83. *Experiments in the Chemistry of Benzthiazole.*

By WILLIAM A. BOGGUST and WESLEY COCKER.

A number of 6-substituted derivatives of benzthiazole have been prepared. It has been shown that some of these are smoothly degraded by hydrazine to *o*-aminothiophenols. When benzthiazole and phenylhydrazine are heated together they act as an oxidation–reduction system, the former being recovered unchanged, and the latter being converted into a mixture of benzene, aniline, ammonia, and nitrogen.

6-Aminobenzthiazole undergoes angular ring-closure in the Skraup reaction, with formation of *pyridino*(2′ : 3′ : 6 : 7)*benzthiazole*. *4′-Hydroxy-6′-methylpyridino*(2′ : 3′ : 6 : 7)*benzthiazole* is also obtained by the cyclisation of *ethyl* β-(6-*benzthiazolylamino*)*crotonate*.

SINCE a good supply of benzthiazole was available to one of us (Cocker, *J. Soc. Chem. Ind.*, 1936, **55**, 28T) an investigation of a number of its simple derivatives was undertaken. The starting point of our work was 6-nitrobenzthiazole which was prepared by a modification of the method described by Mylius (Diss., Berlin, 1883; Jacobsen and Kwaysser, *Annalen*, 1893, **277**, 244). The following benzthiazoles have been prepared: 6-amino-, 6-(p-*dimethylaminobenzylideneamino*)-, 6-(p-*acetamidobenzenesulphonamido*)-, 6-(p-*aminobenzenesulphonamido*)-, 6-*hydroxy*-, 6-*chloro*-, 6-*bromo*-, 6-*cyano*-, 6-*carboxy*-, 6-*carbomethoxy*-, 6-*hydrazino*-, and 6-*carbamido*-. 6-Aminobenzthiazole was prepared by reduction of the nitro-compound with stannous chloride (Mylius, *loc. cit.*), activated iron powder (Clemo and Legg, *J.*, 1947, 544), or ferrous sulphate and ammonia (cf. Friedländer, *Ber.*, 1882, **15**, 2573). 6-Aminobenzthiazole was converted into its *p*-acetamidobenzenesulphonamido-derivative without difficulty, and this compound, and the *p*-aminobenzenesulphonamido-derivative, were examined for inhibitory action against various micro-organisms. Both compounds exhibited inhibitory properties against *Gonococcus* and hæmolytic *Streptococcus*, but both were less effective than sulphanilamide. The low activity was, however, possibly due to the sparingly soluble nature of both compounds in the culture media. Furthermore, both were found to possess relatively high toxicity when tested against mice.

When 6-aminobenzthiazole was diazotised in hydrochloric acid and the diazonium solution was decomposed with copper sulphate and sulphuric acid, 6-chlorobenzthiazole, and not the expected phenol, was obtained. Treatment of the chloro-compound with 3 : 5-dinitrobenzoyl chloride gave 5-chloro-2-(3 : 5-dinitrobenzamido)thiophenol with cleavage of the thiazole ring.

This ring-cleavage is interesting in that benzthiazole derivatives are known to undergo oxidation to the corresponding 2 : 2′-dibenzthiazolyls on treatment with benzoyl chloride (Hofmann, *Ber.*, 1880, **13**, 1229), and we have shown that stearoyl chloride effects this change. On the other hand, a mixture of benzoyl chloride and alkali has been used for opening the thiazole ring (see Morton " The Chemistry of Heterocyclic Compounds ", New York, 1946, p. 408, for numerous references).

The replacement of the diazonium group by chlorine in the presence of cupric salts is known (cf. Hodgson, Birtwell, and Walker, *J.*, 1941, 772), and it appears that such replacements are prevalent with diazonium ions of high positivity. In the case under discussion, the electron-attractive characteristics of the $-N{=}\overset{|}{C}-S-$ group are probably responsible for the reaction mentioned.

Formation of the true phenol proceeded normally by decomposition of the diazonium sulphate.

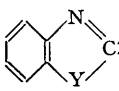
The 6-chloro-, -bromo-, and, -cyano-compounds were also obtained in the normal way by using the appropriate cuprous salt, but attempts to obtain the 6-iodo-compound gave a semi-solid material which decomposed explosively. This was probably due to the formation of a periodide.

An attempt to obtain benzthiazole-6-hydrazide by the reaction of hydrazine with 6-carbomethoxybenzthiazole yielded 2 : 2′-*diamino*-5 : 5′-*dicarbomethoxydiphenyl disulphide*.

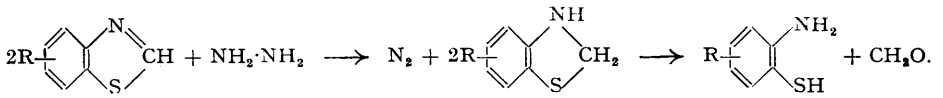
Under the same conditions, benzthiazole yielded 2 : 2′-diaminodiphenyl disulphide ("Intramine") in good yield, and likewise 6-cyanobenzthiazole yielded 2 : 2′-*diamino*-5 : 5′-*dicyanodiphenyl disulphide*. 5 : 5′-Dinitro-2 : 2′-diaminodiphenyl disulphide was similarly obtained from 6-nitrobenzthiazole, and the pyridino(2 : 3′ : 6 : 7)benzthiazole described later yielded 6 : 6′-*diamino*-5 : 5′-*diquinolyl disulphide*. Hydrolysis of the thiazole ring takes place in all these reactions.

A number of methods are known for the opening of thiazole and similar five-membered heterocyclic rings. Thus benzthiazole is hydrolysed to *o*-aminothiophenol by concentrated sodium hydroxide at elevated temperatures (Hofmann, *Ber.*, 1880, **13**, 18), although more recently (B.P. 558,887) it has been shown that less drastic conditions can be employed. Reductive cleavage is quite common. Thus sodium in alcohol has been used for this purpose (Schatzmann, *Annalen*, 1891, **261**, 6; Schuftan, *Ber.*, 1894, **27**, 1009), but so far as we are aware, the use of hydrazine under mild conditions such as those described is new. A somewhat similar reaction involves the formation of 2-formamidophenol when benzoxazole is treated with hydroxylamine, but 2-aminobenzoxazole is simultaneously produced (Skraup, *Annalen*, 1919, **419**, 68).

It was at first thought that either 2-aminobenzthiazole or 2-hydrazinobenzthiazole would be possible intermediates in the formation of the disulphide. The former compound was obtained by amination of benzthiazole with hydroxylamine (Skraup, *loc. cit.*), and the latter was obtained from 2-mercaptobenzthiazole by treatment with hydrazine. The latter preparation follows the work described in the patent literature (D.R.-P. 614,327) in which it is stated that compounds of the type (I) when treated with hydrazine give 2-substituted hydrazino-compounds. However,

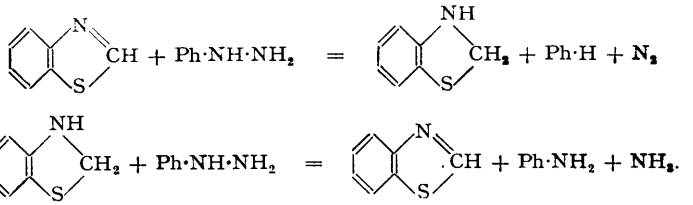
(I.)  (Y = S, O, NH, N·Alk; Z = OH, Cl, SO_3H.)

neither 2-amino- nor 2-hydrazino-benzthiazole suffered ring-cleavage on further heating with hydrazine. In view of the fact that cleavage of thiazole systems by alkaline reducing agents is known (*loc. cit.*), it is considered probable that the benzthiazole is first reduced to the corresponding thiazoline which is then hydrolysed to an aminothiophenol and formaldehyde or some derivative of this, the thiophenol being oxidised in the subsequent manipulation. In agreement with this view is the fact that an inert gas, probably nitrogen, is evolved during the reaction:



Formaldehyde was never detected during the reaction, but the aqueous liquors from which the amino-thiol or the amino-disulphide separated yielded a hygroscopic non-sulphur-containing nitrogenous solid which yielded a benzylidene derivative. Neither compound has been identified.

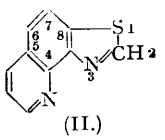
Piperidine, dimethylaniline, and alkaline sodium hydrosulphite (dithionite) did not hydrolyse benzthiazole, but when benzthiazole was heated with phenylhydrazine it was recovered almost quantitatively, whereas the phenylhydrazine was converted into a mixture of nitrogen, ammonia, benzene, and aniline in amounts corresponding to the requirements of the equations below, in which there is an oxidation–reduction system.



The equations given above conform with the known facts about the oxidising and reducing properties of phenylhydrazine. It is also known that benzthiazolines are very readily oxidised even in air (Lankelma and Sharnhoff, *J. Amer. Chem. Soc.*, 1931, **53**, 2654). Small amounts of aniline and ammonia were evolved when phenylhydrazine was refluxed for extended periods, but the amounts obtained were not comparable to those mentioned above, and benzene was not identified.

In view of the physiological activity of many thiazole compounds, and of the importance of the quinoline nucleus in many compounds of chemotherapeutic value, it was considered worth while to prepare compounds of the quinthiazole type. Some such compounds are known and have been prepared by the Skraup reaction. Thus Erlenmeyer and Ueberwasser (*Helv. Chim. Acta*, 1940, **23**, 328) described the preparation of pyridino(2′ : 3′ : 4 : 5)benzthiazole (II).

The mode of preparation leaves the identity of this quinthiazole in no doubt, but the application of the Skraup reaction to 5-aminobenzthiazole, obtained from 2-chloro-5-nitroformanilide *via* 5-nitrobenzthiazole (D.R.-P. 442,773), could lead to either pyridino(3′ : 2′ : 4 : 5)-benzthiazole (III) by angular ring-closure or pyridino(2′ : 3′ : 5 : 6)benzthiazole (IV) by linear ring-closure. 6-Aminobenzthiazole can similarly yield either a linear or an angular quinthiazole.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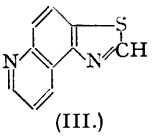
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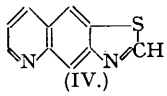
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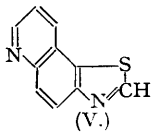
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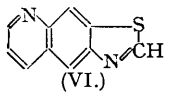
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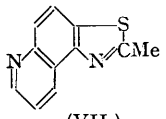
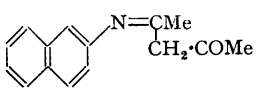
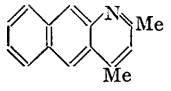

(VII.)

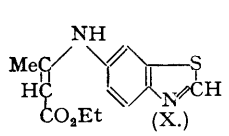
6-Aminobenzthiazole readily undergoes the Skraup reaction when sodium *m*-nitrobenzenesulphonate is used as the oxidising agent. This reaction could give either pyridino(2′ : 3′ : 6 : 7)-benzthiazole (V) or pyridino(3′ : 2′ : 5 : 6)benzthiazole (VI). All the evidence goes to show, however, that the former compound is actually obtained.

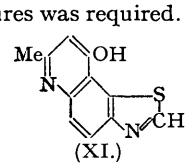
Although as a rule, angular systems are formed in preference to linear systems (cf. Kermack and Weatherhead, *J.*, 1940, 1164), the linear system cannot entirely be ruled out. Thus Cohen *et al.* (*J.*, 1934, 656) obtained 5-chloro-2 : 4-dimethyl-1-aza-anthracene by the ring closure of 4-(5-chloro-2-naphthylimino)pentan-2-one and Clemo and Legg (*J.*, 1945, 830) obtained 2 : 4-dimethyl-6 : 7-benzoquinoline (IX) by the cyclisation of 4-(2-naphthylimino)pentan-2-one (VIII).

(VIII.) 


(IX.)

According to Fries and Wolter (*Annalen*, 1936, **527**, 60) benthiazole occupies a position intermediate between benzoid and naphthoid reactivity, although these authors state that the Skraup reaction with 5-amino-2-methylbenzthiazole leads to the production of 2-methyl pyridino(3′ : 2′ : 4 : 5)benzthiazole (VII). Ochiai and Nisizawa (*Ber.*, 1941, **74**, *B*, 1407) showed that the allyl ether of 6-hydroxy-2-methylbenzthiazole rearranges to give a mixture of 6-hydroxy-2-methyl-7- and -5-allylbenthiazoles in which the former is present in the ratio of 20 to 1. This evidence and that of Fries and Wolter give strong support for the acceptance of the angular form (V) for the quinthiazole now described rather than the linear form (VI). It would also appear likely that the angular structure (XI) would also arise from the cyclisation of the crotonate (X). In view, however, of the work of Cohen *et al.* (*loc. cit.*) and Clemo and Legg (*loc. cit.*), proof of the suggested structures was required.


(X.)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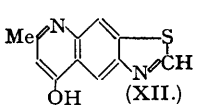
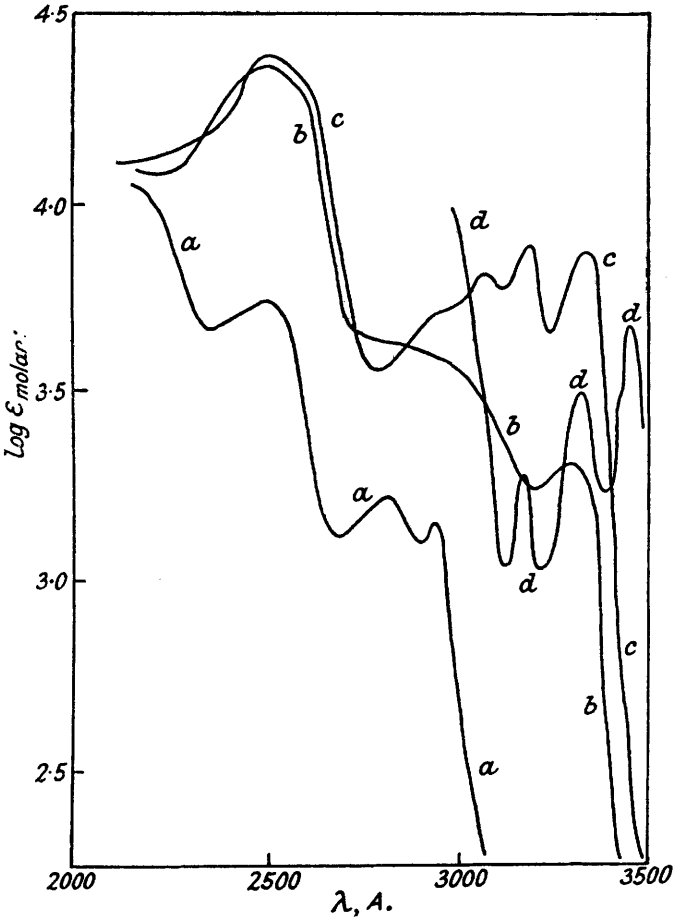

(XII.)

6-Aminobenzthiazole and ethyl acetoacetate were condensed at 28° for 5 days; the product was *ethyl* β-(6-*benzthiazolylamino*)*crotonate* since water was rapidly produced when the reactants were first mixed. There is very considerable evidence that at low temperatures this mode of condensation takes place in preference to that which would lead to the formation of 6-aceto-acetamidobenzthiazole, a reaction which proceeds on the water-bath (cf. Conrad and Limpach, *Ber.*, 1887, **20**, 944; 1888, **21**, 523, 1649; 1891, **24**, 2990; Stark, *Ber.*, 1907, **40**, 3431; Knorr, *Annalen*, 1886, **236**, 112; *Ber.*, 1892, **25**, 772; Coffey, Thompson, and Wilson, *J.*, 1936, 856; Hazlewood, Hughes, and Lyons, *J. Proc. Roy. Soc. N.S.W.*, 1937, **71**, 472). The crotonate was



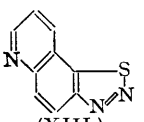
a. *Benzthiazole.*
b. *Pyridino*(2′ : 3′ : 6 : 7)*benzthiazole* (V).
c. 4′-*Hydroxy*-6′-*methylpyridino*(2′ : 3′ : 6 : 7)*benzthiazole* (XI). (*All in alcohol.*)
d. 3-*Chloro*-2 : 4-*dimethyl*-5 : 6-*benzoquinoline* (*Clemo and Legg*).

cyclised by addition to high-boiling paraffin preheated to 270°, a method successfully used for similar cyclisations by Hazlewood, Hughes, and Lyons (*loc. cit.*), and assuming that the cyclisation took place to give an angular structure, 4′-*hydroxy*-6′-*methylpyridino*(2′ : 3′ : 6 : 7)*benzthiazole* (XI) would be the expected product. Spectroscopic evidence shows that this compound and the quinthiazole (V) have similar structures, and it is most likely that they have the angular structures assigned to them. On the other hand cyclisation to give a linear ring system would have led to the production of 4′-hydroxy-6′-methylpyridino(3′ : 2′ : 5 : 6)benthiazole (XII).

In order to establish the structure of the unsubstituted quinthiazole, oxidation to the corresponding quinone by means of chromic oxide in acetic acid was attempted. A quinthiazole of the angular type (V) should yield an orthoquinone capable of detection by quinoxaline

formation, whereas the linear compound (VI) should yield a paraquinone (cf. Clemo and Legg, *loc. cit.*). Unfortunately, however, the quinthiazole was, in every case, recovered unchanged. Quinthiazole failed to condense with maleic anhydride.

In view of the ready cleavage of the thiazole ring with hydrazine, attempts were made to utilise this method to distinguish between the two possible quinthiazoles (V) and (VI), since the former should give 6-amino-5-mercaptoquinoline whilst the latter should yield 6-amino-7-mercaptoquinoline (or the corresponding disulphides) on treatment with hydrazine. The removal of the amino-group from the product of the hydrolysis would then lead to the production of either 5- or 7-mercaptoquinoline. Unfortunately, however, whilst the thiazole was hydrolysed to the corresponding aminoquinoline disulphide, diazotisation of this compound yielded the not unexpected thiadiazole which could be either (XIII) or (XIV) (cf. Jacobsen, *Ber.*, 1888, **21**, 3105; Jannsen, *Annalen*, 1893, **277**, 219). A similar compound, pyridino(3′ : 2′ : 4 : 5)benzthiadiazole (XV), was prepared by Fries and Reitz (*Annalen*, 1936, **527**, 38) by the Skraup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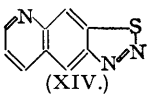
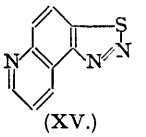

(XIV.)


(XV.)

reaction on 5-aminothiadiazole and its angular structure was justified on the grounds that 4-chloro-5-aminothiadiazole failed to undergo the Skraup reaction. In view of the fact that the new quinthiazole (V) most likely has an angular structure, the thiadiazole prepared from it is probably *pyridino*(2′ : 3′ : 6 : 7)*benzthiadiazole* (XIII).

Thiadiazoles usually decompose when heated above their melting points, yielding thianthrenes (Jacobsen and Ney, *Ber.*, 1889, **22**, 910), but when the thiadiazole (XIII) was heated above its melting point, although decomposition apparently took place, the thiadiazole was either recovered unchanged or a charred mass was produced from which it was impossible to isolate any crystalline product.

Examination of the ultra-violet light absorption of (V) and (XI) lends some support to the probability that these compounds have angular structures. The fig. shows that the ring system in these compounds is essentially the same, and making due allowance for the extra ring in the compounds mentioned the absorption is very similar to that of benzthiazole. The maximum at 2500 A. in each case may be due to the thiazole ring. In thiazole itself the maximum is located at 2400 A., and there is also a similar maximum in anthracene, phenanthrene, and pyridine (Braude, *Ann. Reports*, 1945, 105) to which the thiazoles are somewhat similar in aromaticity. Further, the curves for compounds (V) and (XI) shown in the fig. show a resemblance to those of 2 : 4-dimethyl- and 3-chloro-2 : 4-dimethyl-5 : 6-benzoquinoline (Clemo and Legg, *loc. cit.*) where angular structures are involved, but they are very different from the curves obtained by these authors for 2 : 4-dimethyl-6 : 7-benzoquinoline and other aza-anthracenes. The maxima shown by the quinthiazoles bear the approximate relationship to those shown by benzthiazole that those of phenanthrene do to those of naphthalene (cf. Braude, *loc. cit.*). On the other hand the anthracenes and aza-anthracenes have maxima at higher wave-lengths than the corresponding angular structures.

When 6-aminobenzthiazole was brominated, a mixture of monobromo-compounds was obtained from which pure compounds, m. p. 119—120° and 145—146°, were isolated. The lower-melting compound yielded the quinthiazole (V) with bromine elimination when subjected to the Skraup reaction, and this bromo-compound was probably *7-bromo-6-aminobenzthiazole*. In view of the work of Ochiai and Nisizawa it is likely that the other bromo-compound was 5-bromo-6-aminobenzthiazole, but when it was subjected to the Skraup reaction it yielded a high-melting bromo-compound which did not give correct analyses for the expected 5-bromopyridino(2′ : 3′ : 6 : 7)benzthiazole.

Experimental.

(Microanalyses and ultra-violet light-absorption data are by Drs. Weiler and Strauss, Oxford.)

Benzthiazole, prepared from triply recrystallised sulphate, gave the following maxima in the ultra-violet : 2500 A. (log ϵ 3·74), 2840 A. (log ϵ 3·22), and 2960 A. (log ϵ 3·15).

6-Nitrobenzthiazole.—Crude benzthiazole obtained as described by Cocker (*loc. cit.*) was first purified by a double vacuum distillation. It was then converted into its sulphate which after crystallisation from alcohol was decomposed by alkali. The benzthiazole was distilled and collected at 125—128°/18 mm. Benzthiazole (33 g.) was slowly added with stirring to concentrated sulphuric acid (66 c.c.) at 10—20°. Nitric acid (33 c.c., *d* 1·42) was then added dropwise at 5—10°. Stirring was

continued for a further hour, the temperature being allowed to rise to 20°, and the mixture was poured on ice. The solid product was washed with water, yielding a mixture of nitro-compounds (25 g., m. p. 140—145°). This mixture was purified by extraction with a deficiency of methyl alcohol which left the 6-nitrobenzthiazole undissolved. The required compound was obtained as a pale yellow solid (9·6 g.), m. p. 171—173°. This was considered pure enough for further work, but a pure specimen was obtained, by crystallisation from a large volume of alcohol, as pale yellow needles, m. p. 174° (Mylius, *loc. cit.*).

6-*Aminobenzthiazole.*—(*a*) The nitro-compound (1·0 g.), dissolved in a mixture of methyl alcohol (10·0 c.c.), concentrated hydrochloric acid (10·0 c.c.), and stannous chloride (5·0 g.), was heated under reflux for 15 minutes. The methyl alcohol was then distilled off, and the residue was dissolved in water and strongly basified to remove tin salts. Extraction of the mixture with ether yielded a solid which, after distillation in a vacuum (b. p. 184°/2 mm.), yielded the required amine (0·8 g.), m. p. 81—82°. Crystallisation from benzene–light petroleum yielded long colourless needles, m. p. 84—85° (Mylius, *loc. cit.*, gives m. p. 87°).

(*b*) The nitro-compound (7·5 g.) in alcohol (100 c.c.) was added to etched iron filings (45 g.), and the mixture was refluxed for 3 hours and filtered, and the alcohol removed, leaving the amine (5·3 g.), m. p. 79—82°.

(*c*) The nitro-compound (1 g.), suspended in a solution of ferrous sulphate (18 g.) in water (30 c.c.) containing hydrochloric acid (2 drops), was shaken at 90° with ammonia (*d* 0·88), added in 1 portion of 3·5 c.c. and 3 further portions of 1·25 c.c. After cooling, the sludge was repeatedly extracted with ether, from which the required amine (0·5—0·6 g.) was obtained, m. p. 82—83°. Its *p-dimethylaminobenzylidene* derivative crystallised from alcohol in yellow plates, m. p. 135° (Found : C, 68·05; H, 5·6. $C_{16}H_{15}N_3S$ requires C, 68·3; H, 5·3%).

6-(p-*Acetamidobenzenesulphonamido*)*benzthiazole.*—A mixture of 6-aminobenzthiazole (0·3 g.), *p*-acetamidobenzenesulphonyl chloride (0·5 g.), and acetone (5·0 c.c.) was treated with pyridine (2·0 c.c.). The mixture was warmed to give a clear solution, and left overnight at room temperature. It was then poured into water, yielding a solid (0·6 g.) which after crystallisation from alcohol was obtained as silvery prisms, m. p. 253—254° (decomp.) (Found : C, 51·6; H, 4·0. $C_{15}H_{13}O_3N_3S_2$ requires C, 51·8; H, 3·8%). 6-(p-*Aminobenzenesulphonamido*)*benzthiazole* was obtained by warming this *acetyl* derivative (1·0 g.) on the water-bath with concentrated hydrochloric acid (5·0 c.c.) and water (2·0 c.c.) for 30 minutes. The mixture was basified with sodium carbonate, yielding a solid, which crystallised from alcohol as colourless prisms, m. p. 210·5° (Found : C, 51·2; H, 3·6. $C_{13}H_{11}O_2N_3S_2$ requires C, 51·1; H, 3·6%).

6-*Carbamidobenzthiazole.*—A solution of 6-aminobenzthiazole hydrochloride (1 g.) in water (10 c.c.) was treated with potassium cyanate (1 g.), and the mixture was heated on the water-bath for 15 minutes. The precipititate was washed and dried, yielding the *carbamido*-compound as a white solid (0·6 g.) which crystallised from aqueous methyl alcohol as silvery prisms, m. p. 194° (Found : C, 49·4; H, 3·7. $C_8H_7ON_3S$ requires C, 49·7; H, 3·6%).

6-*Chlorobenzthiazole.*—(*a*) A solution of 6-aminobenzthiazole (1·0 g.) in concentrated hydrochloric acid (2·0 c.c.) and water (5·0 c.c.) was diazotised at 0° with sodium nitrite (0·5 g.) in water (1·0 c.c.). After 30 minutes, the solution was slowly added to a boiling mixture of copper sulphate (10 g.), sulphuric acid (70 g.), and water (40 c.c.). After cooling, the mixture was diluted to 500 c.c. and extracted with chloroform, from which the *chloro*-compound was obtained as an oil (0·5 g.), b. p. 111°/2 mm. It rapidly solidified and was sublimed in a vacuum giving colourless needles, m. p. 41° (Found : C, 49·5; H, 2·4. C_7H_4NClS requires C, 49·6; H, 2·4%). Its *picrate* crystallised from alcohol as bright yellow needles, m. p. 136° (Found : C, 39·4; H, 1·8. $C_{13}H_7O_7N_4ClS$ requires C, 39·15; H, 1·7%). 5-*Chloro*-2-(3 : 5-*dinitrobenzamido*)*thiophenol* was obtained when 6-chlorobenzthiazole was heated gently with an equivalent quantity of 3 : 5-dinitrobenzoyl chloride. It was soluble in sodium hydroxide, and crystallised from dilute alcohol as colourless needles, m. p. 154° (Found : C, 44·4, 44·3; H, 2·35, 2·1. $C_{13}H_8O_5N_3ClS$ requires C, 44·2; H, 2·3%).

(*b*) 6-Aminobenzthiazole (1·0 g.), diazotised in sulphuric acid (1·5 c.c.) and water (3·0 c.c.) with sodium nitrite (0·44 g.), was added to cuprous chloride (0·3 g.) in hydrochloric acid (3·0 c.c.). After 12 hours the mixture was diluted, basified with ammonia, and extracted with ether, yielding the chloro-compound which sublimed as needles (0·6 g.), m. p. 40°.

6-*Bromobenzthiazole.*—6-Aminobenzthiazole (1·0 g.) was diazotised in hydrobromic acid (6·0 c.c., *d* 1·4) and added to a stirred ice-cold solution of cuprous bromide (1·1 g.) in hydrochloric acid (15 c.c.). The mixture was warmed on the water-bath to complete the reaction, cooled, basified with excess of ammonia, and extracted with ether, from which the *bromo*-compound was obtained as an oil (0·85 g.), b. p. 143°/1—2 mm. This quickly solidified; it sublimed in a vacuum as colourless needles, m. p. 55° (Found : C, 40·0; H, 1·9. C_7H_4NBrS requires C, 39·25; H, 1·8%).

6-*Cyanobenzthiazole.*—6-Aminobenzthiazole (2·0 g.) diazotised in hydrochloric acid was added to a warm (40—50°) solution of sodium cuprocyanide prepared from hydrated copper sulphate (3·7 g.) and sodium cyanide (3·3 g.). After 30 minutes on the water-bath, further sodium cyanide was added to decompose the copper complex, and the solution was extracted with ether, from which the *cyano*-compound (1·1 g.) was obtained. It was sublimed in a vacuum, and then crystallised from benzene–light petroleum as long colourless needles, m. p. 138° (Found : C, 59·6; H, 2·8. $C_8H_4N_2S$ requires C, 60·0; H, 2·5%).

Benzthiazole-6-carboxylic Acid.—The *cyano*-compound (0·2 g.) was refluxed for 1 hour with a mixture of concentrated sulphuric acid (4·5 c.c.) and water (3·0 c.c.). This mixture was diluted, basified with sodium carbonate, filtered, and acidified with dilute acetic acid. The precipitated *acid* was collected (0·2 g.) and crystallised from dilute alcohol (charcoal) as colourless needles, m. p. 245—246° (Found : C, 54·0; H, 3·3. $C_8H_5O_2NS$ requires C, 53·6; H, 2·8%). Its *methyl* ester crystallised from dilute methyl alcohol as silvery flakes, m. p. 106—107° (Found : C, 56·4; H, 3·4. $C_9H_7O_2NS$ requires C, 56·0; H, 3·6%). Its *anilide* crystallised from alcohol as glistening plates, m. p. 176° (Found : C, 65·6; H, 3·9. $C_{14}H_{10}ON_2S$ requires C, 66·1; H, 3·9%).

6-*Hydroxybenzthiazole.*—6-Aminobenzthiazole (5·6 g.) dissolved in a solution of sulphuric acid (6·5 c.c.) in water (11·0 c.c.) was diazotised at 0—5° with sodium nitrite (1·6 g.) in water (7·0 c.c.).

After 15 minutes, the solution was added to a boiling solution of sulphuric acid (19 c.c.) in water (94 c.c.). When cool, the mixture was basified with ammonia and extracted with ether, from which the *hydroxy*-compound was obtained (1·5 g.). After sublimation in a vacuum, it crystallised from ethyl acetate–light petroleum as colourless prisms, soluble in sodium hydroxide, m. p. 181—182° (Found: C, 55·25; H, 3·3. C_7H_5ONS requires C, 55·6; H, 3·3%). Its *picrate* crystallised from water as orange-yellow prisms, m. p. 194—195° (Found: C, 42·1; H, 2·5. $C_{13}H_8O_8N_4S$ requires C, 41·1; H, 2·1%).

6-*Hydrazinobenzthiazole*.—6-Aminobenzthiazole (4·0 g.), diazotised in hydrochloric acid, was slowly added to a solution of stannous chloride (14 g.) in concentrated hydrochloric acid (14 c.c.). The mixture was warmed for several minutes, cooled, basified with sodium hydroxide, and extracted with chloroform, from which a solid (3·8 g.), m. p. 93°, was obtained. After 3 crystallisations from benzene (charcoal), the *hydrazine* was obtained as colourless needles, m. p. 101—102° (Found: C, 51·3; H, 4·2. $C_7H_7N_3S$ requires C, 50·9; H, 4·2%).

Pyridino(2′ : 3′ : 6 : 7)*benzthiazole* (V).—6-Aminobenzthiazole (1·0 g.) was mixed to a paste with glycerol (3·0 c.c.) and heated to 110°. A mixture of sodium *m*-nitrobenzenesulphonate (4 g.) and 78% sulphuric acid (12 g.) was then added during 30 minutes, and the mixture was heated at 110° for 12 hours. It was cooled, diluted, and extracted with benzene, from which colourless glistening needles (0·6 g.), m. p. 158—159°, were obtained. The *quinthiazole* was finally crystallised from light petroleum (b. p. 80—100°); m. p. 159—160° (Found: C, 64·0; H, 3·3. $C_{10}H_6N_2S$ requires C, 64·5; H, 3·2%). The ultra-violet light-absorption of this compound in absolute alcohol showed maxima at 2500 A. (log ϵ 4·35) and 3320 A. (log ϵ 3·31). Its *monomethiodide* crystallised from methyl alcohol as orange needles, m. p. 270—271° (Found: I, 38·6. $C_{11}H_9N_2IS$ requires I, 38·7%). Its *picrate* crystallised from boiling xylene in greenish-yellow rosettes, m. p. 238—239° (Found: C, 46·9; H, 2·6. $C_{16}H_9O_7N_5S$ requires C, 46·3; H, 2·2%).

Ethyl β-(6-*Benzthiazolylamino*)*crotonate* (X).—A mixture of 6-aminobenzthiazole (5 g.), freshly distilled ethyl acetoacetate (4 g.), and concentrated hydrochloric acid (1 drop) was left for 4 days at 28°. Water was quickly produced on mixing the reactants, and this was finally removed by dissolving the mixture in ether and drying the solution (Na_2SO_4). The solution was concentrated under reduced pressure to 10 c.c., and the residue then deposited the desired *compound* (6·5 g.) as colourless tablets, m. p. 62°. Crystallisation from light petroleum (b. p. 40—60°)–benzene raised the m. p. to 63° (Found: C, 59·8; H, 5·0. $C_{13}H_{14}O_2N_2S$ requires C, 59·5; H, 5·3%).

4′-*Hydroxy*-6′-*methylpyridino*(2′ : 3′ : 6 : 7)*benzthiazole* (XI).—The above crotonate (2·2 g.) was finely powdered and added to liquid paraffin (30 c.c.) preheated to 270°. The mixture was heated for a further 10 minutes and cooled, and the solid (1·6 g.) was collected and washed with light petroleum. After 2 crystallisations from dilute alcohol, the required *compound* was obtained as colourless micro-needles, m. p. 360—361° (decomp.) (Found: C, 60·5; H, 3·6. $C_{11}H_8ON_2S$ requires C, 61·1; H, 3·7%). The ultra-violet light-absorption of this compound in alcohol showed maxima at 2500 A. (log ϵ 4·38), 3080 A. (log ϵ 3·81), 3200 A. (log ϵ 3·89), and 3380 A. (log ϵ 3·88).

4′-*Chloro*-6′-*methylpyridino*(2′ : 3′ : 6 : 7)*benzthiazole*.—The hydroxy-compound (0·5 g.) was heated for 1 hour under reflux with phosphorus oxychloride (10 c.c.), and the excess of oxychloride was then removed under reduced pressure. After being triturated with ether, the residue solidified. It was collected, washed with more ether, and ground with ammonia. The free *base* was collected, washed with water, and dried. Two crystallisations from alcohol yielded colourless needles (0·3 g.), m. p. 153° (Found: C, 56·4; H, 3·2. $C_{11}H_7N_2ClS$ requires C, 56·3; H, 3·0%). Attempts to condense this compound with 4-amino-1-diethylaminopentane were unsuccessful.

2 : 2′-*Diamino*-5 : 5′-*dicarbomethoxydiphenyl Disulphide*.—Methyl benzthiazole-6-carboxylate (0·7 g.) was refluxed in methyl alcohol (5 c.c.) with hydrazine hydrate (100% : 1·5 c.c.) for 3 hours and left overnight at room temperature. The deposited *disulphide* (0·5 g.) was collected and crystallised from methyl alcohol as brilliant yellow needles insoluble in sodium hydroxide; m. p. 193—194° (Found: C, 52·4; H, 4·3. $C_{16}H_{16}O_4N_2S_2$ requires C, 52·7; H, 4·5).

5 : 5′-*Dinitro*-2 : 2′-*diaminodiphenyl Disulphide*.—6-Nitrobenzthiazole (0·5 g.) was refluxed in absolute alcohol (3 c.c.) with hydrazine hydrate (100% : 1·0 c.c.) for 3 hours. Alcohol was removed under reduced pressure, and the residue was treated with water and filtered. The filtrate was made just acid with hydrochloric acid, and the yellow solid was collected (0·4 g.). On crystallisation from alcohol, the disulphide was obtained as yellow needles insoluble in sodium hydroxide; m. p. 222° (cf. Mylius, *loc. cit.*, who gives m. p. 237°) (Found: C, 42·6; H, 3·0. Calc. for $C_{12}H_{10}O_4N_4S_2$: C, 42·6; H, 3·0%).

2 : 2′-*Diamino*-5 : 5′-*dicyanodiphenyl Disulphide*.—6-Cyanobenzthiazole (0·65 g.), refluxed for 3 hours with hydrazine hydrate (100%, 1·3 c.c.) in absolute alcohol (3·0 c.c.), yielded a low-melting solid on cooling. After dilution with water, the solution was aspirated for several hours, and the precipitated product was collected. Two crystallisations from dilute alcohol gave the *disulphide* as yellow prisms, m. p. 188° (Found: C, 55·5; H, 3·9. $C_{14}H_{10}N_4S_2$ requires C, 56·3; H, 3·4%).

6 : 6′-*Diamino*-5 : 5′-*diquinolyl Disulphide*.—Pyridino(2′ : 3′ : 6 : 7)benzthiazole (V) (0·5 g.), refluxed for 3 hours with hydrazine hydrate (100%; 1 c.c.) in alcohol (3·0 c.c.), yielded an intensely orange solution from which, by operations as described above, an orange powder (0·4 g.) was obtained. This *disulphide* crystallised from alcohol as dark orange prisms, insoluble in sodium hydroxide, m. p. 240° (Found: C, 61·7; H, 4·2. $C_{18}H_{14}N_4S_2$ requires C, 61·7; H, 4·0%).

Pyridino(2′ : 3′ : 6 : 7)*benzthiadiazole* (XIII).—The disulphide (0·6 g.), in N-hydrochloric acid (10·5 c.c.), was diazotised with sodium nitrite (0·3 g.). This solution was added to boiling alcohol (50 c.c.) containing zinc dust (0·5 g.). After boiling for 15 minutes longer the alcohol was removed, and the residue was diluted with water and basified with ammonia, yielding a yellow solid (0·35 g.), m. p. 172°. The *thiadiazole* was crystallised twice from alcohol, and so obtained as very pale yellow needles, m. p. 182° (Found: C, 58·3; H, 3·0. $C_9H_5N_3S$ requires C, 57·7; H, 2·7%). It decomposed when heated above its m. p., and, on refluxing with zinc dust and mineral acid followed by basification, it yielded ammonia.

2 : 2′-*Diaminodiphenyl Disulphide* (" *Intramine* ").—Benzthiazole (10 g.), refluxed for 3 hours with hydrazine hydrate (100%; 20 c.c.) in alcohol (20 c.c.), and the alcohol removed, yielded after treatment

with hydrogen peroxide (100-vol.; 1·5 c.c.), a bright yellow solid (8·5 g.) which crystallised from dilute alcohol as lustrous yellow plates, m. p. 92° (Hofmann, *Ber.*, 1897, **12**, 2359, gives m. p. 93°) (Found: C, 57·6; H, 4·8. Calc. for $C_{12}H_{12}N_2S_2$: C, 58·0; H, 4·8%).

2-Hydrazinobenzthiazole.—2-Mercaptobenzthiazole (0·5 g.) was refluxed in alcohol (3·5 c.c.) with hydrazine hydrate (100%; 2 c.c.) for 3 hours. Ammonia and hydrogen sulphide were evolved, and on cooling, 2-hydrazinobenzthiazole was obtained which crystallised from dilute alcohol as yellow needles, m. p. 199·5° (D.R.-P. 614,327, *loc. cit.*) (Found: C, 51·3; H, 4·2. Calc. for $C_7H_7N_3S$: C, 51·0; H, 4·2%). The same compound was obtained when 2 : 2′-dibenzthiazolyl disulphide was similarly treated with hydrazine hydrate.

Attempted Formation of Pyridino(2′ : 3′ : 6 : 7)benzthiazole–Maleic Anhydride Adduct.—The quinthiazole (V) (0·2 g.), maleic anhydride (0·5 g.), and dry benzene (5·0 c.c.) were refluxed for **6** hours. After filtration from a little solid, hydrogen chloride was passed in, and a hydrochloride, m. p. 246—247°, was collected. This was refluxed in acetone with sodium acetate, the liquid filtered, and the residual sodium acetate extracted with several portions of boiling acetone. From the combined extracts, the original quinthiazole (0·15 g.), m. p. 158°, was recovered.

Reaction of Phenylhydrazine and Benzthiazole.—Benzthiazole (3·0 g.) was heated under reflux with varying amounts of freshly distilled phenylhydrazine for 6 hours. A vigorous reaction set in immediately on heating, and the ammonia evolved was collected in excess of N/10-sulphuric acid. The residual liquid in the reaction flask was distilled, and the benzene collected at 75—80° and characterised as nitrobenzene. The higher-boiling liquid was then dissolved in ether and extracted with 3 portions each of 5 c.c. of 10% hydrochloric acid. The ethereal layer was washed with water, dried (Na_2SO_4), and fractionated to yield benzthiazole, b. p. 225—230°. Its picrate had m. p. 167—168° undepressed by authentic benzthiazole picrate. The acid extract was basified and extracted with ether, from which aniline, b. p. 179—184°, and phenylhydrazine, b. p. 240—245°, were obtained by fractionation. The aniline was characterised as acetanilide and the phenylhydrazine as its benzylidene derivative.

Bromination of 6-Aminobenzthiazole.—A mixture of 6-aminobenzthiazole (0·5 g.), anhydrous sodium acetate (0·5 g.), and chloroform (0·5 c.c.) was cooled to 0°, and a solution of bromine (0·5 c.c.) in chloroform (5·0 c.c.) was slowly added. After 15 minutes, the solid was collected, and triturated with a solution of sodium hydrogen sulphite, then with a solution of sodium carbonate, and finally with water. The dried solid (0·3 g.) had m. p. 138°. After sublimation in a vacuum and crystallisation from dilute alcohol, a *monobromo*-compound was obtained as colourless needles, m. p. **145**—146° (Found: C, 36·9; H, 2·2. $C_7H_5N_2BrS$ requires C, 36·7; H, 2·2%).

In the absence of sodium acetate, another bromination yielded a crude product (0·1 g.), m. p. 95°. Repeated crystallisation from dilute alcohol yielded *7-bromo-6-aminobenzthiazole* as glistening needles, m. p. 119—120° (Found: C, 36·2; H, 2·3%). Bromination in acetic acid in absence of sodium acetate yielded an orange solid, m. p. 230°, which on being washed with sodium hydrogen sulphite and water yielded a mixture of the two bromo-compounds. From the acetic acid mother liquors, the higher-melting bromo-compound was obtained in pure condition. When 7-bromo-6-aminobenzthiazole (1 g.) was heated at 110° with 70% sulphuric acid (12 g.), sodium *m*-nitrobenzenesulphonate (4 g.), and glycerol (3 c.c.) for 12 hours, and the product isolated by basification and extraction with benzene, pyridino-(2′ : 3′ : 6 : 7)benzthiazole, m. p. 158—159° was obtained. When the higher-melting bromo-compound was treated under similar conditions, a new *bromo*-compound was obtained which crystallised from alcohol as needles, m. p. 223° (Found: C, 37·9; H, 2·0%). This has not been identified.

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