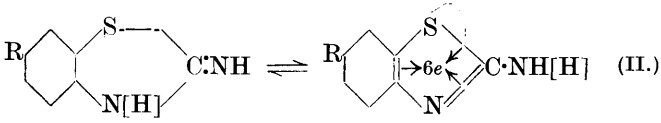
CCLXXXII.—*The Unsaturation and Tautomeric Mobility of Heterocyclic Compounds. Part III. The Effect of Substituents on the Mobility of the Aminobenzthiazole System and on the Bromination of* s-*Diarylthiocarbamides. The Ultra-violet Absorption of Mobile and of Static Semicyclic Amidines of the Benzthiazole Group.*

By ROBERT FERGUS HUNTER and JOHN WILLIAM THOMAS JONES.

IN a study of the tautomerism of substituted 1-aminobenzthiazoles with the object of ascertaining the effect of polar conditions on the behaviour of symmetrical semicyclic triad systems, the 5-substituted bases (I⇌II), in which the para-substituent to the nuclear nitrogen atom can act by virtue of electronic displacements partly similar to those which operate in aromatic substitution (Ingold, Shoppee, and Thorpe, J., 1926, 1477), were chosen as the starting point.

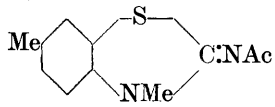


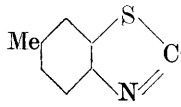
1-*Amino*-5-*methylbenzthiazole* (I⇌II; R = Me), which was examined in greater detail than the other compounds, satisfies the symmetry test of mobility (Ingold and Piggott, J., 1922, **121**, 2381) in that the hydrolysis of both 1-*imino*-2-*acetyl*-5-*methyl*-1 : 2-*dihydrobenzthiazole* (I; R = Me and with Ac in place of [H]) and 1-*acetamido*-5-*methylbenzthiazole* (II; R = Me and Ac in place of [H]), which were synthesised from the corresponding acetyl-*p*-tolylthiocarbamides (Hugershoff, *Ber.*, 1899, **32**, 3649; Wheeler, *Amer. Chem. J.*, 1902, **27**, 270) by treatment with bromine, yielded the same base (I⇌II; R = Me) (compare Hunter, J., 1926, 1385; Hunter and Styles, J., 1928, 3019).

On the other hand, methylation of this aminobenzthiazole by a variety of methods yielded solely 1-*imino*-2 : 5-*dimethyl*-1 : 2-*dihydrobenzthiazole* (I; R = Me and with Me in place of [H]), which we consider to be produced from the amino-aromatic form (II) by the addition of alkyl salt to the nuclear nitrogen atom, followed by elimination of the original " mobile " hydrogen atom in combination with an anion (Hunter and Styles, *loc. cit.*). No trace of the isomeric *methylamino*-derivative (II; R = Me and Me in place of [H]) was encountered (p. 2199).

We attribute this, first, to the greater lability of the unshared electrons of the double-bonded nitrogen atom in the amino-phase (II), and secondly, to the equilibrium in this (and probably also in other similar tautomeric systems) being almost wholly in favour of the aromatic form owing to the conjugating effect of the benzene nucleus of the benzthiazole complex on the double bond (1 : 2) of the amino-phase (II).

This view is supported by the behaviour of the base with phenylcarbimide, a reagent reputed to have very little disturbing effect on the equilibrium of mobile systems, since 1-amino-5-methylbenzthiazole yielded apparently only *one* condensation product (compare Fromm, *Annalen*, 1926, **447**, 259; Fromm and Kapeller-Adler, *ibid.*, 1928, **467**, 240), and also by a comparison of the ultra-violet absorptions of the base and of the static acetyl derivatives (III) and (IV).

(III.) 

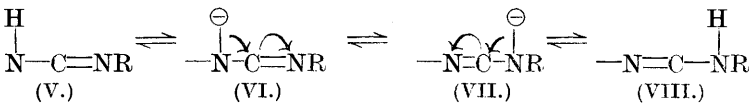


(IV.)

Moreover, 1-amino-5-methylbenzthiazole is acetylated exclusively in the amino-form by acetic anhydride, and its amino-group shows a general aromatic character, giving a diazonium salt which undergoes the Sandmeyer reaction, and provides thereby a convenient method of preparing 1-*chloro*-5-*methylbenzthiazole*.

The production of 1-amino-5-methylbenzthiazole by the hydrolysis of 1-imino-2-acetyl-5-methyl-1 : 2-dihydrobenzthiazole is then explicable by the fact that the iminodihydrobenzthiazole initially formed comes rapidly into equilibrium with the more stable aminobenzthiazole.

The application of the general expression for reversible isomeric change involving a hydrogen atom and an appropriately situated double bond, which has been elaborated by Ingold (*Ann. Reports*, 1927) on the basis of the behaviour of pseudo-acidic substances of this type (Lapworth, J., 1901, **79**, 1265; Branch and Jason-Deelman, *J. Amer. Chem. Soc.*, 1927, **49**, 1765), would necessitate formulating amidine mobility as involving, first, the ionisation of the $\alpha\beta$- or $\beta\gamma$-phases (V and VIII), and secondly, the establishment of an equilibrium between the anions (VI) and (VII).



(V.) (VI.) (VII.) (VIII.)

In the three-carbon system present in indene (Ingold and Piggott, J., 1923, **123**, 1470) and in the pentad keto-enol system studied

by Kon and Linstead and their pupils (J., 1925, **127**, 616; 1927, 262, 2579; *et cet.*), there is no doubt that the mobile hydrogen is acidic and that the ability of substituents to promote prototropic change runs more or less parallel with their degree of electron-attraction power (compare Shoppee, this vol., p. 968). In amidine systems of the type described in this paper, however, the compounds, far from showing any acidity, are highly basic : 1-amino-5-methylbenzthiazole can even be heated with sodium in xylene without change (p. 2198).

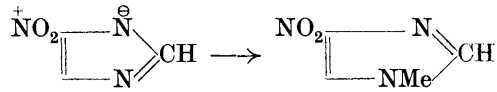
The methylation of 1-amino-5-ethoxybenzthiazole, 5-bromo-1-aminobenzthiazole, and 5-chloro-1-aminobenzthiazole (I⇌II; R = OEt, Br, and Cl respectively) proved analogous to that of 1-amino-5-methylbenzthiazole. These bases yielded the corresponding 5-substituted 1-*imino*-2-*methyl*-1 : 2-*dihydrobenzthiazoles* exclusively, no trace of the isomeric 1-*methylaminobenzthiazoles*, which were synthesised from the corresponding *p*-substituted *s*-phenylmethylthiocarbamides, being detected.

It was possible to apply the symmetry test of mobility only to the first of these cases, because *as*- and *s*-*p*-ethoxyphenylacetylthiocarbamide alone underwent ring formation under the influence of bromine, giving 1-*imino*-2-*acetyl*-5-*ethoxy*-1 : 2-*dihydrobenzthiazole* and 1-*acetamido*-5-*ethoxybenzthiazole* respectively; the p-*bromo*- and p-*chloro*-*phenylacetylthiocarbamides* proved incapable of ring closure.

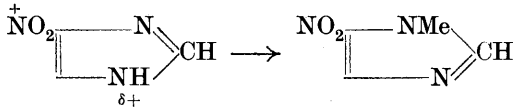
5-*Nitro*-1-*aminobenzthiazole* (I⇌II; R = NO_2), which is readily obtained by mononitration of 1-aminobenzthiazole (compare Bogert and Abrahamson, *J. Amer. Chem. Soc.*, 1922, **44**, 826) and the formula of which follows from its synthesis from *p*-nitrophenylthiocarbimide by way of the thiocarbamide, behaved similarly to the previous bases on methylation with methyl sulphate in the presence of alkali, yielding solely 5-*nitro*-1-*imino*-2-*methyl*-1 : 2-*dihydrobenzthiazole*, a result which had been anticipated in view of the fact that the methylation of 4(or 5)-methylglyoxaline gives 1 : 4- and 1 : 5-dimethylglyoxaline in the proportion of 2·2 : 1 (Pyman, J., 1910, **97**, 1814; 1922, **121**, 2616) whereas 4(or 5)-nitro-5(or 4)-methylglyoxaline gives 5-nitro-1 : 4-dimethylglyoxaline and 4-nitro-1 : 5-dimethylglyoxaline in the proportion of 233 : 1 (Pyman, J., 1923, **123**, 3365; compare also Hazeldine, Pyman, and Winchester, J., 1924, **125**, 1431).

Pyman's experiments indicate that the nitro-group attracts the double bond of the amidine system in the glyoxaline ring and that the methyl group repels it; on the other hand, the behaviour of β-methyl-β-ethylacrylic and β-ethylcinnamic acids indicates that in the three-carbon system the methyl group attracts the double bond, since the stable forms are the βγ-derivatives (Kon and Lin-

stead, J., 1925, **127**, 616; Johnson and Kon, J., 1926, 2748). The conjecture that this difference is due to the experiments on the amidine system being carried out in the absence of alkali whereas those on the three-carbon systems were made in the presence of a large concentration of hydroxyl ions is supported by the fact that, although the methylation of 4(or 5)-nitroglyoxaline with methyl sulphate in water yields 5-nitro-1-methylglyoxaline almost exclusively, in an alkaline medium the isomeric nitromethylglyoxalines are produced in the proportion of 1 : 0·33 in favour of the 4-nitro-1-methyl derivative (Forsyth and Pyman, J., 1925, **127**, 573). Possibly, in an alkaline medium, the anion (IX) is methylated mainly in this form because the positive nitro-group attracts the

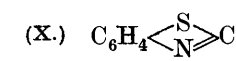
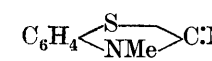
(IX.) 

negative ionic charge. In the absence of alkali, however, ionic dissociation is not favoured and the small positive charge which is to be found at the point of attachment of an ionisable hydrogen atom is repelled by the positive nitro-group, with the result that the glyoxaline reacts to give mainly the 5-nitro-1-methyl derivative.



The almost overwhelming tendency for semicyclic amidines containing aromatic heterocyclic nuclei to react in the aromatic form (Tschitschibabin and Konowalowa, *Ber.*, 1921, **54**, 814; Forsyth and Pyman, J., 1926, 2502) is doubtless due to the greater stability of this form (II), and to the fact that in it the sextuple group (Armit and Robinson, J., 1925, **127**, 1605; Goss and Ingold, J., 1928, 1268; Ingold, *Ann. Reports*, 1928, 119) can be formed without calling on the lone pair of electrons of the nuclear nitrogen atom, which are therefore available for salt formation (compare Bamberger, *Ber.*, 1891, **24**, 1758; 1893, **26**, 1946; *Annalen*, 1893, **273**, 373).

Methylation of 1-anilinobenzthiazole, however, gave a mixture of 1-*phenylmethylaminobenzthiazole* (X) and 1-*phenylimino*-2-*methyl*-1 : 2-*dihydrobenzthiazole* (XI) in the approximate proportion of 1 : 2.

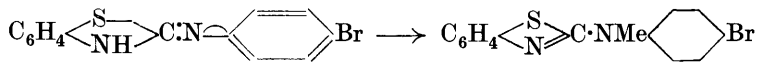
(X.)   (XI.)

This reactivity in the iminodihydro-phase, leading to the 1-methylamino-derivative, is evidently due to the conjugating effect of the phenyl group in the anilino-substituent (compare Linstead and

Williams, J., 1926, 2735), which competes with the benzene nucleus in the benzthiazole system for the double bond (1 : 2) of the aromatic phase (compare Young and Crookes, J., 1906, **89**, 59; Forsyth and Pyman, J., 1926, 2506).

The ultra-violet absorption curve of 1-anilinobenzthiazole in alcohol resembles the curves of 1-amino-5-methylbenzthiazole and 1-acetomethylamido-5-methylbenzthiazole at equimolecular concentrations for wave-lengths between 2450 and 2700 Å.U. and simulates the absorption curve of 1-acetimido-2 : 5-dimethyl-1 : 2-dihydrobenzthiazole from 2800 to 3300 Å.U. (see fig.).

The conjugating effect of the anilino-substituent in 1-anilinobenzthiazole appears to be further enhanced in the case of 4′-bromo-1-anilinobenzthiazole, which reacts with methyl sulphate apparently wholly as 4′-*bromo*-1-*phenylimino*-1 : 2-*dihydrobenzthiazole* (XII), giving the 4′-*bromo*-1-*phenylmethylamino*-base (XIII).



(XII.) (XIII.)

The Structure of the Thiocarbamides, the Mechanism of Benzthiazole Syntheses from Arylthiocarbamides and Bromine, and the Effect of Substituents on the Bromination of Thiocarbanilide Derivatives.

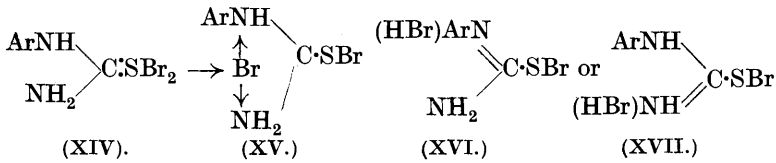
The remarkable generality of the synthesis of 1-aminobenzthiazoles from arylthiocarbamides and bromine (see Part I, this vol., p. 127, footnote, where complete references are given) in contrast to the benzthiazole syntheses recorded in the literature prior to 1925 makes the question of the mechanism of this reaction of considerable interest.

The oxidation of tetrasubstituted thiocarbamides to disulphide derivatives (Lecher, *Annalen*, 1925, **445**, 36) invalidates the arguments in favour of the classical formula, $NH_2 \cdot C(SH){:}NH$, for thiocarbamide, which rests essentially on the oxidation of thiocarbamides containing a hydrogen atom to disulphides. The *X*-ray analysis of thiocarbamide itself (Hendrick, *J. Amer. Chem. Soc.*, 1928, **50**, 2455) indicates, moreover, that the crystalline form of the compound has the thioamide structure, $CS(NH_2)_2$. The salts of the thiocarbamides (Dixon, J., 1917, **111**, 318), such as the hydrobromide of thiocarbamide, can therefore be formulated

$$[(NH_2)_2C{:}\overset{+}{S}H]\bar{B}r,$$

and are evidently the reactive units in the classical experiments on the oxidation of the compounds. The possibility of thiocarbamides being alkylated by way of the thioamide form to give *S*-alkyl derivatives was suggested by Dixon and Taylor eighteen years ago (J., **101**, 2502).

Probably the first action of bromine on an arylthiocarbamide in an inert solvent is the formation of a dibromide (XIV) derived from the thioamide phase, and is followed by the migration of bromine as ion to the nitrogen atoms. The salt (XV) produced could yield either of the tautomerides (XVI) and (XVII) by incipient loosening of hydrogen bromide, elimination of which in a subsequent stage would give rise to a benzthiazole or a 1 : 2-dihydrobenzthiazole.

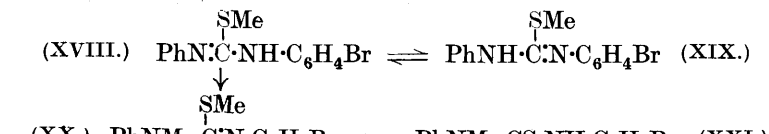


(XIV). (XV.) (XVI.) (XVII.)

The possibility of an arylthiocarbamide reacting in the thiol form cannot, however, be ignored. In a monosubstituted thiocarbanilide, for instance, ring closure being assumed to take place on the unsubstituted nucleus, bromination of the tautomerides $PhN{:}C(SH)\cdot NH\cdot C_6H_4X$ and $PhNH\cdot C(SH){:}N\cdot C_6H_4X$ would lead to the production of a 4′-substituted 1-anilinobenzthiazole and a 4′-substituted 1-phenylimino-1 : 2-dihydrobenzthiazole respectively : *s*-*p*-bromodiphenylthiocarbamide, for example, could yield 4′-bromo-1-anilinobenzthiazole or 4′-bromo-1-phenylimino-1 : 2-dihydrobenzthiazole. Since it gives the 4′-bromo-base (Dyson, Hunter, and Soyka, J., 1929, 458), evidence in favour of the mechanism involved can been obtained by an examination of its products of methylation. The first product of methylation was the expected *S*-methyl derivative (XVIII $\rightleftharpoons$ XIX), and since there is no good reason to suppose that the replacement of the hydrogen atom of the thiol group by methyl will affect the equilibrium in the amidine system

$$PhN{:}C(SH)\cdot NH\cdot C_6H_4Br \rightleftharpoons PhNH\cdot C(SH){:}N\cdot C_6H_4Br,$$

the necessary inferences can be drawn from the behaviour of this derivative. It reacted exclusively in the form (XVIII), yielding S-*methyl*-s-*phenylmethyl*-p-*bromophenylthiocarbamide* (XX), whose constitution follows from its synthesis from s-*phenylmethyl*-p-*bromophenylthiocarbamide* (XXI), which was synthesised from methylaniline and *p*-bromophenylthiocarbimide.



(XVIII.) (XIX.) (XX.) (XXI.)

The inference to be drawn from these experiments is that, in whatever tautomeric form an arylthiocarbamide may react with

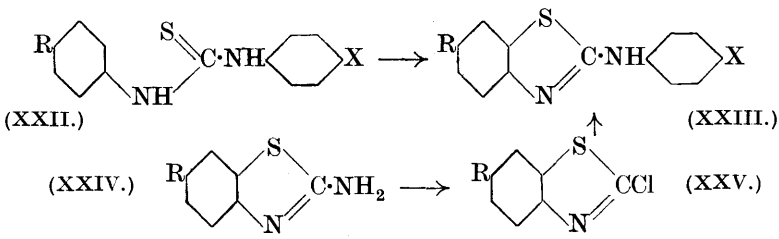
bromine in an inert solvent, the benzthiazole will be produced in the amino-aromatic form.

On this basis a study was made of the effect of substituents on the direction of ring closure in different substituted thiocarbanilides.

In the bromination of *p*-substituted *s*-diphenylthiocarbamides (XXII, R = H; X = NO_2, Cl, Br, EtO) and *p*-substituted *s*-phenyl-*p*-tolylthiocarbamides (XXII, R = Me; X = NO_2, Br, EtO), ring closure invariably took place either on the unsubstituted benzene ring or on the nucleus containing the methyl group, yielding the corresponding 4′-*substituted* 1-*anilinobenzthiazoles* (XXIII, R = H; X = NO_2, Cl, Br, EtO) or 4′-*substituted* 1-*anilino*-5-*methylbenzthiazoles* (XXIII, R = Me; X = NO_2, Br, EtO).

From these results and from the bromination of s-p-*chloro*-p′-*bromo*-, s-p-*nitro*-p′-*bromo*-, and s-p-*bromo*-p′-*ethoxy-diphenylthiocarbamides* (XXII, R = Br, X = Cl; R = Br, X = NO_2; R = EtO, X = Br), which give rise to the corresponding 4′-*chloro*-, 4′-*nitro*-, and 4′-*bromo-benzthiazoles*, the polar series NO_2>Cl>Br>EtO>Me can be inferred.

The anilinobenzthiazoles (XXIII) obtained from the bromination of these thiocarbanilides containing unsymmetrical substituents (XXII) were oriented by means of reactions indicated in the following scheme, advantage being taken of the application of the Sandmeyer reaction to nuclear-substituted 1-aminobenzthiazoles (XXIV):



Attempts were made to orient some of the benzthiazoles by degradative oxidation, but it was found that, unlike the *iso*thiazole nucleus (Reissert and Mann, *Ber.*, 1928, **61**, 1308), the benzthiazole complex resists the attack of all but the most violent reagents, by which deep-seated decompositions are produced.

The reactivity of the chlorine atom in 1-chlorobenzthiazoles shown in the condensation of these substances with aromatic amines (Hofmann, *Ber.*, 1879, **12**, 1126; Hunter and Jones, this vol., p. 941) is perhaps due to the unusually high temperatures of reaction which are possible on account of the high boiling points of the compounds. The true reactivity of the chlorine atom in such compounds is

indicated by the slowness of their hydrolysis to hydroxybenzthiazoles (Hunter, this vol., p. 135).

The bromination of thiocarbamide in carbon disulphide has also been investigated. Under the conditions described on p. 2211, an ill-defined red *perbromide* separates, which rapidly decomposes on exposure to air, evolving hydrogen bromide and yielding a residue of the *bromo*-derivative which is obtained by carrying out the reaction in an alcoholic medium (Claus, *Annalen*, 1875, **179**, 134).

EXPERIMENTAL.

Mobility of 5-Substituted 1-Aminobenzthiazoles.

1-Amino-5-methylbenzthiazole (I⇌II; R = Me). *Synthesis from* as-*Acetyl*-p-*tolylthiocarbamide and from* s-*Acetyl*-p-*tolylthiocarbamide by Way of 1-Imino-2-acetyl-5-methyl*-1 : 2-*dihydrobenzthiazole and 1-Acetamido-5-methylbenzthiazole.*—*as*-Acetyl-*p*-tolylthiocarbamide was prepared by dissolving *p*-tolylthiocarbamide (4 g.) in acetic anhydride (16 c.c.) at 80° and immediately cooling the solution to 0°. After being dried on porous earthenware in a vacuum over potassium hydroxide, it had m. p. 142° (Hugershoff, *Ber.*, 1899, **32**, 3649, recorded m. p. 137°).

A solution of the labile acetylthiocarbamide (5 g.) in chloroform (20 c.c.) was treated with bromine (4 c.c. in 4 c.c. of the same solvent) at 0°, and the bromo-addition compound was reduced with sulphurous acid in the usual way. *1-Imino-2-acetyl-5-methyl*-1 : 2-*dihydrobenzthiazole* separated from ethyl acetate in small yellow prisms, m. p. 192° (Found : S, 15·7. $C_{10}H_{10}ON_2S$ requires S, 15·4%). It was heated under reflux with concentrated hydrochloric acid for 24 hours, and the solution neutralised; the 1-amino-5-methylbenzthiazole obtained was identified by m. p. and mixed m. p. determinations (Hunter, J., 1926, 1399).

The *hydrotribromide* obtained by heating a solution of *s*-acetyl-*p*-tolylthiocarbamide (1 g.) in chloroform (10 c.c.) and bromine (1 c.c.) under reflux on a steam-bath for a few minutes crystallised in orange prisms, m. p. 149° (decomp.) after drying in a vacuum [Found : Br, 53·7. $C_{10}H_{10}ON_2S,HBr(Br_2)$ requires Br, 53·8%]. On reduction with sulphurous acid, it yielded *1-acetamido-5-methylbenzthiazole*, which separated from alcohol–ethyl acetate in colourless prisms, m. p. 216°, and was identical with the product of direct acetylation of 1-amino-5-methylbenzthiazole by acetic anhydride (Found : S, 15·6%). The acetamidomethylbenzthiazole was completely hydrolysed by heating with concentrated hydrochloric acid for 3 hours; the amino-base was identified as in the previous case.

Methylation of 1-Amino-5-methylbenzthiazole and the Synthesis of 1-Acetimido-2 : 5-dimethyl-1 : 2-*dihydrobenzthiazole from* as-p-*Tolyl*-

methylthiocarbamide and from 1-*Acetamido-5-methylbenzthiazole, and the Synthesis of* 1-*Methylamino-5-methylbenzthiazole from* s-p-*Tolylmethylthiocarbamide.*—(i) A suspension of 5 g. of 1-amino-5-methylbenzthiazole in water (50 c.c.) was shaken with 10 c.c. of methyl sulphate; after ½ hour, the mixture was treated with excess of 25% sodium hydroxide solution and extracted with chloroform. The oil obtained by removal of the chloroform could not be induced to crystallise; it was therefore acetylated with acetic anhydride. The product, fractionally crystallised from ethyl acetate, gave 1·15 g. of 1-acetamido-5-methylbenzthiazole (m. p. and mixed m. p. 216°) and 3·72 g. of 1-*acetimido*-2 : 5-*dimethyl*-1 : 2-*dihydrobenzthiazole*, which separated in small prisms, m. p. 168° (Found : S, 14·6. $C_{11}H_{12}ON_2S$ requires S, 14·5%). No trace of the isomeric 1-acetomethylamido-5-methylbenzthiazole could be detected.

(ii) A mixture of 1-amino-5-methylbenzthiazole (2 g.) and methyl iodide (3 c.c.) was heated for 10 hours at 100°. A portion of the product was decomposed by alkali and extracted with chloroform, and the resulting oil acetylated; fractional crystallisation of the product yielded solely the acetimidodimethyl derivative. The remainder of the original methylation product (consisting of nearly pure hydriodide of 1-imino-2 : 5-dimethyl-1 : 2-dihydrobenzthiazole), on recrystallisation from hot alcohol, formed needles, m. p. 290° (decomp. with efferv.), and was identical with the *hydriodide* obtained from the iminodimethyldihydro-base and dilute hydriodic acid (Found : I, 41·1. $C_9H_{10}N_2S,HI$ requires I, 41·5%). A similar experiment in which 1-amino-5-methylbenzthiazole was heated with methyl iodide at 100° for an hour indicated that methylation was almost complete in this time.

(iii) 1-*Amino-5-methylbenzthiazole methosulphate* was prepared by concentrating a solution of 1-amino-5-methylbenzthiazole (1 g.), methyl sulphate (1 c.c.), and methyl alcohol (10 c.c.) on a steam-bath; it crystallised from methyl alcohol in needles, m. p. 160° (Found : S, 22·3. $C_{10}H_{14}O_4N_2S_2$ requires S, 22·2%). The constitution of this methosulphate follows from the fact that its aqueous solution gives the reaction for sulphate ion with barium chloride, and gives an immediate precipitate of 1-imino-2 : 5-dimethyl-1 : 2-dihydrobenzthiazole hydriodide on treatment with a saturated aqueous solution of potassium iodide.

(iv) No dissolution of sodium was observed on heating a mixture of 1-amino-5-methylbenzthiazole (1 g.), xylene (20 c.c.), and sodium (0·5 g.) under reflux for 6 hours. 1·5 G. of powdered sodamide were therefore added to 5 g. of 1-amino-5-methylbenzthiazole in 15 c.c. of warm xylene, and the mixture was heated at 130—140° for 40 minutes under reflux, ammonia being evolved. The mixture was

then cooled, the semi-solid mass obtained was treated with 4 c.c. of methyl iodide (added through the condenser), and the heating was continued for a further 15 minutes. The yellow solid which separated was collected, treated with alkali, and extracted with chloroform. Acetylation of the oil obtained by removal of the chloroform, followed by recrystallisation of the product, yielded 1·25 g. of 1-acetimido-2 : 5-dimethyl-1 : 2-dihydrobenzthiazole accompanied by a certain amount of 1-acetamido-5-methylbenzthiazole. A careful search for 1-acetomethylamido-5-methylbenzthiazole in a similar experiment proved fruitless.

(v) as-p-*Tolylmethylthiocarbamide* was prepared by heating a solution of methyl-*p*-toluidine hydrochloride (1 mol.) and potassium thiocyanate (1 mol.) in water for 12 hours; on recrystallisation from benzene–ligroin, the thiocarbamide formed small prisms, m. p. 109° (Found: S, 17·9. $C_9H_{12}N_2S$ requires S, 17·8%). *Bromination.* A solution of *as*-tolylmethylthiocarbamide (0·5 g.) in chloroform (5 c.c.) was treated with bromine (0·5 c.c.) and the mixture was heated under reflux for 10 minutes, cooled, shaken with excess of sulphurous acid, and basified with ammonia. The oil obtained by extraction with chloroform was acetylated with acetic anhydride; 1-acetimido-2 : 5-dimethyl-1 : 2-dihydrobenzthiazole was then obtained, m. p. 168° alone or when mixed with the specimen already described.

(vi) 0·2 G. of 1-acetamido-5-methylbenzthiazole was heated with 3 c.c. of methyl sulphate for 10 minutes, the solution treated with excess of aqueous ammonia (*d* 0·880), and the product recrystallised from alcohol; 1-acetimido-2 : 5-dimethyl-1 : 2-dihydrobenzthiazole was obtained, m. p. 167°, and 168° when mixed with the specimens described in (i) and (v).

(vii) s-p-*Tolylmethylthiocarbamide.* A solution of *p*-tolylthiocarbimide in absolute alcohol was treated with a 30% excess of a 33% solution of methylamine in the same solvent, and the mixture was concentrated on a steam-bath. On recrystallisation from alcohol, the *thiocarbamide* formed needles, m. p. 126° (Found: S, 18·0. $C_9H_{12}N_2S$ requires S, 17·8%). *Bromination.* The *p*-tolylmethylthiocarbamide (2 g.) in chloroform (15 c.c.) was treated with bromine (3·6 c.c. in 15 c.c. of chloroform) and the solution was heated under reflux for 15 minutes and cooled. The *hydrotetrabromide* of 1-methylamino-5-methylbenzthiazole crystallised in orange-red needles, m. p. 90° (decomp.) after drying in a vacuum [Found: Br (total), 64·0; Br (labile), 49·0. $C_9H_{10}N_2S,HBr(Br_3)$ requires Br (total), 64·2; Br (labile), 48·2%]. On treatment with sulphurous acid and thereafter with ammonia, the hydrotetrabromide yielded 1-*methylamino*-5-*methylbenzthiazole*, which crystal-

*

lised from alcohol in plates, m. p. 152° (Found : S, 17·8. $C_9H_{10}N_2S$ requires S, 18·0%). The hydrotetrabromide underwent nuclear substitution when heated in alcoholic solution, yielding a hydrobromide from which a monobromomethylamino-base was obtained; this separated from methyl alcohol in plates, m. p. 165° (Found : Br, 31·4. $C_9H_9N_2BrS$ requires Br, 31·1%). This base was proved to be 3-*bromo*-1-*methylamino*-5-*methylbenzthiazole* by means of the following synthesis : *m*-Bromo-*p*-toluidine ⟶ *s*-di-*m*-bromo-*p*-tolylthiocarbamide ⟶ *m*-bromo-*p*-tolylthiocarbimide ⟶ *s*-*m*-bromo-*p*-tolylmethylthiocarbamide ⟶ 3-bromo-1-methylamino-5-methylbenzthiazole.

s-*Di*-m-*bromo*-p-*tolylthiocarbamide* was prepared by heating a mixture of *m*-bromo-*p*-toluidine (80 g.), carbon disulphide (75 c.c.), alcohol (60 c.c.), and sulphur (2—3 g.) (compare Hugershoff, *Ber.*, 1899, **32**, 2245) under reflux for 5 hours. On recrystallisation from alcohol, it formed needles (50 g.), m. p. 163° (Found : S, 7·5. $C_{15}H_{14}N_2Br_2S$ requires S, 7·6%).

m-*Bromo*-p-*tolylthiocarbimide* was obtained by heating a mixture of *s*-di-*m*-bromo-*p*-tolylthiocarbamide (10 g.) and acetic anhydride (12 c.c.) for 2 minutes (compare Werner, J., 1891, **59**, 396), pouring the liquid into hot water, and isolating the thiocarbimide by distillation in steam. The pale yellow oil (4 g.) solidified on keeping, and separated from methyl alcohol in prisms, m. p. 53° (Found : Br, 35·3. C_8H_6NBrS requires Br, 35·1%). s-m-*Bromo*-p-*tolylmethylthiocarbamide*, obtained by condensation with methylamine in alcohol, crystallised from ethyl acetate in prisms, m. p. 162° (Found : S, 12·6. $C_9H_{11}N_2BrS$ requires S, 12·4%). Bromination of this compound in chloroform yielded 3-bromo-1-methylamino-5-methylbenzthiazole, m. p. 165° alone and when mixed with the specimen already described.

Bromination of 1-methylamino-5-methylbenzthiazole itself in chloroform solution with excess of bromine yielded a *hydrotribromide* of 3-bromo-1-methylamino-5-methylbenzthiazole; this formed red needles, m. p. 137° (decomp.) [Found : Br (total), 64·0; Br (labile), 33·0. $C_9H_9N_2BrS,HBr(Br_2)$ requires Br (total), 64·3; Br (labile), 32·2%].

1-*Acetomethylamido*-5-*methylbenzthiazole* crystallised from ethyl acetate in needles, m. p. 162° (Found : S, 14·5. $C_{11}H_{12}ON_2S$ requires S, 14·5%).

Interaction of 1-*Amino*-5-*methylbenzthiazole with Phenylcarbimide.*—The carbimide (2 c.c.) was added to a solution of the amino-base (2 g.) in absolute alcohol (10 c.c.) and the mixture was heated on a steam-bath and cooled; 1·6 g. of s-5-*methylbenzthiazolylphenylcarbamide* then separated in white prisms, m. p. *ca.* 310° (Found :

S, 11·7. $C_{15}H_{13}ON_3S$ requires S, 11·3%). Concentration of the mother-liquor furnished unchanged amino-base.

An attempt to prepare *s*-phenylcarbamyl-*p*-tolylthiocarbamide for conversion into *s*-5-methylbenzthiazolylphenylcarbamide by bromination proved unsuccessful, *p*-tolylthiocarbamide and phenylcarbimide being recovered unchanged after being heated together at 80—90°.

1-*Amino*-5-*ethoxybenzthiazole* (I⇌II; R = OEt). *Synthesis from* as-*Acetyl*-p-*ethoxyphenylthiocarbamide and from* s-*Acetyl*-p-*ethoxyphenylthiocarbamide by Way of* 1-*Imino*-2-*acetyl*-5-*ethoxy*-1 : 2-*dihydrobenzthiazole and* 1-*Acetamido*-5-*ethoxybenzthiazole*.—The *hydrotetrabromide* obtained from 4 g. of *as*-acetyl-*p*-ethoxyphenylthiocarbamide (m. p. 144°; Hugershoff, *loc. cit.*, gives m. p. 137°), chloroform (30 c.c.), and bromine (3 c.c. in 6 c.c. of chloroform) at 0° formed orange prisms, m. p. 139° (decomp.) [Found: Br, 57·6. $C_{11}H_{12}O_2N_2S,HBr(Br_3)$ requires Br, 57·5%]. 1-*Imino*-2-*acetyl*-5-*ethoxy*-1 : 2-*dihydrobenzthiazole*, obtained by reduction with sulphurous acid, separated from ethyl acetate in yellow needles, m. p. 147° (Found: S, 14·0. $C_{11}H_{12}O_2N_2S$ requires S, 13·6%), and yielded 1-amino-5-methylbenzthiazole on hydrolysis with concentrated hydrochloric acid. 1-*Acetamido*-5-*ethoxybenzthiazole*, prepared by bromination of *s*-acetyl-*p*-ethoxyphenylthiocarbamide (1 g.; 10 c.c. of chloroform; 1 c.c. of bromine; time of heating, 10 minutes), crystallised from ethyl acetate in needles, m. p. 244° alone and when mixed with the product of acetylation of 1-amino-5-ethoxybenzthiazole (Found: S, 13·3. $C_{11}H_{12}O_2N_2S$ requires S, 13·6%).

Methylation of 1-*Amino*-5-*ethoxybenzthiazole and the Synthesis of* 1-*Methylamino*-5-*ethoxybenzthiazole from* s-p-*Ethoxyphenylmethylthiocarbamide*.—(i) A solution of 5 g. of 1-amino-5-ethoxybenzthiazole in methyl sulphate (10 c.c.) was heated under reflux on a steam-bath for 10 minutes; the mixture was made alkaline with sodium hydroxide, and heating continued for a further 10 minutes. The crude product (4·9 g., m. p. 140°) on recrystallisation from methyl alcohol gave long straw-coloured needles of 1-*imino*-5-*ethoxy*-2-*methyl*-1 : 2-*dihydrobenzthiazole*, m. p. 147° (Found: S, 15·0. $C_{10}H_{12}ON_2S$ requires S, 15·4%); no trace of the isomeric methylamino-base could be detected.

s-p-*Ethoxyphenylmethylthiocarbamide*, obtained from *p*-ethoxyphenylthiocarbimide and methylamine, crystallised from alcohol in prisms, m. p. 129° (Found: S, 15·3. $C_{10}H_{14}ON_2S$ requires S, 15·2%).

1-*Methylamino*-5-*ethoxybenzthiazole*, obtained by bromination of this thiocarbamide, crystallised in white prisms, m. p. 145° (Found: S, 14·8. $C_{10}H_{12}ON_2S$ requires S, 15·4%).

5-Bromo-1-aminobenzthiazole (I⇌II; R = Br).—as-*Acetyl*-p-*bromophenylthiocarbamide* was obtained by dissolving *p*-bromophenylthiocarbamide (rapidly) in acetic anhydride (4 parts) at 80°. When the solution was cooled, the labile thiocarbamide separated in small prisms, m. p. 157°, which isomerised to the stable compound at its m. p. (Found : S, 12·4. $C_9H_9ON_2BrS$ requires S, 11·7%). s-*Acetyl*-p-*bromophenylthiocarbamide* was easily obtained by heating a mixture of *p*-bromophenylthiocarbamide and acetic anhydride at 80° without any precautions; it crystallised in large prisms, m. p. 205° (Found : S, 12·0%).

The action of bromine on these acetyl-*p*-bromophenylthiocarbamides appeared to be of an oxidising nature, since the products were free from sulphur (compare *p*-acetylphenylthiocarbamide; Dyson, Hunter, and Morris, J., 1927, 1192). (i) Bromine was gradually added to a suspension of *s*-acetyl-*p*-bromophenylthiocarbamide in alcohol until the yellow colour persisted; the mixture then became warm and the thiocarbamide dissolved. On keeping, white needles, m. p. 234°, separated which were identical with the *substance* obtained by brominating *s*-acetyl-*p*-bromophenylthiocarbamide in chloroform and reducing the product with sulphurous acid in the usual way (Found : Br, 35·2%). (ii) Perhydrol (4 c.c.) was added to a solution of the acetyl-*p*-bromophenylthiocarbamide in glacial acetic acid (1 g. in 30 c.c.); slight darkening occurred on warming, and white needles separated which proved to be identical with the product obtained in (i).

Methylation of 5-bromo-1-aminobenzthiazole. The 5-bromo-base (10 g.) was heated under reflux on a steam-bath with 30 c.c. of methyl sulphate for ½ hour, and the excess of methyl sulphate decomposed with alkali. A gum was obtained which gradually solidified (9·2 g., m. p. 100—104°). On recrystallisation, this yielded 5-bromo-1-imino-2-methyl-1 : 2-dihydrobenzthiazole identical with that already described (this vol., p. 140). Acetylation of the crude methylation product yielded 5-bromo-1-acetimido-2-methyl-1 : 2-dihydrobenzthiazole, m. p. 219°, identical with the specimen already described (*loc. cit.*) (Found : Br, 28·0. Calc. : Br, 28·1%).

5-Chloro-1-aminobenzthiazole (I⇌II; R = Cl).—as-*Acetyl*-p-*chlorophenylthiocarbamide* formed small prisms, m. p. 157° (Found : S, 14·3. $C_9H_9ON_2ClS$ requires S, 14·0%). s-*Acetyl*-p-*chlorophenylthiocarbamide* formed needles, m. p. 186° (Found : S, 14·4%). Bromination of the stable compound yielded a *substance*, m. p. 227°, which was free from sulphur and yielded *p*-chloroaniline on being hydrolysed by hydrochloric acid for 6 hours.

Methylation of 5-Chloro-1-aminobenzthiazole and the Synthesis of 5-Chloro-1-methylaminobenzthiazole.—(i) A solution of 5-chloro-1-

aminobenzthiazole (1 g.) in 4 c.c. of methyl sulphate and 10 c.c. of alcohol was heated on a steam-bath for 10 minutes, potassium hydroxide (2 g.) added, and the reaction controlled by cooling; the mixture was then diluted with water and extracted with chloroform. The gum obtained by removal of the chloroform was acetylated with acetic anhydride, and the product recrystallised from alcohol, 0·8 g. of *5-chloro-1-acetimido-2-methyl-1 : 2-dihydrobenzthiazole* being obtained in tufts of needles, m. p. 197° (Found : S, 13·5. $C_{10}H_9ON_2ClS$ requires S, 13·3%). (ii) s-p-*Chlorophenylmethylthiocarbamide* separated from dilute methyl alcohol in plates, m. p. 147° (Found : Cl, 17·9; S, 16·2. $C_8H_9N_2ClS$ requires Cl, 17·7; S, 16·0%). *5-Chloro-1-methylaminobenzthiazole*, obtained by bromination of the chlorophenylmethylthiocarbamide, separated from alcohol–ethyl acetate in slender needles, m. p. 214° (Found : Cl, 18·2; S, 16·3. $C_8H_7N_2ClS$ requires Cl, 17·9; S, 16·1%). The *acetyl* derivative, which could not be detected in the material obtained by acetylating the methylation product of 5-chloro-1-aminobenzthiazole, formed plates, m. p. 175° (Found : Cl, 14·6. $C_{10}H_9ON_2ClS$ requires Cl, 14·8%).

5-Nitro-1-aminobenzthiazole (I $\rightleftharpoons$ II; R = NO_2).—(i) A mixture of 1 g. of *p*-nitrophenylthiocarbamide, chloroform (10 c.c.), and bromine (1 c.c.) was heated under reflux, and the bromo-addition compound was reduced with sulphurous acid. The *5-nitro-base* separated from ethyl acetate as an orange microcrystalline powder, m. p. 243° (Found : S, 15·9. $C_7H_5O_2N_3S$ requires S, 16·4%). The *acetyl* derivative formed a pale yellow, microcrystalline powder, m. p. 292° (Found : S, 13·4. $C_9H_7O_3N_3S$ requires S, 13·5%).

(ii) 10 G. of 1-aminobenzthiazole were gradually added to 60 c.c. of nitric acid (*d* 1·5), kept below 5° by means of a freezing mixture. The solution was poured into 600 c.c. of water and made alkaline with ammonia and the precipitated nitro-base was crystallised from ethyl acetate; it had m. p. 242°, and 242—243° when mixed with the specimen described under (i).

Methylation of 5-Nitro-1-aminobenzthiazole and the Nitration of 1-Imino-2-methyl-1 : 2-dihydrobenzthiazole and of 1-Methylaminobenzthiazole.—(i) A solution of the 5-nitro-base (1 g.) in 4 c.c. of methyl sulphate and 10 c.c. of alcohol was heated on a steam-bath and basified, yielding 1·05 g. of a yellow solid, m. p. 140°, readily soluble in alcohol, from which it separated as an orange powder, m. p. 150°. A mixture of this with 5-nitro-1-imino-2-methyl-1 : 2-dihydrobenzthiazole obtained by nitration of the imino-methyldihydrobenzthiazole (compare Hunter, this vol., p. 130) had m. p. 157°. Difficulties in recrystallisation (these substances separate as powders on concentration) prevented the removal of

the impurity which lowered the m. p., but the absence of the isomeric 5-nitro-1-methylamino-base was indicated by the absence of insoluble material.

(ii) 1-Imino-2-methyl-1 : 2-dihydrobenzthiazole (1 g.) was gradually added to nitric acid (*d* 1·5) at 0°, and the product recrystallised from alcohol, *5-nitro-1-imino-2-methyl-1 : 2-dihydrobenzthiazole* being obtained as a pale yellow, microcrystalline powder, m. p. 167° (Found : S, 15·6. $C_8H_7O_2N_3S$ requires S, 15·3%). The *acetyl* derivative formed pale yellow needles, m. p. 292° (Found : S, 12·2. $C_{10}H_9O_3N_3S$ requires S, 12·6%).

(iii) *5-Nitro-1-methylaminobenzthiazole* was prepared by nitration of 1-methylaminobenzthiazole (Hunter, J., 1926, 1385) as in the case of the iminomethyldihydrobenzthiazole. It formed a pale yellow powder, m. p. 272°, which was sparingly soluble in alcohol (Found : S, 15·1. $C_8H_7O_2N_3S$ requires S, 15·3%). The *acetyl* derivative formed small, pale yellow needles, m. p. 241° (Found : S, 12·6. $C_{10}H_9O_3N_3S$ requires S, 12·6%).

Mobility of 1-Anilinobenzthiazoles.

1-Anilinobenzthiazole.—1-Anilinobenzthiazole (1 g.) was heated with 4 c.c. of methyl sulphate on a steam-bath until solution took place (10 minutes); 10 c.c. of 20% potassium hydroxide solution were then added and the mixture was kept for 15 minutes, cooled, and extracted with ether. The oil obtained by removal of the ether was dissolved in acetone, a solution of picric acid (1·2 g.) in the same solvent added, and the mixture kept; 0·83 g. of 1-phenylmethylaminobenzthiazole picrate separated in pale yellow prisms (yield, 36%), m. p. 184°, and 184—185° when mixed with the synthetic specimen described below. The residue, consisting of *1-phenylimino-2-methyl-1 : 2-dihydrobenzthiazole picrate*, formed easily soluble, yellow prisms, m. p. 112° (decomp.) (Found : S, 6·7. $C_{14}H_{11}N_2S,C_6H_3O_7N_3$ requires S, 6·8%). The presence of the *picrate* of 1-anilinobenzthiazole, which forms sparingly soluble, yellow needles, m. p. 223° (Found : S, 7·2. $C_{13}H_9N_2S,C_6H_3O_7N_3$ requires S, 7·0%), could not be detected.

1-Phenylmethylaminobenzthiazole. Hofmann's method of preparing 1-chlorobenzthiazole from phenylthiocarbimide and phosphorus pentachloride at 160° (*Ber.*, 1879, **12**, 1126) is somewhat inconvenient, and the chlorothiazole can be readily prepared from 1-aminobenzthiazole by the Sandmeyer reaction as follows. A mixture of 10 g. of 1-aminobenzthiazole, 70 c.c. of water, and 5 g. of sodium nitrite was rubbed in a mortar, cooled to 0°, and gradually treated with 10 c.c. of concentrated hydrochloric acid; after 5 minutes, the mixture was added to 150 c.c. of concentrated hydro-

chloric acid and boiled and the chlorobenzthiazole (2·7 g.) was isolated by distillation in steam.

A mixture of 1 g. of 1-chlorobenzthiazole and 1 c.c. of methylaniline was heated until a vigorous reaction took place. When the product was basified with ammonia, a non-crystallisable gum was obtained, which was dissolved in warm acetone and converted into the picrate in the usual way. *1-Phenylmethylaminobenzthiazole picrate* crystallised in hard yellow prisms, m. p. 185° (Found: S, 6·8. $C_{14}H_{11}N_2S,C_6H_3O_7N_3$ requires S, 6·8%).

4′-Bromo-1-anilinobenzthiazole.—The yield of 4′-bromo-1-anilinobenzthiazole obtained from *p*-bromo-*s*-diphenylthiocarbamide (Dyson, Hunter, and Soyka, J., 1929, 458) was improved by carrying out the bromination in carbon disulphide, a suspension of 1 g. of the thiocarbamide in carbon disulphide (10 c.c.) being treated with bromine (1 c.c.) and heated under reflux for 5 minutes.

Methylation. (i) 1 G. of 4′-bromo-1-anilinobenzthiazole was heated with 3 c.c. of methyl sulphate, the solution made alkaline with ammonia, and the product collected and fractionally crystallised from ethyl acetate. The first crop of crystals (0·61 g.), m. p. 215°, consisted of unchanged material. The second crop, m. p. 103°, formed long needles, which gave a picrate identical with that obtained from synthetic 4′-bromo-1-phenylmethylaminobenzthiazole.

(ii) By suspending 1 g. of 4′-bromo-1-anilinobenzthiazole in 20 c.c. of water and adding successively 5 c.c. of methyl sulphate and 2 g. of solid potassium hydroxide, complete methylation was effected. The product crystallised from alcohol in needles, m. p. 105° (Found: Br, 25·3. $C_{14}H_{11}N_2BrS$ requires Br, 25·1%), and was proved to be *4′-bromo-1-phenylmethylaminobenzthiazole* by means of the synthesis described hereunder. No isomeric bromophenyliminomethyldihydro-derivative was detected.

4′-Bromo-1-phenylmethylaminobenzthiazole picrate. A mixture of 0·6 g. of 1-chlorobenzthiazole was heated with *p*-bromomethylaniline until effervescence took place. The purple uncrystallisable gum produced was dissolved in acetone and converted into the picrate, which formed small yellow needles, m. p. 242°, identical with that obtained in the methylation described above (Found: S, 5·9. $C_{14}H_{11}N_2BrS,C_6H_3O_7N_3$ requires S, 5·8%).

The Effect of Substituents on the Formation of Arylaminobenzthiazoles from Nuclear-substituted Thiocarbanilides.

(1) *Monosubstituted Thiocarbanilides.*

Bromination of p-*Ethoxy*-s-*diphenylthiocarbamide and the Synthesis of 4′-Ethoxy-1-anilinobenzthiazole from 1-Chlorobenzthiazole and* p-*Phenetidine.*—(i) p-*Ethoxy*-s-*diphenylthiocarbamide*, prepared by

condensation of equimolecular proportions of phenylthiocarbimide and *p*-phenetidine in alcohol, separated from alcohol in soft white plates, m. p. 148° (Found : S, 11·8. $C_{15}H_{16}ON_2S$ requires S, 11·8%).

(ii) A solution of the ethoxydiphenylthiocarbamide (0·5 g.) in carbon disulphide (5 c.c.) was treated with bromine (0·7 c.c.) and heated under reflux for 5 minutes; a bromo-addition compound separated as a red oil which solidified on cooling. On reduction with sulphurous acid and basification with ammonia, this gave a white solid, which crystallised from ethyl acetate in prisms, m. p. 166° alone and when mixed with the 4′-*ethoxy*-1-*anilinobenzthiazole* described below.

(iii) A mixture of 1-chlorobenzthiazole (0·8 g.) and *p*-phenetidine (0·7 g.) was heated over a flame until a violent reaction took place. The product was ground with aqueous ammonia and recrystallised from ethyl acetate, the ethoxyanilinobenzthiazole being obtained in small prisms, m. p. 165° (Found : S, 11·6. $C_{15}H_{14}ON_2S$ requires S, 11·8%).

Bromination of p-*Nitro*-s-*diphenylthiocarbamide and the Synthesis of* 4′-*Nitro*-1-*anilinobenzthiazole from* 1-*Chlorobenzthiazole and* p-*Nitroaniline.*—(i) p-*Nitro*-s-*diphenylthiocarbamide*, prepared from *p*-nitrophenylthiocarbimide and aniline in alcohol, crystallised in pale yellow plates, m. p. 141° (Found : S, 12·0. $C_{13}H_{11}O_2N_3S$ requires S, 11·7%).

(ii) A suspension of the nitrodiphenylthiocarbamide (0·5 g.) in chloroform (10 c.c.) was treated with bromine (1 c.c.), heated under reflux for 10 minutes, cooled, and concentrated under reduced pressure at laboratory temperature; the oily bromo-addition compound produced then gradually crystallised. On reduction with sulphurous acid (in chloroform), the nitro-base was obtained; it separated from alcohol as an orange powder, m. p. 205°. The acetyl derivative, obtained by treatment with acetic anhydride, separated from ethyl acetate as a pale yellow powder, m. p. 172°.

(iii) 4′-*Nitro*-1-*anilinobenzthiazole*, obtained from 1-chlorobenzthiazole and *p*-nitroaniline, had m. p. 212° after recrystallisation from alcohol (Found : S, 12·1. $C_{13}H_{11}O_2N_3S$ requires S, 11·7%), and melted at 207° when mixed with the specimen described under (ii). The *acetyl* derivative had m. p. 180° (Found : S, 10·4. $C_{15}H_{13}O_3N_3S$ requires S, 10·2%), and 175° when mixed with the specimen described under (ii).

Synthesis of 1-*Anilino*-5-*methylbenzthiazole from* 1-*Chloro*-5-*methylbenzthiazole and Aniline and of* 1-*Anilino*-4′-*methylbenzthiazole from* 1-*Chlorobenzthiazole and* p-*Toluidine, and the Bromination of* s-*Phenyl*-p-*tolylthiocarbamide.*—(i) 1-*Chloro*-5-*methylbenzthiazole.* A mixture

of 15 g. of *p*-tolylthiocarbimide and 22 g. of phosphorus pentachloride was heated in a sealed tube at 170° for 6 hours (compare Hofmann, *loc. cit.*), and the product fractionated under reduced pressure, 3 g. of the *chloromethylbenzthiazole* being obtained, b. p. 148—152°/15 mm. (Found: Cl, 19·6. C_8H_6NClS requires Cl, 19·4%). The chloromethylbenzthiazole was more conveniently prepared from 1-amino-5-methylbenzthiazole by the Sandmeyer reaction. A solution of 5 g. of 1-amino-5-methylbenzthiazole in concentrated hydrochloric acid (25 c.c.) and water (15 c.c.) was cooled to 0° and treated with 2·3 g. of sodium nitrite in water (5 c.c.); 50 c.c. of concentrated hydrochloric acid were then added and the mixture was boiled for 5 minutes. On neutralisation and distillation in steam, 0·8 g. of the chloromethylbenzthiazole was obtained.

A mixture of 1-chloro-5-methylbenzthiazole (0·9 g.) and aniline (0·5 g.) was heated until effervescence took place and the gummy product was basified with ammonia. 1-*Anilino*-5-*methylbenzthiazole* crystallised from benzene in needles, m. p. 158° (Found: S, 13·6. $C_{14}H_{12}N_2S$ requires S, 13·3%). The *picrate* was fairly easily soluble in acetone, from which it separated in small yellow crystals, m. p. 216° (Found: S, 6·7. $C_{14}H_{12}N_2S,C_6H_3O_7N_3$ requires S, 6·8%).

(ii) 1-*Anilino*-4′-*methylbenzthiazole*, obtained in a similar manner from 1-chlorobenzthiazole and *p*-toluidine, separated from alcohol in slender needles, m. p. 177° (Found: S, 13·7%). The *picrate* formed sparingly soluble, pale yellow needles, m. p. 238° (Found: S, 7·0%).

(iii) Bromination of *s*-phenyl-*p*-tolylthiocarbamide in chloroform and in carbon disulphide gave products melting indefinitely between 145° and 200°, from which neither of the expected anilinobenzthiazoles could be isolated.

(2) *Disubstituted Thiocarbanilides.*

Bromination of s-p-*Ethoxyphenyl*-p-*tolylthiocarbamide and the Synthesis of* 1-*Anilino*-4′-*ethoxy*-5-*methylbenzthiazole.*—(i) s-p-*Ethoxyphenyl*-p-*tolylthiocarbamide*, prepared by condensation of *p*-tolylthiocarbimide with *p*-phenetidine in alcoholic solution, crystallised in soft white plates, m. p. 137° (Found: S, 11·0. $C_{16}H_{18}ON_2S$ requires S, 11·2%).

(ii) The thiocarbamide (1 g.) in chloroform (10 c.c.) was treated with bromine (1 c.c.) and the mixture was heated for *one* minute, cooled, shaken with sulphurous acid, and basified with ammonia, and the product recrystallised from alcohol–ethyl acetate; the 1-anilino-4′-ethoxy-5-methylbenzthiazole obtained was identified by m. p. and mixed m. p. determination with the specimen described

below. In a similar experiment in which carbon disulphide (10 c.c.) was used as the solvent and the heating was continued for 3 minutes, a bromo-substitution product was obtained, which separated from alcohol–ethyl acetate in hard white prisms, m. p. 156°; this was probably 3-*bromo*-1-*anilino*-4′-*ethoxy*-5-*methylbenzthiazole* (Found : S, 8·9. $C_{16}H_{15}ON_2BrS$ requires S, 8·8%).

(iii) Condensation of *p*-phenetidine with 1-chloro-5-methylbenzthiazole yielded 1-*anilino*-4′-*ethoxy*-5-*methylbenzthiazole*, which separated from ethyl acetate in small crystals, m. p. 171° (Found : S, 11·4. $C_{16}H_{16}ON_2S$ requires S, 11·3%).

Bromination of s-p-*Bromophenyl*-p-*tolylthiocarbamide and the Synthesis of* 4′-*Bromo*-1-*anilino*-5-*methylbenzthiazole.*—(i) s-p-*Bromophenyl*-p-*tolylthiocarbamide*, prepared from *p*-tolylthiocarbimide and *p*-bromoaniline, crystallised in white plates, m. p. 187° (Found : S, 10·2. $C_{14}H_{13}N_2BrS$ requires S, 10·0%).

(ii) The base obtained by bromination of this thiocarbamide (0·5 g.; carbon disulphide, 5 c.c.; time of heating, *one* minute) formed long needles, m. p. 209°, from alcohol–ethyl acetate, and was identical with the 4′-*bromo*-1-*anilino*-5-*methylbenzthiazole* described below (Found : Br, 24·8. $C_{14}H_{11}N_2BrS$ requires Br, 25·1%). The picrate was obtained as a yellow flocculent precipitate from a hot acetone solution of the base and had m. p. 251° (decomp.).

(iii) The thiazole obtained by condensation of 1-chloro-5-methylbenzthiazole with *p*-bromoaniline was identified with the base described under (ii) by m. p. and mixed m. p. determinations. The *picrate* obtained from it had m. p. 250° (decomp.), alone and when mixed with the specimen already described (Found : S, 5·9. $C_{14}H_{11}N_2BrS,C_6H_3O_7N_3$ requires S, 5·8%).

Bromination of s-p-*Nitrophenyl*-p-*tolylthiocarbamide and the Synthesis of* 4′-*Nitro*-1-*anilino*-5-*methylbenzthiazole.*—(i) s-p-*Nitrophenyl*-p-*tolylthiocarbamide*, prepared from *p*-nitrophenylthiocarbimide and *p*-toluidine, crystallised in yellow needles, m. p. 175° (Found : S, 11·2. $C_{14}H_{13}O_2N_3S$ requires S, 11·1%).

(ii) The insoluble 4′-*nitro*-1-*anilino*-5-*methylbenzthiazole* produced by treatment of the thiocarbamide with bromine was purified by boiling with alcohol and was obtained as an orange-coloured powder, m. p. 265° (Found : S, 11·1. $C_{14}H_{11}O_2N_3S$ requires S, 11·2%).

(iii) The same benzthiazole was obtained from the gum formed by fusion of *p*-nitroaniline and 1-chloro-5-methylbenzthiazole and was identified by m. p. and mixed m. p. determinations with the product described under (ii).

Bromination of s-p-*Bromo*-p′-*ethoxydiphenylthiocarbamide and the Synthesis of* 5-*Bromo*-1-*anilino*-4′-*ethoxybenzthiazole.*—(i) s-p-*Bromo*-p′-*ethoxydiphenylthiocarbamide*, prepared from *p*-bromophenylthio-

carbimide and *p*-phenetidine, crystallised from alcohol in soft white plates, m. p. 169° (Found: S, 9·3. $C_{15}H_{15}ON_2BrS$ requires S, 9·1%).

(ii) The bromoethoxydiphenylthiocarbamide (1 g.) was treated in chloroform (10 c.c.) with 1·3 c.c. of bromine, and the mixture boiled for *one* minute. The base produced by reduction with sulphurous acid crystallised from ethyl acetate in white needles, m. p. 198° (Found: Br, 23·2. $C_{15}H_{13}ON_2BrS$ requires Br, 22·9%). Its constitution as 4′-*bromo*-1-*anilino*-5-*ethoxybenzthiazole* is deduced from its non-identity with the isomeric 5-bromo-1-anilino-4′-ethoxybenzthiazole which was rationally synthesised as described in (iii). In an almost identical experiment in which carbon disulphide was used as the solvent instead of chloroform and heating was continued for 5 minutes, a product was obtained which separated from ethyl acetate in small crystals, m. p. 226°, and was probably 3 : 4′-*dibromo*-1-*anilino*-5-*ethoxybenzthiazole* (Found: Br, 36·1. $C_{15}H_{12}ON_2Br_2S$ requires Br, 37·2%).

(iii) The following is a more convenient synthesis of 1-chloro-5-bromobenzthiazole than the method of heating *p*-bromophenylthiocarbimide and phosphorus pentachloride under pressure described by Dyson, Hunter, and Soyka (J., 1929, 458). 5-Bromo-1-aminobenzthiazole (15 g.) was suspended in a mixture of 50 c.c. of water and 10 c.c. of concentrated hydrochloric acid at 0° and diazotised with sodium nitrite (7 g.) in water (20 c.c.). Concentrated hydrochloric acid (100 c.c.) was then added, the mixture boiled for 5 minutes, and the chlorobromobenzthiazole (2·3 g.) isolated by distillation in steam.

5-*Bromo*-1-*anilino*-4′-*ethoxybenzthiazole*, prepared by fusing the chlorobromobenzthiazole with *p*-phenetidine, separated from ethyl acetate in small plates contaminated with a purple impurity which could not be removed completely by recrystallisation; m. p. 199° (Found: Br, 22·9. $C_{15}H_{13}ON_2BrS$ requires Br, 22·9%).

A number of attempts to apply the Sandmeyer reaction to 1-amino-5-ethoxybenzthiazole with the object of preparing 1-chloro-5-ethoxybenzthiazole for the rational synthesis of 4′-bromo-1-anilino-5-ethoxybenzthiazole were unsuccessful.

Bromination of s-p-*Chloro*-p′-*bromodiphenylthiocarbamide and the Synthesis of* 4′-*Chloro*-5-*bromo*-1-*anilinobenzthiazole*.—(i) s-p-*Chloro*-p′-*bromodiphenylthiocarbamide*, prepared from *p*-bromophenylthiocarbimide and *p*-chloroaniline, separated from alcohol in long white prisms, m. p. 187° (Found: S, 9·7. $C_{13}H_{10}N_2ClBrS$ requires S, 9·4%).

(ii) The chlorobromodiphenylthiocarbamide (1 g.) in carbon disulphide (10 c.c.) was treated with bromine (1·3 c.c.), and the

mixture heated under reflux for 15 minutes. *4′-Chloro-5-bromo-1-anilinobenzthiazole* separated from alcohol in woolly needles, m. p. 218° (0·1760 g. gave 0·1680 g. of mixed silver halides. $C_{13}H_8N_2ClBrS$ requires 0·1720 g.).

(iii) The condensation product obtained from 1-chloro-5-bromobenzthiazole and *p*-chloroaniline was basified and recrystallised from alcohol; it then formed woolly needles, m. p. 217° alone and when mixed with the specimen described under (ii).

Bromination of s-p-*Bromo*-p′-*nitrodiphenylthiocarbamide and the Synthesis of 5-Bromo-4′-nitro-1-anilinobenzthiazole.*—(i) s-p-*Bromo*-p′-*nitrodiphenylthiocarbamide*, prepared from *p*-nitrophenylthiocarbimide and *p*-bromoaniline, formed yellow needles, m. p. 186° (Found : S, 9·0. $C_{13}H_{10}O_2N_3BrS$ requires S, 9·1%).

(ii) A mixture of the thiocarbamide (0·5 g.), chloroform (6 c.c.), and bromine (0·5 c.c.) was boiled under reflux for 8 minutes. The precipitated oil, which solidified, was reduced and basified in the usual way; the *5-bromo-4′-nitro-1-anilinobenzthiazole* obtained separated from alcohol as a microcrystalline yellow powder, m. p. 258° (Found : Br, 22·8. $C_{13}H_8O_2N_3BrS$ requires Br, 22·8%).

(iii) Bromonitroanilinobenzthiazole obtained from 1-chloro-5-bromobenzthiazole and *p*-nitroaniline had m. p. 259°, and 258—259° when mixed with the specimen obtained from the bromonitrodiphenylthiocarbamide.

Mobility of the Triad (Prototropic) Systems of the Thiocarbamide Complex.

Methylation of s-p-*Bromodiphenylthiocarbamide and* S-*Methyl*-s-p-*bromodiphenylthiocarbamide and the Synthesis of* S-*Methyl*-s-*phenylmethyl*-p-*bromophenylthiocarbamide from* p-*Bromophenylthiocarbimide and Methylaniline by Way of* s-*Phenylmethyl*-p-*bromophenylthiocarbamide.*—(i) S-*Methyl*-s-p-*bromodiphenylthiocarbamide*, $C_6H_4Br{\cdot}NH{\cdot}C(SMe){:}NPh$. A mixture of 4 g. of *s-p*-bromodiphenylthiocarbamide, alcohol (4 c.c.), and methyl iodide (1·5 c.c.) was heated under reflux on a steam-bath until solution took place (10 minutes). The product was basified with sodium carbonate solution and extracted with chloroform, the S-*methyl* derivative being obtained. This compound crystallised in long, white, waxy needles, m. p. 78° (Found : Br, 24·4. $C_{14}H_{13}N_2BrS$ requires Br, 24·9%), and was very soluble in all ordinary solvents. On being heated with mineral acids, it decomposed, yielding methyl mercaptan.

(ii) S-*Methyl*-s-*phenylmethyl*-p-*bromophenylthiocarbamide*,

$$C_6H_4Br{\cdot}N{:}C(SMe){\cdot}NMePh.$$

S-Methyl-*s-p*-bromodiphenylthiocarbamide was recovered unchanged after being heated with methyl iodide. 2 G. of this

S-methylthiocarbamide were therefore heated with 3 c.c. of methyl sulphate on a steam-bath for 15 minutes. Sodium carbonate solution was then added and after ½ hour the mixture was extracted with chloroform; removal of the chloroform furnished a gum which gradually crystallised. S-*Methyl*-s-*phenylmethyl*-p-*bromophenylthiocarbamide* formed soft prisms, m. p. 93° (Found: Br, 23·7. $C_{15}H_{15}N_2BrS$ requires Br, 23·9%).

(iii) s-*Phenylmethyl*-p-*bromophenylthiocarbamide*, prepared by condensing equimolecular quantities of *p*-bromophenylthiocarbimide and methylaniline, crystallised from alcohol in white prisms, m. p. 156° (Found: Br, 24·6. $C_{14}H_{13}N_2BrS$ requires Br, 24·9%).

(iv) *Methylation of* s-*phenylmethyl*-p-*bromophenylthiocarbamide*. 2 G. of the carbamide were heated on a steam-bath with 2 c.c. of methyl sulphate and 10 c.c. of alcohol for 5 minutes; the mixture was basified with sodium carbonate solution and extracted with chloroform. The gum obtained by removal of the chloroform crystallised in waxy needles, m. p. 88°, and 90° when mixed with the specimen of the *S*-methyl derivative described under (ii). On treatment with mineral acids, *S*-methyl-*s*-phenylmethyl-*p*-bromophenylthiocarbamide decomposed with liberation of methyl mercaptan.

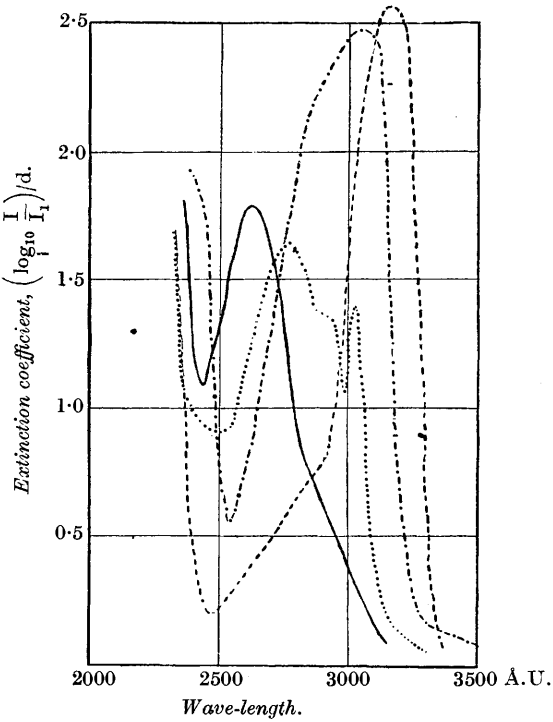
Bromination of Thiocarbamide.

Claus's Bromo-derivative.—(i) Bromine was added to a solution of thiocarbamide (0·5 g.) in alcohol (15 c.c.) until the yellow colour persisted (absorption approx. 0·3 c.c.); white prisms then separated which had m. p. 191° (decomp. with efferv.) (Claus, *loc. cit.*, gives m. p. 176°). (ii) Bromine (1 c.c.) was added to a suspension of thiocarbamide (1 g.) in carbon disulphide (10 c.c.); a red *perbromide* then separated which was collected on porous earthenware. On exposure in the laboratory, this product decomposed with evolution of hydrogen bromide, yielding a colourless residue, m. p. 178°, which melted at 182° when mixed with the specimen described under (i) (Found: S, 19·7. Calc. for CH_3N_2BrS: S, 20·7%). It dissolved readily in cold water, in which the apparent molecular weight was 87 (*w*, 0·132 g.; *W*, 10·87 g.; depression, 0·26°. CH_3N_2BrS requires *M*, 155). An aqueous solution (acid to litmus) gave with silver nitrate solution a precipitate which decomposed into silver bromide and silver sulphide on being heated.

Absorption Spectra Measurements.

The aminobenzthiazoles were purified by repeated crystallisation and dried at 100°. Equimolecular solutions were made in absolute alcohol and a specimen of the alcohol was placed in the alternative path of the photometer.

After preliminary experiments, each solution was diluted with an equal volume of alcohol, and the dilutions were examined in cells, 2 cm. thick, under identical conditions with a Judd–Lewis sector photometer in conjunction with a Hilger E 3 quartz spectrograph. The concentrations were : (I) 1-amino-5-methylbenzthiazole, 0·0200 g./l.; (II) 1-acetomethylamido-5-methylbenzthiazole, 0·0268 g./l.; (III) 1-acetimido-2 : 5-dimethyl-1 : 2-dihydrobenzthiazole, 0·0268



g./l.; (IV) 1-anilinobenzthiazole, 0·0276 g./l. The results are in the following table, where ε denotes the extinction coefficient, and λ the wave-lengths in Å.U. of the maxima and minima on the curves (see fig.).

	I.		II.				III.		IV.	
Log ε	1·8	1·1	1·4	1·05	1·64	0·9	2·58	0·2	2·48	0·55
λ, max.	2662		3029		2780		3165		3050	
λ, min.		2437		2990		2500		2490		2545

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