acetate (150 ml.) and hydrogenated at atmospheric pressure and 20° using 5% palladium–charcoal catalyst (250 mg.). The calculated quantity of hydrogen was absorbed in 90 min. The catalyst was filtered off and the filtrate evaporated. The residue was recrystallized from light petroleum (b. p. 40—60°) to give colourless prisms of the acid (4·55 g.), m. p. 65—66° (lit.,[23] 65°) (Found: C, 68·4; H, 7·5; Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%).

[22] Colonna and Andrisano, *Pubbl. ist. chim. univ. Bologna*, 1943, No. 5, 3.
[23] Yoshida and Akagi, *J. Pharm. Soc. Japan*, 1952, **72**, 317.

β-(3-*Chloro*-4-*methoxyphenyl*)*propionic acid*. A suspension of 3-chloro-4-methoxycinnamic acid (2 g.) in acetic acid (50 ml.) was hydrogenated at 70—75° and atmospheric pressure with 5% palladium–charcoal (100 mg.). The catalyst was filtered off, the solvent evaporated, and the residue (1·8 g.) recrystallized from light petroleum (b. p. 80—100°) to give colourless microcrystals of the *acid* (1·4 g.), m. p. 119—120° (Found: C, 55·6; H, 5·1. $C_{10}H_{11}ClO_3$ requires C, 55·9; H, 5·2%).

5-*Chloro*-2-p-*methoxyphenethylbenzothiazole*. β-*p*-Methoxyphenylpropionic acid (12·2 g.) and thionyl chloride (40 ml.) were heated under reflux for 2 hr. The excess of thionyl chloride was removed by distillation and sodium-dried benzene (50 ml.) was added to the residue, then evaporated. The crude acid chloride was dissolved in dimethylaniline (60 ml., purified by refluxing for 1 hr. with 5% of its weight of toluene-*p*-sulphonyl chloride followed by distillation) and the solution gassed with nitrogen for ½ hr. 2-Amino-4-chlorobenzenethiol (10·8 g.) was added and the solution heated at its boiling point for ½ hr. under nitrogen. After cooling, the mixture was poured into N-hydrochloric acid (750 ml.) and set aside overnight. The precipitated solid (21·4 g.) was collected and crystallized from ethanol to give the *benzothiazole* (17·1 g.) as colourless plates, m. p. 103—104° (Found: C, 63·3; H, 4·6. $C_{16}H_{14}ClNOS$ requires C, 63·3; H, 4·6%). Hydroxyphenylalkylbenzothiazoles were prepared from their methyl ethers by demethylation with pyridine hydrochloride as described in Part III [1] and these phenols were alkylated to give the phenylalkylbenzothiazole basic ethers with 2-diethylaminoethyl chloride hydrochloride and potassium carbonate in acetone, also as described in Part III.[1] The 2-*phenethylbenzothiazoles* described in Table 2 were prepared by the general methods illustrated above, as were the following 2-benzylbenzothiazoles: 2-*benzyl*-5-*chlorobenzothiazole*, plates (81%), m. p. 78—79° (from ethanol) (Found: C, 65·3; H, 4·2. $C_{14}H_{10}ClNS$ requires C, 64·75; H, 3·8%); 5-*chloro*-2-(p-*methoxybenzyl*)*benzothiazole*, plates (50%), m. p. 89° (from aqueous methanol) (Found: C, 61·8; H, 4·3. $C_{15}H_{12}ClNOS$ requires C, 62·2; H, 4·2%); 5-*chloro*-2-(p-*hydroxybenzyl*)*benzothiazole*, microcrystals (50%) , m. p. 155—156° (from aqueous ethanol) (Found: C, 60·5; H, 3·6. $C_{14}H_{10}ClNOS$ requires C, 61·0; H, 3·7%); 5-*chloro*-2-(p-2-*diethylaminoethoxybenzyl*)*benzothiazole citrate*, prisms (78%), m. p. 143—144° (decomp.) (from ethanol) (Found: C, 55·2; H, 5·6. $C_{26}H_{31}ClN_2O_8S$ requires C, 55·1; H, 5·5%).

2-(3-*Acetyl*-4-*methoxyphenethyl*)-5-*chlorobenzothiazole*. A solution of 5-chloro-2-*p*-methoxyphenethylbenzothiazole (3·0 g.) in nitrobenzene (20 ml.) was added to a mixture of acetyl chloride (0·78 g.) and aluminium chloride (1·33 g.) in nitrobenzene (10 ml.) over 45 min., with stirring, keeping the temperature below 5°. The mixture was stirred at room temperature for 4 hr., poured into N-hydrochloric acid, and the nitrobenzene removed by steam distillation. The organic residue was extracted with ether and the dried ($MgSO_4$) extract evaporated to leave an oily solid (1·33 g.), m. p. 80—82°, which on crystallization from light petroleum (b. p. 60—80°) gave the *benzothiazole* (1·15 g.) as white microcrystals, m. p. 83—84° (Found: C, 62·7: H, 4·6. $C_{18}H_{16}ClNO_2S$ requires C, 62·5; H, 4·7%).

Benzothiazoles (I; Y = CH_2·S, CH_2·O, CH_2·NH, NH·CH_2).—5-*Chloro*-2-p-*hydroxyphenylthiomethylbenzothiazole*. 2-Amino-4-chlorobenzenethiol (4·7 g.) and *p*-hydroxyphenylmercaptoacetic acid [9] (5·2 g.) were heated in a sealed tube in an atmosphere of nitrogen at 130° for 48 hr. The brown oil so obtained was triturated with ether and the colourless solid (1·95 g.) removed and crystallized from ethyl acetate to give colourless prisms (1·17 g.), m. p. 219—224°, of the *benzothiazole*; further recrystallizations raised the melting point to 222—224° (Found: C, 54·8; H, 3·7. $C_{14}H_{10}ClNOS_2$ requires C, 54·3; H, 3·3%).

5-*Chloro*-2-(p-2-*diethylaminoethoxyphenylthiomethyl*)*benzothiazole citrate*. This compound was obtained from the above phenol by the normal alkylation as colourless *microcrystals* (26%, m. p. 104—106° (decomp.) (from ethanol–ether) (Found: C, 52·5; H, 5·4. $C_{26}H_{31}ClN_2O_8S_2$. requires C, 52·1; H, 5·2%).

5-*Chloro*-2-(p-2-*diethylaminoethoxyanilinomethyl*)*benzothiazole*. 5-Chloro-2-toluene-*p*-sulphonyloxymethylbenzothiazole [24] (3·52 g.) and *p*-2-diethylaminoethoxyaniline (1·04 g.) were heated at 85° for 6 hr. The melt solidified on cooling and was dissolved in hot chloroform, the chloroform was cooled, washed with N-sodium hydroxide solution, and extracted with N-hydrochloric acid. The extract was made alkaline, the oily precipitate extracted with chloroform, and the extract evaporated to give a solid residue (1·05 g.). Crystallization from light petroleum (b. p. 60—80°) gave pale yellow needles (0·5 g.), m. p. 83—84°, of the *benzothiazole*

[24] U.S.P. 2,932,649 (*Chem. Abs.*, 1960, **54**, 21132).

TABLE 2.

2-Phenethylbenzothiazoles.

Compound	R^1	R^2	Y	Yield (%)	M. p.	Cryst. from [a]	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
(IIIa)	H	5-Cl	$CH_2{\cdot}CH_2$	52	100—101°	A	66·1	4·7	$C_{15}H_{12}ClNS$	65·8	4·4
(IIIc)	H	H	$CH_2{\cdot}CH_2$ [b]	44	87·5—88·5	B					
(IIIc)	Cl	H	$CH_2{\cdot}CH_2$	55	111·5—112·5	C	63·2	4·8	$C_{16}H_{14}ClNOS$	63·3	4·6
(IIIc)	Cl	5-Cl	$CH_2{\cdot}CH_2$	58	119—121	D	56·9	4·0	$C_{16}H_{13}Cl_2NOS$	56·8	3·9
(IIIc)	Br	5-Cl	$CH_2{\cdot}CH_2$	70	99·5—100·5	A	50·2	3·5	$C_{16}H_{13}BrClNOS$	50·2	3·4
(IIIc)	H	5-Cl	$CH_2{\cdot}CH(Me)$	41	68—68·5	E	63·7	4·9	$C_{17}H_{16}ClNOS$	64·25	5·1
(IIIc)	H	5-Cl	$CH(Me){\cdot}CH_2$	60	200/0·5 [c]		64·7	5·4	$C_{17}H_{16}ClNOS$	64·25	5·1
(IIIc)	H	6-Cl	$CH_2{\cdot}CH_2$	37	98—99	F	62·8	5·1	$C_{16}H_{14}ClNOS$	63·3	4·6
(IIIb)	H	H	$CH_2{\cdot}CH_2$	58	167·5—168·5	A	70·0	5·15	$C_{15}H_{13}NOS$	70·5	5·1
(IIIb)	Cl	H	$CH_2{\cdot}CH_2$	69	142—144	C	61·9	4·3	$C_{15}H_{12}ClNOS$	62·2	4·2
(IIIb)	H	5-Cl	$CH_2{\cdot}CH_2$	46	162—164	A	62·7	4·6	$C_{15}H_{12}ClNOS$	62·2	4·2
(IIIb)	Cl	5-Cl	$CH_2{\cdot}CH_2$	29	122—123	C	55·1	3·0	$C_{15}H_{11}Cl_2NOS$	55·55	3·4
(IIIb)	Br	5-Cl	$CH_2{\cdot}CH_2$	32	117—118·5	A–G	49·3	3·1	$C_{15}H_{11}BrClNOS$	48·9	3·0
(IIIb)	H	5-Cl	$CH_2{\cdot}CH(Me)$	55	180—181	H–D	63·85	4·6	$C_{16}H_{14}ClNOS$	63·3	4·6
(IIIb)	H	5-Cl	$CH(Me){\cdot}CH_2$ [d]	37	103—104 [e]	A–G	60·0	4·9	$C_{16}H_{16}ClNO_2S$	59·7	5·0
(IIIb)	H	6-Cl	$CH_2{\cdot}CH_2$	63	143—144	A–G	61·5	4·1	$C_{15}H_{12}ClNOS$	62·2	4·2
(IIIb)	Ac	5-Cl	$CH_2{\cdot}CH_2$	43 [f]	114·5—115	A	61·7	4·3	$C_{17}H_{14}ClNO_2S$	61·6	4·25
(IIId)	H	H	$CH_2{\cdot}CH_2$ [g]		122—123 [e]	K	59·0	6·3	$C_{27}H_{34}N_2O_8S$	59·3	6·3
(IIId)	Cl	H	$CH_2{\cdot}CH_2$ [h]	62	168—169	G	59·2	6·2	$C_{21}H_{26}Cl_2N_2OS$	59·3	6·2
					151—151·5 [i]	M	51·9	6·4	$C_{23}H_{34}BrClN_2O_3S$	51·7	6·4
(IIId)	H	5-Cl	$CH_2{\cdot}CH_2$ [h]	87	179—180	G	58·8	6·4	$C_{21}H_{26}Cl_2N_2OS$	59·3	6·2
(IIId)	Cl	5-Cl	$CH_2{\cdot}CH_2$ [h]	45	174—174·5	E–N	54·9	5·6	$C_{21}H_{25}Cl_3N_2OS$	54·8	5·5
(IIId)	Br	5-Cl	$CH_2{\cdot}CH_2$ [h]	70	169—170·5	G	49·9	5·1	$C_{21}H_{25}BrCl_2N_2OS$	50·0	5·0
(IIId)	H	5-Cl	$CH_2{\cdot}CH(Me)$ [g]	70	128—129 [e]	A	56·3	5·9	$C_{28}H_{35}ClN_2O_8S$	56·5	5·9
(IIId)	H	5-Cl	$CH(Me){\cdot}CH_2$ [h]	39	149—150	M–N	60·3	6·5	$C_{22}H_{28}Cl_2N_2OS$	60·1	6·4
(IIId)	H	6-Cl	$CH_2{\cdot}CH_2$	38	55—56	A–G	65·3	6·4	$C_{21}H_{25}ClN_2OS$	64·85	6·5
					169—170 [h]	M	59·4	6·1	$C_{21}H_{26}Cl_2N_2OS$	59·3	6·2
(IIId)	Ac	5-Cl	$CH_2{\cdot}CH_2$ [h]	50	184·5—185·5	A–N	59·5	6·2	$C_{23}H_{28}Cl_2N_2O_2S_2$	59·1	6·0

[a] A, Ethanol; B, propan-2-ol; C, light petroleum (b. p. 80—100°); D, light petroleum (b. p. 60—80°); E, n-hexane; F, methanol; G, water; H, benzene; K, ethyl methyl ketone; M, acetone; N, ether. [b] Ried and Hinsching, Annalen, 1956, **600**, 47. [c] B. p./mm. [d] Hydrate. [e] Decomp. [f] Heated at 200° for 2 hr. [g] Citrate. [h] Hydrochloride. [i] Ethobromide dihydrate.

(Found: C, 61·6; H, 6·1. $C_{20}H_{24}ClN_3OS$ requires C, 61·65; H, 6·2%). The *dihydrochloride* was prepared in ether with hydrogen chloride and was crystallized from methanol–ether as colourless needles, m. p. 191—192° (Found: C, 51·6; H, 5·7. $C_{20}H_{26}Cl_3N_3OS$ requires C, 51·9; H, 5·7%).

N-(p-2-*Diethylaminoethoxybenzyl*)*phthalimide*. Anhydrous potassium carbonate (15 g.) and *p*-(2-diethylaminoethoxy)benzyl chloride hydrochloride (16·8 g.) were added to a suspension of potassium phthalimide (11·1 g.) in AnalaR acetone (300 ml.). The mixture was heated under reflux for 24 hr. and the inorganic solid was filtered from the cooled solution, washed with acetone, and the filtrate and washings evaporated to give an oily residue (18·0 g.). This was extracted with light petroleum (b. p. 60—80°) and the cooled extract deposited colourless needles (13·4 g.) of the *phthalimide*, m. p. 81·5—82° (from light petroleum) (Found: C, 71·6; H, 6·9. $C_{21}H_{24}N_2O_3$ requires C, 72·1; H, 7·1%).

p-2-*Diethylaminoethoxybenzylamine*. The above phthalimide (14·0 g.) and 80% hydrazine hydrate (2·8 g.) were dissolved in ethanol (100 ml.) and heated under reflux for 2 hr. The solution was cooled, concentrated hydrochloric acid (20 ml.) added, and the mixture warmed on a water-bath for 10 min. The precipitated 1,4-dihydroxyphthalazine (5·5 g.) was filtered from the cooled solution and washed with N-hydrochloric acid. The ethanol was evaporated from the filtrate and washings, the residue made strongly alkaline with 40% sodium hydroxide solution, and the precipitated oil extracted with ether. The extract was dried ($MgSO_4$) and evaporated, and the residue (9 g.) distilled to give the amine as a clear oil (5·1 g.), b. p. 108—109°/0·2 mm. (lit.,[25] 130°/0·3 mm.); *dipicrate*, yellow needles, m. p. 162—163° (from ethanol) (Found: C, 44·0; H, 4·2. $C_{25}H_{28}N_8O_{15}$ requires C, 44·1; H, 4·1%).

2-(p-2-*Diethylaminoethoxybenzylamino*)*benzothiazole*. 2-Chlorobenzothiazole (1·7 g.) was added with stirring over 15 min. to *p*-2-diethylaminoethoxybenzylamine (2·2 g.) at 90—100° and the mixture heated at 150° for 6 hr. The cooled mixture was dissolved in ether and N-hydrochloric acid, the ether extracted again with acid, and the extract made alkaline with sodium hydrogen carbonate solution. The precipitated product was extracted with ether and the extract dried ($MgSO_4$) and evaporated to give a solid residue (2·8 g.). Crystallization from light petroleum (b. p. 80—100°) gave the *benzothiazole* as colourless plates (2·2 g.), m. p. 113—113·5° (Found: C, 67·4; H, 7·0. $C_{20}H_{25}N_3OS$ requires C, 67·6; H, 7·1%). The *citrate*, prepared in methanol, formed colourless microcrystals, m. p. 116—118° (from ethanol–ether) (Found: C, 56·8; H, 6·1. $C_{26}H_{33}N_3O_8S$ requires 57·0; H, 6·1%).

5-*Chloro*-2-(p-*hydroxyphenoxymethyl*)*benzothiazole*. 2-Amino-4-chlorobenzenethiol (4·0 g.) and *p*-hydroxyphenoxyacetic acid [26] (4·2 g.) were heated in a sealed tube at 150° for 3 hr. The mixture was cooled, partly dissolved in sodium hydrogen carbonate solution and ether, and the insoluble solid filtered off. Recrystallization of this from ethanol gave colourless needles of the *benzothiazole*, (2·6 g.), m. p. 181—182° (Found: C, 57·8; H, 3·5. $C_{14}H_{10}ClNO_2S$ requires C, 57·6; H, 3·5%). The ether solution was extracted with N-sodium hydroxide solution, the alkaline extract made acid, and the precipitated solid (1 g.), m. p. 174—175°, was collected. Recrystallization from ethanol gave a further quantity (0·8 g.) of the product.

5-*Chloro*-2-(p-2-*diethylaminoethoxyphenoxymethyl*)*benzothiazole*. The above phenol (2·0 g.) was alkylated in acetone (50 ml.) with 2-diethylaminoethyl chloride hydrochloride (1·2 g.) and potassium carbonate (10 g.) to give the *basic ether* as colourless microcrystals (1·0 g.) m. p. 112—113° (from ethanol) (Found: C, 61·9; H, 6·3. $C_{20}H_{23}ClN_2OS$ requires C, 61·4; H, 5·9%). The *citrate*, prepared in methanol, formed colourless microcrystals, m. p. 156—156·5° (from methanol–ether) (Found: C, 53·4; H, 5·4. $C_{26}H_{31}ClN_2O_9S$ requires C, 53·5; H, 5·4%).

Benzylthiobenzothiazoles (I; Y = $S{\cdot}CH_2$).—3-*Chloro*-4-*hydroxybenzaldehyde*. *p*-Hydroxybenzaldehyde (244 g.; technical) was dissolved in acetic acid (600 ml.) and sulphuryl chloride (170·8 ml., 5% excess) was added over 1 hr. with stirring, keeping the temperature between 15° and 25°. A solid precipitated after the final addition. The mixture was set aside overnight and the solid (244·5 g.) removed. The filtrate was concentrated (200 ml.) and, on cooling, gave a further 26·8 g. of solid. The combined products were extracted with boiling water (3750 ml.) and filtered from a high-melting insoluble residue. On cooling, the extract deposited white needles of 3-chloro-4-hydroxybenzaldehyde (224·0 g.), m. p. 132—133° (lit., 132—133°,[14] 139° [27]).

[25] U.S.P. 2,879,293 (*Chem. Abs.*, 1959, **53**, 16066).
[26] Carter and Lawrence, *J.*, 1900, **77**, 1226.
[27] Biltz, *Ber.*, 1904, **37**, 4032.

3-Bromo-5-chloro-4-hydroxybenzaldehyde. 3-Chloro-4-hydroxybenzaldehyde (10·4 g.) was dissolved in acetic acid (50 ml.), and bromine (10·7 g.) in acetic acid (10 ml.) added over ½ hr., with stirring, at room temperature. The mixture was heated on a water-bath for 6 hr., cooled, and the precipitated solid (11·5 g.) collected. Crystallization from benzene gave *3-bromo-5-chloro-4-hydroxybenzaldehyde* as white needles (9·85 g.), m. p. 157—158° (Found: C, 35·4; H, 1·9. $C_7H_4BrClO_2$ requires C, 35·7; H, 1·7%).

3-Chloroanisaldehyde. Anisaldehyde (27·2 g.) was dissolved in acetic acid (100 ml.), and sulphuryl chloride (28·3 g.) was added with stirring over ½ hr., keeping the temperature below 20°. The mixture was stirred for 2½ hr. at room temperature, heated at 40—45° for a further 2 hr., and finally heated at 90—100° for ½ hr. The acetic acid was distilled off and the residue distilled to give an almost colourless liquid (24·7 g.), b. p. 100—104°/0·2 mm. (lit.,[13] 128°/5 mm.), which solidified on standing to a pink solid. Recrystallization from light petroleum (b. p. 40—60°) gave 3-chloroanisaldehyde as white needles (15·8 g.), m. p. 55—56° (lit., 53°,[13] 62° [14]).

Dialkylaminoalkoxybenzaldehydes.—The compounds are described in Table 3 and were prepared by the general methods given in Part III.[1]

Dialkylaminoalkoxybenzyl Alcohols.—These compounds were prepared from the above aldehydes either by Cannizzaro reaction or by catalytic reduction. Illustrative examples are given below and the compounds are described in Table 4.

(*a*) *Cannizzaro reduction.* A solution of potassium hydroxide (42 g.) in methanol (100 ml.) was heated to 60° and a suspension of paraformaldehyde (13·5 g.) and *p*-2-diethylaminoethoxybenzaldehyde (66·3 g.) in methanol (100 ml.) was added with stirring over 20 min. The temperature was kept at 60—70° during the addition and for a further 3 hr., after which the mixture was distilled until the internal temperature reached 101°. Water (150 ml.) was added to the cooled residue and the mixture was extracted with benzene which was evaporated to give a brown oil. Distillation gave *p*-2-diethylaminoethoxybenzyl alcohol [27] as a colourless liquid (50·7 g.) b. p. 148—150°/0·5 mm., n_D^{20} 1·5278; *benzoyl derivative citrate*, white microcrystals, m. p. 107—109° (decomp.) (from acetone) (Found: C, 59·9; H, 6·4. $C_{26}H_{33}NO_{10}$ requires C, 60·1; H, 6·4%).

(*b*) *Catalytic reduction.* *p*-2-Diethylaminoethoxybenzaldehyde (10 g.) in ethanol (40 ml.) was hydrogenated at 60 atm. and room temperature with platinum oxide catalyst (50 mg.) for 4 hr. The residual oil, after removal of catalyst and solvent, was distilled to give the above alcohol (9·2 g.), b. p. 142°/0·2 mm. (lit.,[28] 196—199°/14 mm.), n_D^{20} 1·5279.

Dialkylaminoalkoxybenzyl Chlorides.—These compounds (Table 5) were obtained by the following method as the hydrochlorides. 4-(2-Diethylaminoethoxy)-3-methoxy- and 3-chloro-4-(2-diethylaminoethoxy)-5-methoxy-benzyl chloride hydrochlorides, 4-(2-diethylaminoethoxy) α-methylbenzyl chloride hydrochloride, and 2-chloro-2-(*p*-2-diethylaminoethoxy)phenylpropane hydrochloride were also prepared but could not be purified.

Thionyl chloride (20 ml.) was added cautiously through a reflux condenser to a solution of *p*-2-diethylaminoethoxybenzyl alcohol (10 g.) in chloroform (20 ml.) and the mixture boiled for 2 hr. The solvent and the excess of thionyl chloride were evaporated and the residue triturated with ether to give a colourless solid (12·7 g.). Crystallization from ethanol–ether gave colourless plates of p-2-*diethylaminoethoxybenzyl chloride hydrochloride* (9·2 g.), m. p. 122—124° (Found: C, 56·3; H, 7·55; Cl, 25·8; N, 5·1. $C_{13}H_{21}Cl_2NO$ requires C, 56·1; H, 7·6; Cl, 25·5; N, 5·0%).

p-2-*Diethylaminoethoxy-α-methylbenzyl Alcohol.*—Methylmagnesium iodide was prepared from magnesium turnings (3·6 g.) and methyl iodide (21·3 g.) in ether (60 ml.). To this was added *p*-2-diethylaminoethoxybenzaldehyde (16·5 g.) in ether (30 ml.) over 75 min., keeping the temperature between 0° and 5°. The mixture was warmed to room temperature over 15 min. and heated under reflux for 1 hr. Ice-cold water (100 ml.) was added with stirring to the cooled mixture which was set aside overnight. The mixture was made strongly alkaline with 40% sodium hydroxide, extracted with ether, and filtered through Metasil. The aqueous layer was separated from the filtrate, extracted with ether, and the combined extracts dried ($MgSO_4$). The oil (15·4 g.) which was obtained on evaporation was distilled to give the α-methylbenzyl alcohol as a colourless liquid (13·3 g.), b. p. 140—142°/0·3 mm. The above basic alcohol (0·5 g.) and citric acid (0·44 g.) were dissolved in methanol (10 ml.), heated under reflux for 15 min., and ether then added to the warm solution to turbidity. On cooling, white crystals

[28] Rohmann and Meisel, *Arch. Pharm.*, 1961, **294**, 538.

TABLE 3.

Dialkylaminoalkoxybenzaldehydes (I; R = CHO).

Compound	Substituents	Method [a]	Yield (%)	M. p.[b] or b. p./mm.	Cryst. from [c]	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
(Id)	2-Cl	*C*	66	140—144°/0·17						
				129 [d]	A	50·6	6·1	$C_{19}H_{26}ClNO_9$	50·9	5·85
(Id)	3-Cl	*C*	92	152—154/0·3 [e]						
		A	50							
				124—125 [d]	A	51·2	6·0	$C_{19}H_{26}ClNO_9$	50·9	5·85
(Ie)	3-Cl	*C*	56	130/0·3						
				133 [d]	A	49·0	5·8	$C_{17}H_{22}ClNO_9$	48·6	5·3
(If)	3-Cl	*C*	76	136/0·15						
				101·5 [d]	A–B	51·6	6·3	$C_{20}H_{28}ClNO_9$	52·0	6·1
(Ig)	3-Cl	*C* [f]	68	152—154/0·6						
				141—142 [g]	A–C	48·2	4·8	$C_{20}H_{23}ClN_4O_9$	48·1	4·65
(Ih)	3-Cl	*C* [f]	38 [h]	128—130/0·15						
				100—101 [d]	D	50·6	5·9	$C_{19}H_{26}ClNO_9$	50·9	5·85
(Ii)	3-Cl	*C* [f]	73	166—167/0·3		66·2	8·5	$C_{17}H_{26}ClNO_2$	65·5	8·4
				163—164 [i]	A–B	57·3	7·55	$C_{19}H_{28}ClNO_6$	56·8	7·0
(Ij)	3-Cl	*C*	56	85—86·5	E	57·6	6·3	$C_{13}H_{16}ClNO_3$	57·9	6·0
(Id)	3-I	*C*	55 [h]	166/0·4						
				150—151 [d]	A–B	42·8	5·1	$C_{19}H_{26}INO_9$	42·3	4·9
(Id)	3-Cl, 5-Cl	*C*	44 [h]	142/0·2						
				148—149 [d]	A	47·5	5·5	$C_{19}H_{25}Cl_2NO_9$	47·3	5·2
(Id)	3-Br, 5-Cl	*C*	84 [j]	144—145 [d]	A	43·2	4·7	$C_{19}H_{25}BrClNO_9$	43·3	4·8
(Id)	3-Br, 5-Br	*C*	67 [j]	158 [d]	F–B	39·6	4·6	$C_{19}H_{25}Br_2ClNO_9$	39·9	4·4
(Id)	3-OMe	*A*	60	154—156/0·4						
		C	34							
				123—124 [d]	A	53·7	6·3	$C_{20}H_{29}NO_{10}$	54·2	6·6
(Id)	2-Cl, 5-OMe	*C*	84	164—166/0·2						
				147—148 [d]	A	50·6	5·9	$C_{20}H_{28}ClNO_{10}$	50·3	5·9
(Id)	3-Cl, 5-OMe	*C*	77	139—140/0·3						
		A	4							
				130—131 [d]	A–B	50·3	5·7	$C_{20}H_{28}ClNO_{10}$	50·3	5·9
(Ia)	2-Br, 5-O·$[CH_2]_2$·NEt_2	*C* [f]	58	156—160/0·2						
				111—112 [d]	A–B	46·1	5·7	$C_{19}H_{26}BrNO_9$	46·3	5·3
(Ia)	4-Cl, 2-O·$[CH_2]_2$·NEt_2	*C*	56	137/0·4						
				97—98 [d]	D	51·1	6·1	$C_{19}H_{26}ClNO_9$	50·9	5·85
(Ia)	5-Br, 2-O·$[CH_2]$·NEt_2	*C*	43	54·5—55·5	G	52·3	6·1	$C_{13}H_{18}BrNO_2$	52·0	6·0
				118 [d]	A	47·4	6·1	$C_{19}H_{26}BrNO_9$	46·3	5·3
(Ia)	3-Cl, 5-Cl, 2-O·$[CH_2]_2$·NEt_2	*C*	67	120—124/0·13						
				124—125 [d]	H	47·2	5·5	$C_{19}H_{25}Cl_2NO_9$	47·3	5·2

[a] As described in Part III.[1] [b] All salts melted with decomposition. [c] A, ethanol; B, ether; C, water; D, acetone; E, light petroleum (b. p. 80—100°); F, methanol; G, light petroleum (b. p. 60—80°); H, propen-2-ol. [d] Citrate. [e] n_D^{25} 1·5456. [f] Equimolar quantities of aldehyde and alkyl halide used. [g] Picrate. [h] Product partly decomposed on distillation. [i] Oxalate. [j] Product decomposed on distillation, yield of undistilled aldehyde.

TABLE 4.

Dialkylaminoalkoxybenzyl alcohols (I; R = CH_2OH).

Compound	Substituents	Yield (%)	M. p. or b. p./mm.	Cryst. from [a]	Found (%) C	Found (%) H	Formula	(Required %) C	(Required %) H
(Id)			111—113° [b]	A–B					
			106—107 [c]	C–B	54·6	7·1	$C_{19}H_{29}NO_9$	55·0	7·0
			109·5—110 [d]	D	50·7	5·6	$C_{19}H_{24}N_4O_9$	50·4	5·3
(Id)	2-Cl	84	136—140/0·17						
			103 [c]	A	50·6	6·5	$C_{19}H_{28}ClNO_9$	50·7	6·3
(Id)	3-Cl	74	157—158/0·3 [e]						
			114—115 [c]	A–B	50·9	6·6	$C_{19}H_{28}ClNO_9$	50·7	6·3
(Ie)	3-Cl	44	132/0·1						
			135—136 [d]	F	44·3	4·55	$C_{17}H_{19}ClN_4O_9$	44·5	4·2
(If)	3-Cl	49	171—172/0·5						
			99—100 [c]	A–B	51·8	6·45	$C_{20}H_{30}ClNO_9$	51·8	6·5
(Ig)	3-Cl	56	168—172/0·3		61·7	8·1	$C_{14}H_{22}NO_2Cl$	61·9	8·2
(Ih)	3-Cl	21	140—142/0·2						
			105—106 [c]	A–B	50·2	6·1	$C_{19}H_{28}ClNO_9$	50·7	6·3
(Ii)	3-Cl	44	182—184/0·4						
			139—140 [b]	E	58·6	8·6	$C_{17}H_{29}Cl_2NO_2$	58·3	8·3
(Ij)	3-Cl	30	68—68·5	G	57·7	6·7	$C_{13}H_{18}ClNO_3$	57·5	6·7
			190—192/0·3						
(Id)	3-Br	65	163—166/0·3						
			118—119 [c]	E	46·5	5·8	$C_{19}H_{28}BrNO_9$	46·2	5·7
(Id)	3-I	27	180—200/0·5						
			110—111 [c]	A–B	41·8	5·3	$C_{19}H_{27}INO_9$	42·2	5·2
(Id)	3-Cl, 5-Cl	44	166—168/0·15						
			118—119 [c]	A–B	46·6	5·6	$C_{19}H_{27}Cl_2NO_9$	47·1	5·6
(Id)	3-OMe	64	167—168/0·35						
			108—109 [c]	A	54·2	7·1	$C_{20}H_{31}NO_{10}$	53·9	7·0
(Id)	2-Cl, 5-OMe	66	51—52	G	58·6	7·3	$C_{14}H_{22}ClNO_3$	58·4	7·7
			134—135 [c]	A	49·8	6·4	$C_{20}H_{30}ClNO_{10}$	50·0	6·3
(Id)	3-Cl, 5-OMe	56	186—187/0·5						
			125—126 [d]	A	46·5	5·2	$C_{20}H_{25}ClN_4O_{10}$	46·5	4·9
(Ia)	3-O·$[CH_2]_2$·NEt_2	58	124—126/0·1						
			93 [c]	A	54·7	6·8	$C_{19}H_{29}NO_9$	54·9	7·0
(Ia)	2-Br, 5-O·$[CH_2]_2$·NEt_2	55	180—182/0·5						
			113—114 [c]	A–B	46·5	6·0	$C_{19}H_{28}BrNO_9$	46·2	5·7
(Ia)	2-O·$[CH_2]_2$·NEt_2	88	132—134/0·9						
			118 [b]	H–K	60·3	8·6	$C_{19}H_{29}NO_9$	60·1	8·5
(Ia)	4-Cl, 2-O·$[CH_2]_2$·NEt_2	78	128—134/0·1						
			84—85 [c]	C–B	51·1	6·4	$C_{19}H_{28}ClNO_9$	50·7	6·3
(Ia)	5-Br, 2-O·$[CH_2]_2$·NEt_2	89	136—138/0·1						
			94—95 [c]	A–B	45·8	5·7	$C_{19}H_{28}BrNO_9$	46·2	5·7
(Ia)	3-Cl, 5-Cl, 2-O·$[CH_2]_2$·NEt_2	82	132—136/0·14						
			109 [c]	A	47·0	5·8	$C_{19}H_{27}Cl_2NO_9$	47·1	5·6

[a] A, ethanol; B, ether; C, methanol; D, benzene; E, acteone; F, water; G, n-hexane; H, ethyl methyl ketone; K, dioxan. [b] Hydrochloride. [c] Citrate, melting with decomposition. [d] Picrate. [e] n_D^{25} 1·5382.

TABLE 5.

Dialkylaminoalkoxybenzyl chloride (I; R = CH_2Cl) hydrochlorides.

Compound	Substituents	Yield (%)	M. p.	Cryst. from [a]	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
(Id)	2-Cl	17	131—132·5°	C	49·7	6·5	$C_{13}H_{20}Cl_3NO$	49·9	6·5
(Id)	3-Cl	80	116·5—117·5	D	50·4	6·5	$C_{13}H_{20}Cl_3NO$	49·9	6·5
(Ie)	3-Cl	60	117—118 [b]	A–B	46·7	5·5	$C_{11}H_{16}Cl_3NO$	46·4	5·65
(If)	3-Cl	64	110—112	D–B	51·2	6·9	$C_{14}H_{22}Cl_3NO$	51·5	6·8
(Ig)	3-Cl	60	109—110 [b]	E	50·7	7·0	$C_{15}H_{24}Cl_3NO$	51·5	6·8
(Ih)	3-Cl	32	157—158	D	50·3	6·4	$C_{13}H_{20}Cl_3NO$	49·9	6·5
(Ii)	3-Cl	62	130—131	D–B	55·6	7·9	$C_{17}H_{28}Cl_3NO$	55·4	7·6
(Ij)	3-Cl	75	183—183·5	A	47·8	5·5	$C_{13}H_{18}Cl_3NO$	47·8	5·55
(Id)	3-Br	66	125—127 [b]	A–B	44·2	5·7	$C_{13}H_{20}BrCl_2NO$	43·7	5·65
(Id)	3-I	70	138—139	D	38·6	5·1	$C_{13}H_{20}Cl_2INO$	38·6	5·0
(Id)	3-Cl, 5-Cl	73	119—121 [b]	D–B	44·8	5·2	$C_{13}H_{19}Cl_4NO$	44·9	5·5
(Id)	2-Cl, 5-OMe	75	133—134 [b]	D	49·6	6·6	$C_{14}H_{22}Cl_3NO_2$	49·2	6·45
(Ia)	3-O·$[CH_2]_2$·NEt_2	72	112	C	55·7	7·6	$C_{13}H_{21}Cl_2NO$	56·1	7·6
(Ia)	2-Br, 5-O·$[CH_2]_2$·NEt_2	89	154—155 [b]	A–B	44·1	6·0	$C_{13}H_{20}BrCl_2NO$	43·7	5·65
(Ia)	2-O·$[CH_2]_2$·NEt_2	81	124—125 [b]	F	56·2	7·4	$C_{13}H_{21}Cl_2NO$	56·1	7·6
(Ia)	4-Cl, 2-O·$[CH_2]_2$·NEt_2	58	129—130	D	50·2	6·7	$C_{13}H_{20}Cl_3NO$	49·9	6·5
(Ia)	5-Br, 2-O·$[CH_2]_2$·NEt_2	61	141—143	E	43·9	5·7	$C_{13}H_{20}BrCl_2NO$	43·7	5·65
(Ia)	3-Cl, 5-Cl, 2-O·$[CH_2]_2$·NEt_2	40	146—148	G	45·1	5·2	$C_{13}H_{19}Cl_4NO$	45·0	5·5

[a] A, ethanol; B, ether; C, isopropyl acetate; D, acetone; E, ethyl acetate; F, dioxan; G, propan-2-ol. [b] Decomp.

separated which were recrystallized from absolute ethanol–ether to give the *citrate* as white microcrystals, m. p. 79—81° (decomp.) (Found: C, 55·6; H, 7·4. $C_{20}H_{31}NO_9$ requires C, 55·9; H, 7·3%).

2-(p-2-*Diethylaminoethoxyphenyl*)*propan*-2-*ol*.—Methylmagnesium iodide was prepared from magnesium shavings (2·15 g.), and methyl iodide (12·7 g.) in ether (40 ml.). The mixture was cooled in ice and salt and a solution of *p*-2-diethylaminoethoxyacetophenone [29] (10·5 g.) in ether (20 ml.) added at 0—5°. The mixture was heated under reflux for 1 hr., cooled, ice-cold water (100 ml.) added cautiously, and set aside overnight. After being made strongly alkaline with 40% sodium hydroxide, the mixture was extracted with ether and filtered through Metasil. The aqueous layer was separated, extracted with ether, and the combined ether extracts dried ($MgSO_4$). Evaporation of the ether left an oil (8·1 g.) which was distilled to give the propanol as a colourless liquid (6·5 g.), b. p. 143—145°/0·7 mm. The above basic alcohol (0·25 g.) and citric acid (0·21 g.) were dissolved in methanol (10 ml.) and heated under reflux for 15 min. Ether was added to the warm solution to turbidity and, on cooling, white crystals separated. Recrystallization from ethanol–ether gave the *citrate*, m. p. 102—103° (decomp.) (Found: C, 56·8; H, 7·2. $C_{21}H_{33}NO_9$ requires C, 56·9; H, 7·5%).

Benzothiazole-2-*thiols*.—7-*Chlorobenzothiazole*-2-*thiol*. Hydrogen sulphide, saturated with carbon disulphide and water, was passed into a solution of sodium sulphide nonahydrate (40 g.) in water (150 ml.) until saturation occurred. 2,3-Dichloronitrobenzene (19·2 g.) was added and the mixture heated under reflux for 20 hr. with hydrogen sulphide saturated with carbon disulphide and water passing through. The mixture was steam-distilled to remove any 2,3-dichloroaniline, the aqueous residue acidified, and the precipitated solid filtered off and washed with water. The solid was extracted with warm 8N-ammonia solution (2 × 250 ml.), the solution filtered from insoluble material, and the cooled filtrate acidified. The precipitated product (14·5 g.) was recrystallized from aqueous ethanol to give white needles of the *thiol* (7·2 g.), m. p. 245—247° (Found: C, 42·0; H, 2·15. $C_7H_4ClNS_2$ requires C, 41·7; H, 2·0%).

4,6-*Dichlorobenzothiazole*-2-*thiol by Herz reaction*. A mixture of *o*-chloroaniline (25·5 g.) and glacial acetic acid (20 ml.) was cooled to −10° and sulphur monochloride (100 ml.) added, keeping the temperature below 25°. The mixture was heated to 50° over ½ hr., kept between 50 and 60° for 1½ hr., and finally raised to 70—80° for 1 hr. Benzene (400 ml.) was added to the cooled mixture, the red-brown thiazathionium chloride (44·8 g.), m. p. 219—222°, filtered off and washed with benzene and then ether. The chloride was added to water (1 l.) and ether (500 ml.) with stirring over 1 hr., stirred for a further 1 hr., and the undissolved solid filtered off. The aqueous layer was separated, the undissolved solid resuspended in it and the mixture stirred with more ether (500 ml.) for 1 hr. The separation was repeated to give an insoluble brown solid (6·6 g.), m. p. 110—114°, not depressed on admixture with sulphur. The aqueous layer was extracted with ether (2 × 200 ml.) and the combined extracts dried and decolourised by stirring for 1 hr. with magnesium sulphate and charcoal. The ether was evaporated, the last traces at room temperature, to give the thiazathionium hydroxide as a pink solid (24·2 g.), m. p. 120—121° (decomp.). The hydroxide (11·2 g.) was added over 20 min. with stirring to sodium hydroxide (5 g.) in water (100 ml.). The mixture was stored for 10 min. and the insoluble material (0·8 g.) filtered off. Carbon disulphide (5 ml.) was added to the filtrate which was heated under reflux for 6 hr. with a stream of carbon dioxide saturated with carbon disulphide and water passing through. The carbon disulphide was evaporated, when the solid which had precipitated during the reaction redissolved. The hot solution was acidified and the precipitated solid collected, washed with water, and crystallized from acetic acid to give white needles of the *dichloro-thiol* (7·2 g.), m. p. 244—245° (after rapid heating to 230°) (Found: C, 35·9; H, 1·4; N, 6·0. $C_7H_3Cl_2NS_2$ requires C, 35·6; H, 1·3; N, 5·9%).

6-*Chlorobenzothiazole*-2-*thiol* was also prepared by Herz reaction as above from aniline in 29% yield, white needles, m. p. 257—259° (after rapid heating to 245°) (from ethyl acetate) (lit., 250—252°,[16] 244—245° [30]).

2-*Amino*-4,5-*dichlorobenzothiazole*.—Bromine (18·0 g.) was added with stirring to 2,3-dichlorophenylthiourea (16·6 g.) in chloroform (30 ml.), keeping the mixture below 30°, then stirred at room temperature for 2 hr. After boiling the mixture under reflux for 2 hr. then cooling, the chloroform was decanted from the solid, which was boiled with chloroform (30 ml.)

[29] Najer, Chabrier, and Guidicelli, *Bull. Soc. chim. France*, 1956, 1672.
[30] B.P. 873,602.

then filtered off. The residue was stirred into water (100 ml.) saturated with sulphur dioxide, the mixture filtered, and the solid residue suspended in hot water (100 ml.). The suspension was made alkaline with ammonia, allowed to cool overnight, and the solid (12·1 g.) removed and washed with water. Recrystallization of the *benzothiazole* from propan-2-ol gave white needles m. p. 275—276° (decomp.) (Found: C, 38·4; H, 1·95. $C_7H_4Cl_2N_2S$ requires C, 38·4; H, 1·8%).

2-*Amino*-4,7-*dichlorobenzothiazole*.—Prepared as above (38%) this formed white needles. m. p. 265—266° (decomp.) (from ethanol) (Found: C, 38·3; H, 2·0. $C_7H_4Cl_2N_2S$ requires C, 38·4; H, 1·8%).

2-*Bromo*-4,5-*dichlorobenzothiazole*.—2-Amino-4,5-dichlorobenzothiazole (8·8 g.) was added to 48% w/w hydrobromic acid (25 ml.) at 10° with stirring. The mixture was cooled to −10°, bromine (19·2 ml.) added over 20 min. at −5° to −10°, and then sodium nitrite (7·3 g.) in water (10 ml.) at 0—5° over 30 min., with stirring. The mixture was stirred for 2 hr. in an ice-bath and made alkaline with sodium hydroxide (15 g.) in water (15 ml.), added over 45 min. keeping the temperature below 20°. The mixture was stirred for 20 min. and the red solid (15·75 g.) filtered off and washed with water. This solid was extracted with light petroleum (b. p. 60—80°) and the extract filtered from an insoluble red solid (1·8 g.), m. p. >300°. The cooled filtrate deposited white needle clusters (5 g.), which were recrystallized from light petroleum (b. p. 80—100°) to give 2-*bromo*-4,5-*dichlorobenzothiazole* (5·0 g.), m. p. 139—139·5° (Found: 29·7; H, 1·0. $C_7H_2BrCl_2NS$ requires C, 29·2; H, 0·7%). A further 2·1 g. were obtained from the mother-liquors.

2-*Bromo*-4,7-*dichlorobenzothiazole*.—Prepared in 58% yield as in the example above, this formed white needles, m. p. 97—98° [from light petroleum (b. p. 60—80)] (Found: C, 29·4; H, 1·0. $C_7H_2BrCl_2NS$ requires C, 29·7; H, 0·7%).

4,5-*Dichlorobenzothiazole*-2-*thiol*. 2-Bromo-4,5-dichlorobenzothiazole (5·7 g.) and thiourea (1·67 g.) were heated under reflux in ethanol (50 ml.) for 4 hr. The mixture was cooled and the precipitated solid (4·3 g.) filtered off. Evaporation of the liquors to half volume gave a further quantity (300 mg.). The combined products were extracted with 8N-ammonia solution (100 ml.) and filtered through Metasil. The acidified filtrate precipitated a white solid (3·96 g.), which was crystallized from acetic acid to give white needles of 4,5-*dichlorobenzothiazole*-2-*thiol* (2·95 g.), m. p. 231—232° (Found: C, 35·5; H, 1·55. $C_7H_3Cl_2NS$ requires C, 35·6; H, 1·3%). Also prepared by this method were 4,7-*dichlorobenzothiazole*-2-*thiol*, white needles (84%), m. p. 218—219° (from ethyl acetate) (Found: C, 35·5; H, 1·8. $C_7H_3Cl_2NS_2$ requires C, 35·6; H, 1·3%) and 4-*chloro-benzothiazole*-2-*thiol* (from 2-bromo-4-chlorobenzothiazole [15]), white needles (63%), m .p. 205—206° (from ethanol) (Found: C, 41·9; H, 2·2. $C_7H_4ClNS_2$ requires C, 41·7; H, 1·85%). 6-Nitrobenzothiazole-2-thiol, prepared in 67% yield by Cutter and Golden's method,[18] except that the nitration temperature was kept between 30 and 40°, formed yellow needles, m. p. 254—256° (from acetic acid).

5-*Chloro*-6-*nitrobenzothiazole*-2-*thiol*.—2,2′-Bis-(5,5′-dichlorobenzothiazolyl)disulphide (9 g.) was added to sulphuric acid (27 ml.; *d* 1·84) with stirring. The solution was cooled to 25° and a mixture of nitric acid (3·8 ml.; *d* 1·5) and sulphuric acid (6 ml.; *d* 1·84) added with stirring at 25—35°. The mixture was stirred at room temperature for 1 hr. and poured into water (600 ml.). The precipitated fawn solid was collected, washed with water, and suspended in water (100 ml.). A solution of sodium sulphite heptahydrate (16·0 g.) in N-sodium hydroxide (100 ml.) was added and the mixture stirred until the solid dissolved. The red solution was filtered, and the filtrate added, with stirring, to boiling 5% hydrochloric acid (600 ml.). The precipitated yellow solid was collected, washed with water, and dried with benzene in a Dean–Stark apparatus. The dry benzene solution was concentrated (300 ml.) and a little insoluble material filtered off. On cooling, orange needle clusters (4·25 g.) separated which, on further recrystallization from benzene then aqueous ethanol (charcoal), gave 5-chloro-6-nitrobenzothiazole-2-thiol (2·65 g.) as yellow needles, m. p. 222—224° (decomp.) (lit.,[31] 212—219°) (Found: C, 34·9; H, 1·5. Calc. for $C_7H_3ClN_2O_2S_2$: C, 34·1; H, 1·2%). A further quantity (300 mg.) was obtained from the first benzene mother liquors. Attempts to obtain other pure products in significant yield from the reaction were unsuccessful.

Benzylthiobenzothiazoles.—These compounds (Table 6) were obtained by condensation of benzyl chlorides with 2-mercaptobenzothiazoles, as illustrated below.

2-[3-*Chloro*-4-(2-*diethylaminoethoxy*)*benzylthio*]*benzothiazole*. Technical benzothiazole-2-thiol

[31] Logemann, Galimberti, Tosolini, De Carneri, and Coppi, *Farmaco* (*Pavia*), *Ed. Sci.*, 1961, **16**, 795.

TABLE 6.

2-Benzylthiobenzothiazoles (III; Y = S·CH_2).

Compound	Other substituents	Yield (%)	M. p.	Cryst. from [a]	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
(IIId)		64	116—117°	A–B	55·4	5·8	$C_{26}H_{32}N_2O_8S_2$	55·3	5·7
(IIId)	2-Chloro [b]	[c]	141	A	52·6	5·6	$C_{26}H_{31}ClN_2O_8S_2$	52·1	5·2
(IIId)	3-Chloro		124—125 [d]	D–B	53·8	5·4	$C_{22}H_{25}ClN_2O_5S_2$	53·2	5·1
			113—113·5 [e]	A	49·4	4·0	$C_{26}H_{26}ClN_5O_8S_2$	49·1	4·1
			139—140·5 [f]	D–B	51·0	5·4	$C_{22}H_{28}BrClN_2OS_2$	51·2	5·47
(IIIe)	3′-Chloro [b]	71	142—143	A	50·3	4·7	$C_{24}H_{27}ClN_2O_8S_2$	50·5	4·8
(IIIf)	3′-Chloro [b]	81	149—150	A	52·4	5·4	$C_{27}H_{33}ClN_2O_8S_2$	52·9	5·4
(IIIg)	3′-Chloro [b]	44	84—85	A–B	52·6	5·35	$C_{27}H_{33}ClN_2O_8S_2$	52·9	5·4
(IIIh)	3′-Chloro [b]	45	154—155	A–B	52·0	5·15	$C_{26}H_{31}ClN_2O_8S_2$	52·1	5·21
(IIIi)	3′-Chloro	[c]	124—125 [d]	D	56·0	6·2	$C_{26}H_{33}ClN_2O_5S_2$	56·5	6·0
(IIIj)	3′-Chloro [b]	67	84—85	E	57·6	5·15	$C_{20}H_{21}ClN_2O_2S_2$	57·1	5·0
			62—63	A–B	50·8	4·8	$C_{26}H_{29}ClN_2O_8S_2$	50·9	4·8
(IIId)	3′-Bromo [b]	74	106—108	A–B	48·6	4·8	$C_{26}H_{31}BrN_2O_8S_2$	48·5	4·85
(IIId)	3′-Iodo [b]	79	123—124	A–B	45·2	4·4	$C_{26}H_{31}IN_2O_8S_2$	45·2	4·5
(IIId)	3′,5′-Dichloro [b]	74	136—137	A	48·7	5·0	$C_{26}H_{30}Cl_2N_2O_8S_2$	49·3	4·8
(IIId)	3′-Methoxy [b]	68 [c]	94—95	D–B	54·0	5·55	$C_{27}H_{34}N_2O_9S_2$	54·5	5·8
(IIId)	2′-Chloro-5′-methoxy [b]	73	138—139	A	51·5	5·3	$C_{27}H_{33}ClN_2O_9S_2$	51·55	5·3
(IIId)	3′-Chloro-5′-methoxy [b]	67 [c]	133—133·5	A	51·3	5·5	$C_{27}H_{33}ClN_2O_9S_2$	51·55	5·3
(IIIa)	3′-(2-Diethylaminoethoxy) [b]	78	129	A	55·4	5·8	$C_{26}H_{32}N_2O_8S_2$	55·3	5·7
(IIIa)	2′-Bromo-5′-(2-diethylaminoethoxy) [b]	74	116·5—117·5	A–B	48·5	5·0	$C_{26}H_{31}BrN_2O_8S_2$	48·5	4·85
(IIIa)	2′-(2-Diethylaminoethoxy) [b]	86	125	F	55·2	6·1	$C_{26}H_{32}N_2O_8S_2$	55·3	5·7
(IIIa)	4′-Chloro-2′-(2-diethylaminoethoxy) [b]	81	154—155	A	52·2	5·55	$C_{26}H_{31}ClN_2O_8S_2$	52·1	5·2
(IIIa)	5′-Bromo-2′-(2-diethylaminoethoxy) [b]	72	134—135	A–B	48·9	5·05	$C_{26}H_{31}BrN_2O_8S_2$	48·5	4·85
(IIIa)	3′,5′-Dichloro-2′-(2-diethylaminoethoxy) [b]	80	151·5	A	49·0	4·55	$C_{26}H_{30}Cl_2N_2O_8S_2$	49·3	4·8
(IIId)	4-Chloro [b]	80	103—104	D	51·7	5·6	$C_{26}H_{31}ClN_2O_8S_2$	52·1	5·2
(IIId)	3′,4-Dichloro [b]	60	115—116·5	D	49·7	5·4	$C_{26}H_{30}Cl_2N_2O_8S_2$	49·3	4·8
(IIId)	3′,4,5′-Trichloro [b]	73	144—145	A	47·2	4·7	$C_{26}H_{29}Cl_3N_2O_8S_2$	46·75	4·4
(IIId)	5-Chloro [b]	40	129—131	A	52·4	5·4	$C_{26}H_{31}ClN_2O_8S_2$	52·1	5·2
(IIId)	3′,5-Dichloro [b]	80	129—130	A–B	49·4	4·9	$C_{26}H_{30}Cl_2N_2O_8S_2$	49·3	4·8
(IIId)	3′,5,5′-Trichloro [b]	67	144—145	A	46·9	4·6	$C_{26}H_{29}Cl_3N_2O_8S_2$	46·75	4·8
(IIId)	3′-Bromo-5-chloro [b]	77	125—127	A	46·1	4·8	$C_{26}H_{30}BrClN_2O_8S_2$	46·1	4·45
(IIId)	5-Chloro-3′-methoxy [b]	68 [c]	98—99	D–B	51·4	5·4	$C_{27}H_{32}ClN_2O_9S_2$	51·55	5·3
(IIId)	3′,5-Dichloro-5′-methoxy	70 [c]	135—136	A	48·8	4·9	$C_{27}H_{32}Cl_2N_2O_9S_2$	48·9	4·85
(IIId)	6-Chloro [b]	62	131—132	A	52·1	5·6	$C_{26}H_{31}ClN_2O_8S_2$	52·1	5·2
(IIId)	2′,6-Dichloro [b]	69	148·5	A	48·8	4·55	$C_{26}H_{30}Cl_2N_2O_8S_2$	49·3	4·8
(IIId)	3′,6-Dichloro [b]	72	140—141	A	48·8	4·7	$C_{26}H_{30}Cl_2N_2O_8S_2$	49·3	4·8
(IIId)	3′-Bromo-6-chloro [b]	72	140—141	A	45·9	4·7	$C_{26}H_{30}BrClN_2O_8S_2$	46·1	4·45
(IIId)	6-Chloro-3′-iodo [b]	75	145—146	A–B	42·7	4·35	$C_{26}H_{30}ClIN_2O_8S_2$	43·1	4·2
(IIId)	3′,5′,6-Trichloro [b]	38 [c]	134·5—135·5	A	47·2	4·8	$C_{26}H_{29}Cl_3N_2O_8S_2$	46·75	4·4
(IIId)	6-Chloro-3′-methoxy [b]	61 [c]	119—120	A	51·7	5·3	$C_{27}H_{33}ClN_2O_9S_2$	51·55	5·3

TABLE 6. (*Continued.*)

Compound	Other substituents	Y (%)	M. p.	Cryst. from [a]	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
(IIId)	2′,6-Dichloro-5′-methoxy [b]	67	165—166	A	49·4	5·4	$C_{27}H_{32}Cl_2N_2O_9S_2$	48·9	4·85
(IIId)	3′,6-Dichloro-5′-methoxy [b]	72 [c]	136—137	A	48·6	4·6	$C_{27}H_{32}Cl_2N_2O_9S_2$	48·9	4·85
(IIIa)	6-Chloro-3′-(2-diethylaminoethoxy) [b]	79	127—128	A	51·7	5·25	$C_{26}H_{31}ClN_2O_8S_2$	52·1	5·2
(IIIa)	6-Chloro-2′-(2-diethylaminoethoxy) [b]	75	139·5	A	52·0	5·6	$C_{26}H_{31}ClN_2O_8S_2$	52·1	5·2
(IIId)	7-Chloro [b]	72	128—129	A	52·0	5·4	$C_{26}H_{31}ClN_2O_8S_2$	52·1	5·2
(IIId)	3′,7-Dichloro [b]	75	128—129	A	49·0	4·3	$C_{26}H_{30}Cl_2N_2O_8S_2$	49·3	4·8
(IIId)	3′,5′,7-Trichloro [b]	44 [c]	106—107	A	47·3	4·9	$C_{26}H_{29}Cl_3N_2O_8S_2$	46·75	4·4
(IIId)	4,6-Dichloro		61—62	C	55·0	5·35	$C_{20}H_{22}Cl_2N_2OS_2$	54·4	5·0
		72 [b]	117—118	A	49·8	4·8	$C_{26}H_{30}Cl_2N_2O_8S_2$	49·3	4·8
(IIId)	3′,4,6-Trichloro	80	90—90·5	E	50·5	4·9		50·5	4·5
				A	46·4	4·4	$C_{26}H_{29}Cl_3N_2O_8S_2$ [b]	46·75	4·4
(IIId)	3′,4,5′,6-Tetrachloro [b]	76	150—151	A	44·8	4·3	$C_{26}H_{28}Cl_4N_2O_8S_2$	44·4	4·0
(IIId)	4,5-Dichloro [b]	77	135—136	A	49·1	4·9	$C_{26}H_{30}Cl_2N_2O_8S_2$	49·3	4·8
(IIId)	3′,4,5-Trichloro [b]	72	141—142	A–B	46·3	4·1	$C_{26}H_{29}Cl_3N_2O_8S_2$	46·75	4·4
			124—125 [d]	D	65·0	6·6		65·3	6·1
(IIId)	4,7-Dichloro [b]	75	114—115	D	49·9	4·7	$C_{26}H_{30}Cl_2N_2O_8S_2$	49·3	4·8
(IIId)	3′,4,7-Trichloro [b]	76	122—123	A	46·6	4·4	$C_{26}H_{29}Cl_3N_2O_8S_2$	46·75	4·4
(IIId)	3′-Chloro-6-iodo [b]	41	128—129	D	43·1	4·3	$C_{26}H_{30}ClIN_2O_8S_2$	43·1	4·2
(IIId)	5-Chloro-α-methyl [b]	38 [c]	104—106	G–B	53·0	5·5	$C_{27}H_{33}ClN_2O_8S_2$	52·9	5·4
(IIId)	3′-Chloro-5-methyl [b]	73	126—127	A	52·7	5·8	$C_{27}H_{33}ClN_2O_8S_2$	52·9	5·4
(IIId)	3′-Chloro-6-methyl [b]	76	117—118	A	53·2	5·7	$C_{27}H_{33}ClN_2O_8S_2$	52·9	5·4
(IIId)	3′-Chloro-6-nitro	55	124—125	H	53·6	5·2	$C_{20}H_{22}ClN_3O_3S_2$	53·2	4·9
			195—196 [g]	A	48·7	4·8	$C_{20}H_{23}Cl_2N_3O_3S_2$	49·3	4·8
			175—175·5 [b]	K	48·3	5·0	$C_{26}H_{30}ClN_3O_{10}S_2$	49·5	4·7
(IIId)	3′-5-Dichloro-6-nitro [b]	73	149—150	K	45·6	4·4	$C_{26}H_{29}Cl_2N_3O_{10}S_2$	46·1	4·3
(IIId)	6-Amino-3′-chloro	65	90—90·5	H	57·0	5·8	$C_{20}H_{24}ClN_3OS_2$	56·9	5·7
			146—147 [d]	A	51·9	5·3	$C_{22}H_{26}ClN_3O_5S_2$	51·6	5·1
(IIId)	6-Amino-3′,5-dichloro	34	96—97	H	52·2	5·1	$C_{20}H_{23}Cl_2N_3OS_2$	52·6	5·1
			137—138 [d]	A–B	48·4	5·0	$C_{22}H_{25}Cl_2N_3O_5S_2$	48·4	4·6
(IIId)	6-Acetamido-3′-chloro [h]	52	124—125	M	56·6	5·6	$C_{22}H_{26}ClN_3O_2S_2$	56·9	5·65
			105—107 [b]	D	51·0	5·4	$C_{28}H_{34}ClN_3O_9S_2$	51·3	5·2
(IIId)	4,5,6,7-Tetrahydro [b]	40	110—111	D	55·0	6·5	$C_{26}H_{36}N_2O_8S_2$	54·9	6·4
(IIId)	3′-Chloro-4,5,6,7-tetrahydro [b]	73	112—113	D	51·9	5·8	$C_{26}H_{35}ClN_2O_8S_2$	51·8	6·0

[a] A, ethanol; B, ether; C, light petroleum (b. p. 40—60°); D, acetone; E, light petroleum (b. p. 60—80°); F, propan-2-ol; G, ethanol; H, light petroleum (b. p. 80—100°); K, 50% aqueous ethanol; M, benzene. [b] Citrate, melting with decomposition. [c] Impure dialkylaminoalkoxybenzyl chloride hydrochloride was used. [d] Oxalate, melting with decomposition. [e] Picrate. [f] Ethobromide. [g] Hydrochloride. [h] Prepared by acetylation of 6-amino-3′-chloro-4′-(2-diethylaminoethoxybenzylthio)benzothiazole with acetyl chloride.

was purified by solution in N-sodium hydroxide (charcoal), filtration, and reprecipitation with hydrochloric acid to give an off-white solid, m. p. 179—180°. The thiol (45 g.) was dissolved in AnalaR acetone (1 l.), anhydrous potassium carbonate (400 g.) and 3-chloro-4-(2-diethylaminoethoxy)benzyl chloride hydrochloride (83·1 g.) were added and the mixture boiled under reflux with stirring for 24 hr. The inorganic salts were removed by filtration, washed with acetone, and the filtrate evaporated to give a brown oil which was dissolved in ether (250 ml.) and washed with sodium hydroxide, sodium hydrogen carbonate, and water. Evaporation of the dried ($MgSO_4$) ether solution gave a light brown oil (96 g.) which was converted into the *citrate* (129 g.), m. p. 106—107° (decomp.) (from 95% ethanol) (Found: C, 59·3; H, 5·6. $C_{20}H_{23}ClN_2S_2$ requires C, 59·0; H, 5·7%). The free *base*, obtained from the pure citrate, crystallized at −18° from light petroleum (b. p. 40—60°) to give white plates, m. p. 40—41° (Found: C, 59·3; H, 5·6; Cl, 8·5; N, 6·6; S, 15·0. $C_{20}H_{23}ClN_2OS_2$ requires C, 59·0; H, 5·7; Cl, 8·7; N, 6·9; S, 15·7%).

2-(p-2-*Diethylaminoethoxybenzyl*)*thiobenzoxazole citrate*, white microcrystals (46%), m. p. 119—120° (from acetone) (Found: C, 56·6; H, 5·55. $C_{26}H_{32}N_2O_9S$ requires C, 56·9; H, 5·9%) and 2-[3-*chloro*-4-(2-*diethylaminoethoxy*)*benzylthio*]*benzoxazole citrate*, white microcrystals (69%), m. p. 112—113° (from ethanol–ether) (Found: C, 53·9; H, 5·5. $C_{26}H_{31}ClN_2O_9S$ requires C, 53·6; H, 5·3%) were obtained by the above method from benzoxazole-2-thiol.

2-p-*Acetoxybenzylthiobenzothiazole and* 3-p-*Acetoxybenzylbenzothiazol*-2-*thione*.—Benzothiazole-2-thiol (3·6 g.) was treated with *p*-acetoxybenzyl bromide (5 g.) in the manner described above. The residue from evaporation of acetone was treated with ether and N-sodium hydroxide solution and an insoluble colourless solid (2·23 g.) removed and crystallized from benzene to give the *thione*, m. p. 155—156°, $\lambda_{max.}$ 225 and 326 mμ (ε 25,100 and 33,100) (Found: C, 61·4; H, 4·2. $C_{16}H_{13}NO_2S$ requires C, 60·95; H, 4·15%). Evaporation of the ether extract gave an oil (3·8 g.) which was extracted with light petroleum (b. p. 60—80°) and the insoluble solid (0·93 g.) removed and crystallized from benzene to give a further amount (0·8 g.) of thione. The petroleum extract gave, on cooling, colourless microcrystals (1·3 g.) of 2-p-*acetoxybenzylthiobenzothiazole*, m. p. 79—80°, $\lambda_{max.}$ 225, 282, 290, and 301 mμ (ε 30,200, 13,500, 12,900, and 11,000) (Found: C, 61·4; H, 4·3. $C_{16}H_{13}NO_2S_2$ requires C, 60·95; H, 4·15%). When this experiment was repeated no benzothiazole-2-thione was obtained but 2-*p*-acetoxybenzylthiobenzothiazole was isolated in 35% yield.

Benzothiazolines.—3-p-*Chlorobenzylbenzothiazolone*. This compound was obtained by alkylation of benzothiazolone with *p*-chlorobenzyl chloride using acetone and potassium carbonate as colourless *needles* (83%) m. p. 84·5—85° [from light petroleum (b. p. 80—100°)] (Found: C, 61·5; H, 4·05. $C_{14}H_{10}ClNOS$ requires C, 61·0; H, 3·7%).

2-p-*Chlorobenzylaminobenzenethiol*. The above benzothiazolone (10·8 g.) was added to a solution of potassium hydroxide (10 g.) in water (20 ml.) and ethanol (80 ml.) and the mixture was boiled under reflux in a nitrogen atmosphere for 4 hr. The mixture was evaporated, the residue treated with water (100 ml.) and concentrated hydrochloric acid (20 ml.), and the resulting solution neutralized with acetic acid. The oil which separated was dissolved in ether and, after recovery in the usual manner, was distilled under nitrogen to give 2-(p-*chlorobenzylamino*)*benzenethiol* as a colourless liquid (5·7 g.), b. p. 187—189°/0·5 mm. (Found: C, 62·3; H, 5·3. $C_{13}H_{12}ClNS$ requires C, 62·5; H, 4·8%).

2-p-2-*Diethylaminoethoxyphenyl*-3-*methylbenzothiazoline*. A mixture of *o*-methylaminobenzenethiol (2·8 g.) and *p*-2-diethylaminoethoxybenzaldehyde (4·4 g.) was heated to 150° under nitrogen over 30 min. and kept at this temperature for 5 min. The product was distilled and the fraction (4·4 g.), b. p. 212—218°/0·2 mm., collected. Redistillation gave the pure *benzothiazoline*, b. p. 182—186°/0·15 mm. (Found: C, 69·7; H, 7·8. $C_{20}H_{26}N_2OS$ requires C, 70·1; H, 7·65%); *picrate*, m. p. 160—161° (from acetone) (Found: C, 54·3; H, 5·0. $C_{26}H_{29}N_5O_8S$ requires C, 54·6; H, 5·1%).

3-(p-*Chlorobenzyl*)-2-(p-2-*diethylaminoethoxyphenyl*)*benzothiazoline hydrochloride*. Under the same conditions 2-*p*-chlorobenzylaminobenzenethiol (2·7 g.) and *p*-2-diethylaminoethoxybenzaldehyde (2·5 g.) gave a product (2·0 g.), b. p. 200—222°/0·2 mm. This oil (0·5 g.) was dissolved in ether, the solution saturated with dry hydrogen chloride, and the precipitated *benzothiazoline hydrochloride* collected, white needles (0·16 g.), m. p. 211—213° (from ethanol–ether) (Found: C, 63·1; H, 6·5. $C_{20}H_{30}ClN_2OS$ requires C, 63·8; H, 6·2).

5-*Chloro*-2-(p-2-*diethylaminoethoxyphenyl*)-3-*methylbenzothiazoline*. A mixture of 4-chloro-2-methylaminobenzenethiol (2·4 g.) and *p*-2-diethylaminoethoxybenzaldehyde (3·6 g.) was

heated at 100° for 3 hr. under nitrogen. The product was distilled to give the *chlorobenzothiazoline* (3·5 g.), b. p. 220—224°/0·2 mm. (Found: C, 63·5; H, 7·25. $C_{20}H_{25}ClN_2OS$ requires C, 63·7; H, 6·7%); *picrate*, m. p. 134—136° (from ethanol) (Found: C, 51·5; H, 5·0. $C_{26}H_{28}ClN_5O_8S$ requires C, 51·5; H, 4·65%).

2-*Styrylbenzothiazoles*.—5-*Chloro*-2-p-*methoxystyrylbenzothiazole*. 5-Chloro-2-methylbenzothiazole (3·7 g.), anisaldehyde (2·7 g.), and concentrated hydrochloric acid (5 drops) were heated at 150° in a sealed tube for 2 hr. The cooled mixture was shaken with ether and the insoluble solid (2·8 g.) collected. Recrystallization from ethanol gave yellow needles of 5-*chloro*-2-p-*methoxystyrylbenzothiazole* (2·05 g.), m. p. 154—155° (Found: C, 63·8; H, 4·2. $C_{16}H_{12}ClNOS$ requires C, 63·7; H, 4·0%). The ether extract was washed with sodium hydrogen sulphite solution, N-sodium hydroxide solution, and N-hydrochloric acid. The dried ($MgSO_4$) ether solution was evaporated and the solid residue (0·9 g.), m. p. 110—130°, crystallized from 50% benzene–light petroleum (b. p. 60—80°) then from ethanol to give a further quantity (0·08 g.) of the product. The benzene mother-liquors from the above crystallization were evaporated and the residue extracted with light petroleum (b. p. 60—80°). The extract deposited an oil on cooling but on decantation and standing a yellow solid (0·25 g.) separated. Recrystallization from light petroleum (b. p 60—80°) gave pale yellow needles of 5-*chloro*-2-[2-*hydroxy*-2-(p-*methoxyphenyl*)*ethyl*]*benzothiazole* (0·13 g.), m. p. 115—116° (Found: C, 59·8; H, 4·1. $C_{16}H_{14}ClNO_2S$ requires C, 60·1; H, 4·4.

5-*Chloro*-2-(p-2-*diethylaminoethoxystyryl*)*benzothiazole hydrochloride*. 5-Chloro-2-methylbenzothiazole (9·2 g.), *p*-2-diethylaminoethoxybenzaldehyde (22 g.) and concentrated hydrochloric acid (10 ml.) were heated to 150° for 3 hr. Trituration with ether and N-hydrochloric acid (30 ml.) gave the sparingly soluble *hydrochloride* (13·6 g.), m. p. 233—235° (from water) (Found: C, 59·4; H, 6·1. $C_{21}H_{24}Cl_2N_2OS$ requires C, 59·6; H, 5·7%).

2-(p-2-*Diethylaminoethoxystyryl*)*benzothiazole hydrochloride* was obtained in a similar manner, m. p. 211·5—212·5° (from propan-2-ol) (Found: C, 64·7; H, 6·5. $C_{21}H_{25}ClN_2OS$ requires C, 64·8; H, 6·5%).

Reduction of 5-*Chloro*-2-(p-2-*diethylaminoethoxystyryl*)*benzothiazole Hydrochloride*.—The hydrochloride (2·0 g.) was heated under reflux with acetic acid (25 ml.) and zinc dust (2·5 g.) for 20 min. The cooled solution was decanted from the excess of zinc into 40% sodium hydroxide solution (100 ml.), the zinc washed with acetic acid (5 ml.), and the washings decanted into the alkaline mixture. An oily solid separated. Water (100 ml.) was added, the solid extracted with ether, the ether dried ($MgSO_4$), and evaporated. The residual yellow oil (1·7 g.) was dissolved in sodium-dried ether (30 ml.), filtered from an insoluble solid, m. p. 156—159°, and the filtrate was saturated with hydrogen chloride. The yellow oily solid which precipitated was collected and recrystallized from water to give 5-chloro-2-(*p*-2-diethylaminoethoxyphenethyl)benzothiazole (0·32 g., 16%), m. p. 178—180°, identical with that prepared above. The ether-insoluble material was recrystallized from ethanol to give pale yellow needles (0·09 g.), m. p. 158—159° (Found: C, 64·7; H, 6·4%).

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