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CLXXIX.—*Aminobenzthiazoles. Part III. The Tautomerism and Unsaturation of the Aminothiazole System.*

By Robert Fergus Hunter.

As one of the three objects * of this investigation (see Part I, J., 1925, **127**, 2023), the mobility of the symmetrical triad system

$$[H]\cdot N\cdot C\therefore N \rightleftharpoons N\therefore C\cdot N[H]$$

* A fourth object, *viz.*, the study of the relation between unsaturation and mobility in tautomeric triad systems of the aminothiazole type, is of particular interest in connexion with the whole philosophical aspect of tautomerism involving a mobile hydrogen atom (compare Thorpe, J., 1923, **123**, 1361; Kon, Stevenson, and Thorpe, J., 1922, **121**, 650), and will be fully dealt with in a later paper. In the 5-bromo-1-alkylaminobenzthiazoles, the increasing molecular volume of the alkyl group in the ethyl, *n*-propyl, *n*-butyl, *iso*butyl series tends to enhance the aminothiazole phase of the system, and consequently to increase the stability of the dibromo-addition compounds. Indeed, in the ethyl series Mr. Soyka and myself were able

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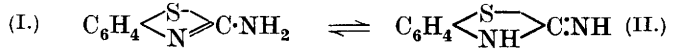
in 1-amino- and substituted 1-aminobenzthiazoles has been examined, with the result that the tautomerism of the 1-aminobenzthiazole system (I) with the corresponding 1-imino-1 : 2-dihydrobenzthiazole complex (II) has been established.



(I.) (II.)

There are three tests for the mobility of symmetrical triad systems (Ingold and Piggott, J., 1922, **121**, 2381; 1923, **123**, 1470): (A) The symmetry test, (B) the fission test, and (C) the substitution test (compare also Farrow and Ingold, J., 1924, **125**, 2543). Only the first and third of these tests are applicable to the system under discussion. There exists already in the literature of 1-aminobenzthiazole evidence of the symmetry type. Thus, whilst the classical synthesis of this compound from 1-chlorobenzthiazole (Hofmann, *Ber.*, 1879, **12**, 1126) is usually regarded as a proof of the constitution (I), its synthesis from phenylthiosemicarbazide (Fischer and Besthorn, *Annalen*, 1882, **212**, 326) * can be formulated only in terms of the iminodihydro-structure (II).

The symmetry test, however, was more definitely established by the synthesis of 1-acetylaminobenzthiazole (VII) and 1-*imino*-2-*acetyl*-1 : 2-*dihydrobenzthiazole* (VIII) from the *bromides* (V) and (VI), respectively, which were obtained by bromination of the stable and labile forms of acetylphenylthiocarbamide (Hugershoff, *Ber.*, 1899, **32**, 3649; Wheeler, *Amer. Chem. J.*, 1902, **27**, 270; Hunter, *loc. cit.*). On hydrolysis, the two isomeric acetyl derivatives

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to isolate both forms of the dibromide, which must be regarded as being of the type $[H]NBr_2{\cdot}C{:}NEt$ and $NBr_2{:}C{\cdot}N[H]Et$, respectively. These forms were strikingly different in physical properties and in their reducibility by hydriodic acid (compare West, J., 1924, **125**, 710 and other papers). Both gave the same ethylamino-base on reduction with sulphurous acid and, moreover, the labile form was converted into the more stable form by boiling for some time with a mixture of bromine and chloroform. This conversion shows that it is at least probable that at some stage an equilibrium $[H]NBr_2{\cdot}C{:}NEt \rightleftharpoons NBr_2{:}C{\cdot}N[H]Et$, which is apparently a case of retarded mobility (Kon and Linstead, J., 1925, **127**, 815) involving quinquevalent nitrogen, may occur. In view of this, it has seemed desirable to institute a series of experiments on the bromination both of mobile and of "nascently" mobile (compare Goss and Ingold, J., 1925, **127**, 2776) systems of the amidine type.

In the bromination of *s*-di-*β*-naphthylthiocarbamide in chloroform (J., 1925, **127**, 2270) two forms of the hexabromide of 2-*β*-naphthylamino-*α*-naphthathiazole were accidentally isolated, and only one of these was obtained by bromination of the naphthathiazole base itself.

* Fischer and Besthorn's "phenylthiocarbazine," obtained by the action of 20% hydrochloric acid on phenylthiosemicarbazide at 125—130°, was shown by Hugershoff (*Ber.*, 1903, **36**, 3134) to be 1-aminobenzthiazole.

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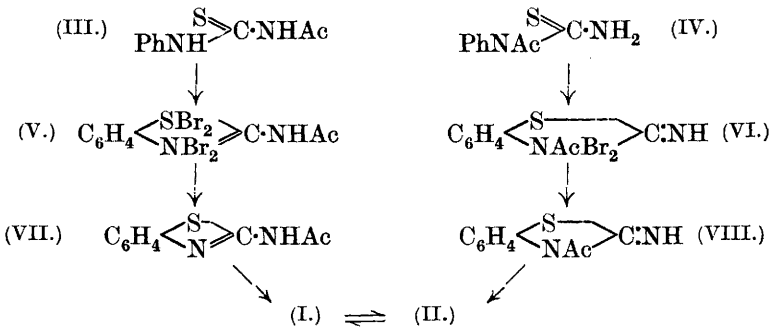
(VII and VIII) yielded the same 1-aminobenzthiazole (or 1-imino-1 : 2-dihydrobenzthiazole).



With regard to the third test (C), it was found that 1-aminobenzthiazole methylates almost exclusively in the imino-form (II), yielding 1-*imino*-2-*methyl*-1 : 2-*dihydrobenzthiazole* (XI), whose constitution was established by rational synthesis from *as*-methylphenylthiocarbamide (IX) by way of the *dibromide* (X). During the methylation a more soluble isomeride was also produced. This, owing to experimental difficulties, could not be obtained pure, but it was undoubtedly 1-*methylaminobenzthiazole* (XIV), which was also synthesised from *s*-methylphenylthiocarbamide (XII) by way of the *tetrabromide* (XIII). [Formulæ IX, X, and XI are IV, VI, and VIII, respectively, and XII, XIII, and XIV are III, V, and VII, respectively, all with Me in place of Ac.]

The ethylation of 1-aminobenzthiazole proved more troublesome than the methylation. The bulk of the product was, however, finally identified as 1-*imino*-2-*ethyl*-1 : 2-*dihydrobenzthiazole*, whose constitution was established by its synthesis from *as*-ethylphenylthiocarbamide by way of the *tetrabromo*-addition compound as in the case of the corresponding methyl derivative.

The acetylation of 1-aminobenzthiazole was studied in the hope of isolating both acetyl derivatives (VII and VIII). The base acetylated almost completely in the amino-form (I), giving 1-acetylaminobenzthiazole, and although on several occasions the presence of a small amount of a low-melting acetyl derivative was observed, the second isomeride could not be isolated pure.

The substitution test (C), therefore, supports the symmetry test (A), since with a reagent favouring the imino-form, the triad system reacts almost completely in this form, the methyl group attaching itself almost exclusively to the less basic nitrogen atom (Marckwald, *Annalen*, 1895, **286**, 343; von Pechmann, *Ber.*, 1895, **28**, 869, 2362; 1897, **30**, 1779; Cohen and Marshall, J., 1910, **97**, 328), whilst with

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acetic anhydride, which favours the amino-form, the amidine system reacts almost completely in the latter form, yielding the 1-acetylamino-derivative.

Although experimental difficulties prevented the isolation in a pure condition of two methyl or ethyl derivatives, there can be no doubt that in both cases both alkyl derivatives were actually present, for Pyman has shown (J., 1923, **121**, 367, 3359) that, on alkylation, an amidine whose two nitrogen atoms differ in basicity invariably yields two alkyl derivatives, a very small quantity of the isomeride corresponding to the more basic form of the amidine accompanying a large quantity of the more readily formed alkyl derivative. The two nitrogen atoms in the aminothiazole system differ considerably in basicity, this being shown by the base acetylating almost completely in the more basic form.

Mobility in 1-aminobenzthiazole having thus been established, the general chemistry of the substance was studied. The base was readily converted into an unstable diazonium chloride, which coupled with β-naphthol in the usual way. Attempts to convert the diazonium chloride into 1-hydroxybenzthiazole, however, invariably yielded 1-*aminoazobenzthiazole hydrochloride*,

$$C_6H_4\!<\!\overset{S-}{N}\!>\!C\cdot N_2\cdot C_6H_3\!<\!\overset{S-}{N}\!>\!C\cdot NH_2,HCl$$

(compare Hantzsch and Popp, *Annalen*, 1889, **250**, 257).

The aminothiazole appeared to react in the normal way with formaldehyde and acetaldehyde, but pure condensation products could not be isolated. Attempts to condense the base with benzaldehyde failed. This is readily understood, however, since the formation of the benzylidene derivative would involve the removal of both the mobile hydrogen atom and the potentially mobile hydrogen atom of the triad system.

The base benzoylated normally, giving 1-*benzoylaminobenzthiazole*, which on treatment with an excess of bromine yielded a *tetrabromide* (formula as V). Under the influence of dilute alcohol this yielded 5-*bromo*-1-*benzoylaminobenzthiazole*. The fact that the presence of a benzoyl group only allows the formation of a tetrabromide in circumstances in which 1-acetylaminobenzthiazole readily passes into a *hexabromide* is probably to be attributed to the steric effect of the phenyl group in the benzoylamino-residue.

1-Aminobenzthiazole reacts very readily with sodium hypochlorite, yielding a deep purple dye of the rosaniline type.

On treating 1-aminobenzthiazole hydrochloride with alcoholic ethyl nitrite, neither the expected 1-imino-2-nitroso-1 : 2-dihydrobenzthiazole nor benzthiazole itself was produced, but the *hydrochloride* of a new base, isomeric with 1-aminobenzthiazole, which

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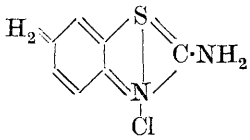
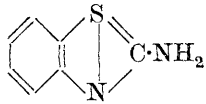
crystallised in beautiful ruby-red prisms. The *base* itself was very pale yellow. A similar reaction was observed in the cases of 1-amino-3-methyl- and 1-amino-5-methyl-benzthiazole. Possibly the intensely coloured hydrochloride and the base may have formulæ (XV) and (XVI)), respectively (compare Kehrmann, *Ber.*, 1906, **39**, 914; Smiles and Hilditch, J., 1908, **93**, 145, 1687; Battegay and Vechot, *Bull. Soc. chim.*, 1925, **37**, 1271).

XV.)   (XVI.)

The tautomerism of 5-bromo-1-aminobenzthiazole and 5-bromo-1 imino-1 : 2-dihydrobenzthiazole was established by means of the symmetry test (A). The hexabromide of 1-acetylaminobenzthiazole, $C_6H_4<\begin{matrix}SBr_4^-\\NBr_2\end{matrix}>C\cdot NHAc$, was converted into 5-*bromo*-1-*acetyl-aminobenzthiazole*, and the dibromide of 1-imino-2-acetyl-1 : 2-dihydrobenzthiazole (VI) into the isomeric 5-*bromo*-1-*imino*-2-*acetyl*-1 : 2-*dihydrobenzthiazole*, by treatment with dilute alcohol (compare Hunter, J., 1925, **127**, 2026). On hydrolysis both these 5-bromo-acetyl derivatives yielded the same 5-bromo-1-aminobenzthiazole (formula as I or II). The fission test (B) is inapplicable in this case, and the substitution test (C) was not investigated in view of the difficulties encountered in the previous case.

In view of the curious observations made regarding the bromides of the *o*-, *m*-, and *p*-toluidinomethylbenzthiazoles (*loc. cit.*), the bromo-addition compounds of 1-amino-3-methyl-, 1-amino-4-methyl- and 1-amino-5-methyl-benzthiazole were examined. Whereas *o*-tolylthiocarbamide readily passed into the *dibromide* of the first, *m*-tolylthiocarbamide gave the labile *tetrabromide* of the second, $C_6H_3Me<\begin{matrix}SBr_2^-\\NBr_2\end{matrix}>C\cdot NH_2$, whilst *p*-tolylthiocarbamide yielded a more stable *tribromo*-addition compound of the last, which is doubtless the hydrobromide of the dibromide. This tribromide was on one occasion isolated in two forms (compare the case of 2-β-naphthylamino-α-naphthathiazole hexabromide, J., 1925, **127**, 2274).

Bromination of *m*-xylylthiocarbamide gave the *tetrabromide* of 1-amino-3 : 5-dimethylbenzthiazole, which is the most labile amino-thiazole bromide so far isolated. The instability is clearly to be attributed to the methyl groups in positions 3 and 5, there being no possibility either of *o*- or of *p*-migration of bromine into the aromatic nucleus (compare Fries, *Annalen*, 1906, **346**, 128).

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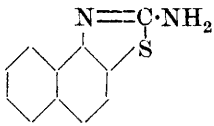
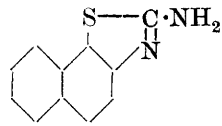
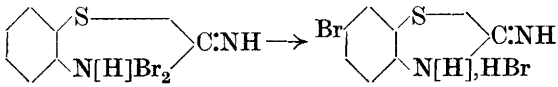
Lastly, the bromides of 2-amino-β-naphthathiazole (XVII) and 2-amino-α-naphthathiazole (XVIII) were examined. Both α- and β-naphthylthiocarbamide on bromination readily yielded the *tetrabromides* of (XVII) and (XVIII), respectively. These are compounds of the usual type, but are more stable than the bromides of the aminobenzthiazole series, no doubt owing to the presence of the naphthalene nucleus, since the bromo-addition compounds of 2-β-naphthylamino-α-naphthathiazole (*loc. cit.*) are remarkably stable under ordinary laboratory conditions.

(XVII.)   (XVIII.)

1-Imino-2-methyl-1 : 2-dihydrobenzthiazole (XI) on bromination yielded a stable orange-yellow *tribromide* of the type obtained by exposing the higher bromides of the 1-tolylaminodimethylbenzthiazole series (*loc. cit.*) to moist air.

The dibromide of 1-aminobenzthiazole (XIX) (Hugershoff, *Ber.*, 1901, **34**, 3130; 1903, **36**, 3121) obtained by brominating phenylthiocarbamide in chloroform, on treatment with warm water, is instantly converted into 5-bromo-1-imino-1 : 2-dihydrobenzthiazole hydrobromide (XX).

(XIX.)  (XX.)

This transformation is clearly a para-migration, analogous in some respects to the *N*-bromoacetanilide ⟶ *p*-bromoacetanilide isomerisation (Chattaway and Orton, J., 1899, **75**, 1046; 1900, **77**, 134, 152, 789, 797), but differing from it in that the nitrogen atom is in the quinquevalent state. The passage of the dibromide into the bromo-hydrobromide can be explained by means of a bridged form of the benzthiazole nucleus (XXI) (compare Ingold, J., 1922, **121**, 1133, 1143) analogous to the formula which Shearer (*Proc. Phys. Soc.*, 1923, **35**, ii, 81) has assigned to naphthalene on the basis of *X*-ray analysis.*

* The parachors (J., 1925, **127**, 1525 and later papers) of 1-aminobenzthiazole and of certain other benzthiazole derivatives are being determined by Dr. Sugden in the hope that they may give some indication of the intra-annular exchanges which take place in the benzthiazole system. Unfortunately, the difference between the calculated values of the parachor for the ordinary form of 1-aminobenzthiazole (I or II) ([P] = 311·9) and for the bridged form suggested in this paper as a phase of the benzthiazole system ([P] = 308·9) is very small (Sugden, private communication) and may not be capable of definite experimental detection.

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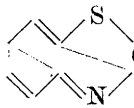
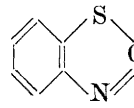
The bridged formula (XXI) represents only *one* of the intra-annular phases of benzthiazole, in tautomeric equilibrium with the

(XXI.)  ⇌  (XXII.)

normal phase (XXII), which is the usually accepted structure for the substance. The bridged form involves a hypothetical form of the thiazole nucleus, analogous to the bridged formula of thiophen (Farmer, Ingold, and Thorpe, J., 1922, **121**, 134) and the intra-annular five-carbon nucleus (*idem*, *loc. cit.*; Ingold, Seeley, and Thorpe, J., 1923, **123**, 863; Grimwood, Ingold, and Thorpe, *ibid.*, p. 3303). The strikingly aromatic properties of the thiazole nucleus (Hantzsch and collaborators, *loc. cit.*) suggest that the thiazole ring must, if the views of Ingold and his collaborators (J., 1922, **121**, 1133, 1143; 1923, **123**, 2066, 2081) regarding aromatic nuclei are correct, be a tautomeric system, although in view of the difficulties which heterocyclic nuclei present in this connexion from the experimental point of view (Ingold and Piggott, J., 1922, **121**, 2749; Ingold, J., 1924, **125**, 87), the problem of obtaining direct evidence of a bridged form of the thiazole nucleus appears at the present time to be insoluble. Evidence of a bridged form of the benzthiazole system must, however, be taken as *indirect* evidence on this point, and a series of experiments has been instituted in the hope of proving that the bridged formula (XXI) represents *one* phase of the benzthiazole system. With regard to the 1-amino-benzthiazole dibromide ⟶ 5-bromo-1-imino-1 : 2-dihydrobenzthiazole hydrobromide change, it is suggested, not that this transformation is a proof of the bridged structure of the benzthiazole nucleus, but merely that it is best explained on the basis of the latter. The exceedingly beautiful fluorescence of certain benzthiazole derivatives (Hunter, *Chemical News*, 1923, **127**, 385) is noteworthy in connexion with the problem of the bridged phase (compare Kaufmann, *Ahrens Vorträge*, 1908, **12**, 35; Ingold, J., 1922, **121**, 1134).

Experimental.

(Substances exhibiting amino–iminodihydro-tautomerism are named on the basis of their amino-formula).

The Mobility of 1-*Aminobenzthiazole.*

Methylation.—1-Aminobenzthiazole (2 g.) was heated with methyl iodide (1·6 c.c.) at 100° for 5 hours. The product, after being treated with alkali and with hot water to remove any unchanged amino-base, crystallised from alcohol in plates, m. p. 115°. After

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recrystallisation from benzene it melted at 122° and did not depress the m. p. of an authentic specimen of 1-imino-2-methyl-1 : 2-dihydrobenzthiazole (XI). It was further characterised by the formation of the stable, yellow-orange tribromo-addition compound (page 1393).

In an experiment similar to the above, the methylation product was extracted with cold ether and alcohol. The extract on evaporation yielded a clear pale yellow gum, which could not be crystallised, consisting of the more soluble methyl derivative. After the gum had solidified, it melted at about 114°. Mixed with a specimen of 1-methylaminobenzthiazole, it melted at 120° after softening at about 100°.

Ethylation.—1-Aminobenzthiazole (2 g.) and ethyl iodide (1·5 c.c.) were heated at 100° for 5—6 hours. The product, after treatment with alkali and warm water, was usually obtained as a tenacious gum, which sometimes solidified on standing for some weeks. On trituration with ether the product sometimes crystallised. It had m. p. 85° and was identified as 1-imino-2-ethyl-1 : 2-dihydrobenzthiazole (mixed melting point determination).

Acetylation.—A solution of 8 g. of 1-aminobenzthiazole in acetic anhydride (30 c.c.) was heated under reflux and cooled and the crystalline acetyl derivative was collected. The filtrate was mixed with alcohol and evaporated; small needles, m. p. 115°, were thus obtained. The acetyl derivative (7 g.) was extracted with boiling alcohol; the residue of small prisms had the same m. p., 186°, as the lustrous plates of 1-acetylaminobenzthiazole deposited from the extract. The remaining liquors were fractionally crystallised, but although low-melting substances (m. p. 120°) were frequently obtained, 1-imino-2-acetyl-1 : 2-dihydrobenzthiazole could not be isolated pure. The yield of pure 1-acetylaminobenzthiazole was almost quantitative. The crude acetylation product had no action on sodium hypobromite, showing the absence of unchanged base.

1-*Imino-2-methyl*-1 : 2-*dihydrobenzthiazole Dibromide* (X).—*as*-Methylphenylthiocarbamide (1 g.) in chloroform (10 c.c.) was gradually treated with a solution of bromine (0·8 c.c.) in chloroform (3 c.c.); a bulky orange precipitate separated which redissolved with evolution of heat and hydrogen bromide. The mixture was refluxed for 2 minutes and cooled; the bulk of the product then separated in tile-red crystals. The filtrate gradually deposited the *dibromide* in glistening, orange-red needles which, after drying in a vacuum over potassium hydroxide, sintered and softened at 125° (Found: Br, 49·8. $C_8H_8N_2Br_2S$ requires Br, 49·4%). The dibromide had the usual properties of these compounds, and slowly became yellow in the air with loss of bromine.

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1-*Imino*-2-*methyl*-1 : 2-*dihydrobenzthiazole* (XI).—The dibromide, suspended in sulphurous acid, was treated with sulphur dioxide until a colourless solution was obtained. This, on being made alkaline with ammonia, deposited the free methyl base in small prisms, m. p. 123° (Found : S, 18·9. $C_8H_8N_2S$ requires S, 19·5%).

1-*Imino*-2-*methyl*-1 : 2-*dihydrobenzthiazole Tribromide*.—The methyl derivative (0·2 g.) dissolved in chloroform (7 c.c.) was slowly treated with an excess of a 20% solution of bromine in the same solvent; an orange precipitate of the bromo-addition compound was obtained. The mixture was warmed and then cooled in ice. The *tribromide*, after being dried in a vacuum, was obtained in minute, orange prisms which lightened at 230—240° and became white without melting at 245° [Found : Br, 59·8. $(C_8H_8N_2Br_3S)_2$ requires Br, 59·4%].

1-*Methylaminobenzthiazole Tetrabromide* (XIII).—A solution of *s*-methylphenylthiocarbamide (4 g.) in chloroform (25 c.c.) was gradually treated with bromine (3·2 c.c.) and heated under reflux for a few minutes. On cooling, the *tetrabromide* crystallised in rosettes of shining, scarlet needles, m. p. 65—67° (decomp.), which were dried in a vacuum over potassium hydroxide (Found : Br, 66·1. $C_8H_8N_2Br_4S$ requires Br, 66·1%).

The tetrabromide was exposed to the air for 20 hours (compare 1-anilinobenzthiazole tetrabromide ⟶ tribromide transformation; J., 1925, **127**, 2026), losing bromine with the formation of a yellow-orange *dibromide*. This was extracted with chloroform, and separated on scratching in small, orange-yellow prisms which, after drying in a vacuum, sintered at 136° and charred at 191° (Found : Br, 48·8. $C_8H_8N_2Br_2S$ requires Br, 49·4%). The dibromide, however, differed from the tribromides of the 1-arylaminobenzthiazoles (*loc. cit.*) in losing more bromine on prolonged exposure to air.

Bromo-substitution Derivatives.—The tetrabromide dissolved readily in hot absolute alcohol, and on diluting the solution with water and concentrating it, a crystalline mass of the hydrobromides of the bromo-substitution products was obtained. This was treated with ammonia and the liberated bases were crystallised from ethyl acetate–alcohol, from which silky, lustrous plates of a mixture of monobromo- and dibromo-substitution derivatives were obtained, m. p. 203°; these could not be separated (Found : Br, 46·8. $C_8H_7N_2BrS$ requires Br, 37·0%. $C_8H_6N_2Br_2S$ requires Br, 49·9%). This behaviour is curious, for in all previous experiments on the bromination of substituted benzthiazoles it was possible to introduce only one bromine atom into the benzene nucleus (Hunter, this vol., p. 540).

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1-*Methylaminobenzthiazole* (XIV).—The tetrabromide was suspended in sulphurous acid and treated with sulphur dioxide. The crystalline paste of salts obtained was slowly added to a strong solution of ammonia, in which it dissolved. The base crystallised on cooling, and a further small quantity was obtained by extracting the filtrate with ether. The base was obtained from dilute alcohol in tufts of silky needles, m. p. 135°, and finally from absolute alcohol in prisms, m. p. 138° (Found: S, 19·8. $C_8H_8N_2S$ requires S, 19·5%).

1-*Imino*-2-*ethyl*-1 : 2-*dihydrobenzthiazole tetrabromide* was obtained from *as*-ethylphenylthiocarbamide (3 g.) and bromine (2·2 c.c.) in chloroform by the method for preparing the dibromide (X). After drying in a vacuum over potassium hydroxide, the tetrabromide was obtained in glistening, vermilion-orange prisms, m. p. 160—161° (decomp., with previous sintering) (Found: Br, 62·6. $C_9H_{10}N_2Br_4S$ requires Br, 64·3%).

1-*Imino*-2-*ethyl*-1 : 2-*dihydrobenzthiazole*, prepared by reducing the preceding tetrabromide (10 g.) in the usual way, was obtained as a gum which solidified; it crystallised from alcohol in pale yellow prisms, m. p. 86° (Found: S, 18·1. $C_9H_{10}N_2S$ requires S, 17·9%).

Labile Acetylphenylthiocarbamide.—Phenylthiocarbamide (16 g.) was heated with acetic anhydride (14 c.c.) at 80° (Hugershoff, *loc. cit.*). The product crystallised from ethyl acetate in prisms, m. p. 136°; after recrystallisation it melted at 138°.

1-*Imino*-2-*acetyl*-1 : 2-*dihydrobenzthiazole Dibromide* (VI).—(A) The labile acetylphenylthiocarbamide (2 g.) dissolved in chloroform (25 c.c.) was gradually treated with bromine (1·2 c.c.). Heat and hydrogen bromide were evolved in the usual way and crystallisation took place in the hot solution towards the end of the bromination. The mixture was refluxed for a short time, cooled, and the *dibromide* collected and dried in a vacuum; it was then obtained in glistening orange prisms, m. p. 130—132° (decomp.) (Found: Br, 45·6. $C_9H_8ON_2Br_2S$ requires Br, 45·5%).

(B) The acetylphenylthiocarbamide (2 g.) dissolved in 12 c.c. of chloroform was gradually treated with 1·6 c.c. of bromine; hydrogen bromide was evolved and a dark red tar produced. The solvent was decanted off and the tar boiled for 1 minute with 20 c.c. of absolute alcohol, being thereby changed into fine purplish-red prisms, which were dried in a vacuum. This *dibromide* sintered at about 160° and melted at 173° (decomp.) (Found: Br, 42·3%).

This dibromide showed the most striking stability to air, and appreciably lost bromine only over a period of some weeks. It was also more slowly reduced by sulphurous acid than the other bromides of 1-imino-2-acetyl-1 : 2-dihydrobenzthiazole.

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1-*Imino*-2-*acetyl*-1 : 2-*dihydrobenzthiazole Dibromide Hydrobromide*.—The labile acetylphenylthiocarbamide (4 g.) dissolved in chloroform (30 c.c.) was gradually treated with bromine (3 c.c.), and the mixture boiled. The product consisted of small, shining, dark chocolate-coloured prisms which were dried in the usual way. They became suddenly orange at 178° and melted at 180° (decomp.) (Found: Br, 55·6. $C_9H_8ON_2Br_2S,HBr$ requires Br, 55·7%). This bromide had the usual properties, being reduced by sulphurous acid and converted into the substitution derivative by treatment with diluted alcohol, and was strikingly similar to the dibromide of 4′-amino-1-phenyl-5-methylbenzthiazole (J., 1925, **127**, 1318) in appearance and stability in air.

1-*Imino*-2-*acetyl*-1 : 2-*dihydrobenzthiazole* (VIII).—This was obtained from the dibromide by means of sulphurous acid and ammonia in the usual way. It separated from 20% alcohol in minute crystals, m. p. 118—120° (Found: S, 17·2. $C_9H_8ON_2S$ requires S, 16·7%).

Hydrolysis. A part of the product was hydrolysed with 60% sulphuric acid, the solution neutralised at 0°, and the product recrystallised from hot water. Lustrous plates of 1-aminobenzthiazole were thus obtained which, alone or mixed with a genuine specimen, melted at 126°. The base was further characterised by the formation of the dibromide and of benzthiazole-1-azo-β-naphthol.

Specimens of the acetyl derivative have sometimes been obtained from alcohol–ethyl acetate in pale yellow prisms, m. p. 140° (or higher); these also yield 1-aminobenzthiazole on hydrolysis with 60% sulphuric acid, but have not yet been fully investigated.

Stable Acetylphenylthiocarbamide.—The labile acetyl derivative (18 g.) was kept at 150—160° for 10 minutes and then at 170—180° for an equal time. The product crystallised from alcohol–ethyl acetate in prisms, m. p. 170—171°, as recorded (*loc. cit.*).

1-*Acetylaminobenzthiazole Tetrabromide* (V).—When stable acetylphenylthiocarbamide (1 g.) in chloroform (7 c.c.) was slowly treated with bromine (0·9 c.c.), hydrogen bromide was evolved and a clear red gum separated. The mixture was boiled and cooled. On being rubbed, the gum solidified to a mass of orange-red prisms which were dried in the usual way; m. p. 137—139° (Found: Br, 61·8. $C_9H_8ON_2Br_4S$ requires Br, 62·5%).

1-*Acetylaminobenzthiazole* (VII) was obtained from the tetrabromide (1 g.) in the usual way. It crystallised from alcohol in prisms, m. p. 186°, and was identical with the acetyl derivative obtained by the direct acetylation of 1-aminobenzthiazole.

1-*Benzoylaminobenzthiazole*, obtained from 1-aminobenzthiazole

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(1 g.) by the Schotten-Baumann method, crystallised from alcohol in prisms, m. p. 186° (Hugershoff, *loc. cit.*).

1-*Benzoylaminobenzthiazole Tetrabromide*.—The benzoyl derivative (0·4 g.) dissolved in 5 c.c. of chloroform was treated with bromine (0·3 c.c.), and the solution boiled. On cooling, the *tetrabromide* crystallised in silky, orange-yellow plates which, after drying in a vacuum, lightened in colour at about 170° and became colourless and lost bromine at about 185° (Found: Br, 56·8. $C_{14}H_{10}ON_2Br_4S$ requires Br, 55·8%).

5-*Bromo*-1-*benzoylaminobenzthiazole*.—A solution of the tetrabromide in alcohol was boiled, diluted, and evaporated, the white, crystalline product was treated with ammonia, and the *bromo*-derivative was dried and recrystallised from ethyl acetate, separating in small prisms, m. p. 226° (Found: Br, 25·2. $C_{14}H_9ON_2BrS$ requires Br, 24·0%).

Benzthiazole-1-*azo*-β-*naphthol*.—A solution of aminobenzthiazole (1·5 g.) in 20 c.c. of dilute hydrochloric acid was diazotised in the usual way, and the product coupled with 1·4 g. of β-naphthol dissolved in 8 c.c. of 5% sodium hydroxide solution. The orange-brown azo-compound was collected and extracted with ether; the extract, on evaporation in a vacuum at room temperature, left the azo-compound in deep purple-red prisms, m. p. 146° after sintering at 140° (Found: S, 10·3. $C_{17}H_{11}ON_3S$ requires S, 10·5%). The product dyed cotton a fugitive shade of yellow. On reduction with tin and hydrochloric acid it gave 1-aminobenzthiazole, which was identified by its m. p. and by the m. p. of its mixture with a genuine specimen.

1-*Aminoazobenzthiazole*.—A solution of diazotised 1-aminobenzthiazole (prepared from 4 g. of the base in 50 c.c. of water and 10 c.c. of concentrated hydrochloric acid) was boiled for an hour, filtered from tar [which did not yield any trace of 1-hydroxybenzthiazole (Jacobson, *Ber.*, 1886, **19**, 1811) on extraction with alkali] and concentrated. The red crystals of the *hydrochloride* obtained separated from alcohol (animal charcoal) in yellow prisms, m. p. 232° (decomp.) after softening at 224°. The *base* was obtained by treating it with ammonia and was crystallised from ether and from boiling water, separating in small, cream-white, lustrous plates, m. p. 135° (Found: S, 21·6. $C_{14}H_9N_5S_2$ requires S, 20·7%). On reduction with tin and hydrochloric acid, 1-aminobenzthiazole was isolated and identified (m. p. and mixed m. p. determination).

Reaction of 1-*Aminobenzthiazole with Sodium Hypochlorite*.—The base (1 g.) in 30 c.c. of water was gradually treated with 50 c.c. of 0·3*N*-sodium hypochlorite. The purple precipitate produced after being washed with a little ether, separated from chloroform-

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light petroleum at 20° in dark purple crystals, which softened at 156—158°. The compound had dyeing properties of the usual type.

ψ-Aminobenzthiazole Hydrochloride (XV).—The hydrochloride from 5 g. of 1-aminobenzthiazole was suspended in 80 c.c. of alcohol at 5° and slowly treated with 16·5 c.c. of a 15% alcoholic solution of ethyl nitrite. The mixture became yellow on addition to 50 c.c. of boiling alcohol and thereafter bright orange on refluxing for a short time. On spontaneous evaporation, clusters of hard, shining, ruby-red prisms were obtained, which were washed with ether and recrystallised from alcohol. The *hydrochloride* was thus obtained in deep orange needles, m. p. 239—240° (Found: Cl, 19·6. $C_7H_6N_2S,HCl$ requires Cl, 19·1%).

ψ-Aminobenzthiazole (XVI).—The bright yellow base obtained by treating the red hydrochloride with ammonia (*d* 0·880) was dried and recrystallised from "sodium-dried" benzene at 20°, separating in slender, pale yellow needles which sintered and softened at 129° and melted to a clear purple-red liquid at 131° (Found: N, 18·4; S, 21·6. $C_7H_6N_2S$ requires N, 18·7; S, 21·3%). Its mixture with 1-aminobenzthiazole commenced to soften at 120° and melted indefinitely at about 127°. On treating the base with hydrochloric acid the red hydrochloride was at once regenerated.

ψ-Amino-3-toluthiazole Hydrochloride.—The hydrochloride from 1 g. of 1-amino-3-methylbenzthiazole (p. 1398) was suspended in 25 c.c. of alcohol and treated with 3 c.c. of ethyl nitrite solution. A *hydrochloride* was obtained as in the previous case in ruby-red prisms which sintered at 140° and showed colour change at 145° (Found: Cl, 18·0. $C_7H_8N_2ClS$ requires Cl, 18·7%). On treatment with ammonia a base similar to the previous one was obtained.

ψ-Amino-5-toluthiazole hydrochloride was obtained from 1-amino-5-methylbenzthiazole in red prisms which sintered at 130°, darkened at 140° and softened at about 150°.

The Mobility of 5-Bromo-1-aminobenzthiazole.

5-Bromo-1-aminobenzthiazole dibromide, prepared from *p*-bromophenylthiocarbamide (1 g.) and bromine (0·8 c.c.) in chloroform (10 c.c.) in the usual way, separated, on cooling, as a red gum which solidified in orange-red needles, softening at 80—82° (Found: Br, 63·5. $C_7H_5N_2Br_3S$ requires Br, 61·7%). By successive treatment with sulphurous acid and ammonia it was converted into 5-bromo-1-aminobenzthiazole, m. p. 211°, identical with the bromo-substitution product obtained by dissolving 1-aminobenzthiazole dibromide in hot water (Hugershoff, *loc. cit.*).

1-Acetylaminobenzthiazole Hexabromide.—1-Acetylaminobenzthiazole (0·5 g.) in chloroform (6 c.c.) was slowly treated with

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bromine (0·4 c.c.), and the solution boiled after some time. The *hexabromide* crystallised from the warm liquid, on scratching, in small, orange-red prisms which, after being dried, turned yellow at 130°, lost bromine at about 140°, and became colourless at about 160° (Found: Br, 71·6. $C_9H_8ON_2Br_6S$ requires Br, 71·4%).

5-*Bromo*-1-*acetylaminobenzthiazole*.—A solution of the preceding hexabromide in alcohol was diluted with a little water and concentrated. The white, crystalline product, after treatment with dilute ammonia, crystallised from ethyl acetate in prisms, m. p. 223° (Found: Br, 30·0. $C_9H_7ON_2BrS$ requires Br, 29·5%). On hydrolysis with 50% sulphuric acid, impure 5-bromo-1-aminobenzthiazole (m. p. 184°) was obtained which melted at 198° when mixed with an authentic specimen.

5-*Bromo*-1-*imino*-2-*acetyl*-1 : 2-*dihydrobenzthiazole*.—A solution of the dibromo-addition compound of 1-imino-2-acetyl-1 : 2-dihydrobenzthiazole in alcohol was diluted with water, concentrated on a steam-bath, decanted from a small purple residue, and evaporated. The resin thus obtained became hard on treatment with ammonia and thereafter crystallised from alcohol–ethyl acetate in small plates, m. p. 199—200° (Found: Br, 30·0. $C_9H_7ON_2BrS$ requires Br, 29·5%).

On hydrolysis with 40% sulphuric acid and neutralisation, 5-bromo-1-aminobenzthiazole (m. p. 204°) was obtained; this crystallised from alcohol in prisms which, alone or mixed with 5-bromo-1-aminobenzthiazole prepared from 1-aminobenzthiazole dibromide, melted at 210°.

Homologues of 1-*Aminobenzthiazole.*

1-*Amino*-3-*methylbenzthiazole Dibromide*.—The solution obtained by treating 2 g. of *o*-tolylthiocarbamide in 20 c.c. of chloroform with bromine (1·5 c.c.) was refluxed and concentrated; on cooling, lustrous orange plates of the *dibromide* crystallised, m. p. 110° (effervescence) (Found: Br, 49·6. $C_8H_8N_2Br_2S$ requires Br, 49·4%). The dibromide was unstable and decomposed with loss of bromine on exposure to air. It dissolved in alcohol, and from the solution, diluted with water and thereafter concentrated, white needles of the *hydrobromide* of bromo-1-amino-3-methylbenzthiazole were obtained which became yellow at 260° and charred at about 290° (Found: Br, 49·8. $C_8H_7N_2BrS,HBr$ requires Br, 49·7%). The *base* obtained by treating the hydrobromide with ammonia separated from alcohol–ethyl acetate in tufts of silky needles, m. p. 212° (Found: Br, 33·1. $C_8H_7N_2BrS$ requires Br, 32·9%).

1-*Amino*-3-*methylbenzthiazole* was obtained from the dibromide by reduction with sulphurous acid and sulphur dioxide in the usual

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way. It crystallised from 50% alcohol in small, lustrous plates, m. p. 136°, and resembled 1-aminobenzthiazole in odour (Found : S, 19·8. $C_8H_8N_2S$ requires S, 19·5%). The diazotised base gave a red azo-dye on coupling with alkaline β-naphthol.

1-*Amino*-5-*methylbenzthiazole Dibromide Hydrobromide*.—*p*-Tolylthiocarbamide (2 g.) was brominated in chloroform as in the previous case. The bromo-addition compound was obtained in small, glistening orange-red prisms, m. p. 134° (decomp.) after sintering at 128° (Found : Br, 59·0. $C_8H_8N_2Br_2S,HBr$ requires Br, 59·2%). The tribromide was very unstable in air. Treatment of its alcoholic solution with water produced the hydrobromide of the bromo-substitution derivative, which crystallised in silky needles. The base obtained by treatment with ammonia crystallised from alcohol (80%) in small prisms, m. p. 210° (Found : Br, 33·0. $C_8H_7N_2BrS$ requires Br, 32·9%).

By brominating *p*-tolylthiocarbamide (1 g.) in chloroform under similar conditions to the above, the tribromide was on one occasion obtained in bright red prisms, m. p. 106° (decomp.) (Found : Br, 59·5%).

1-*Amino*-5-*methylbenzthiazole*, obtained by reduction of the tribromide, crystallised from 50% alcohol in small, glistening prisms, m. p. 142°, having the usual faint odour of these bases (Found : S, 19·1. $C_8H_8N_2S$ requires S, 19·5%). The base yielded an unstable diazonium chloride which coupled with alkaline β-naphthol, giving a red azo-dye of the usual type.

1-*Amino*-4-*methylbenzthiazole Tetrabromide*.—Prepared from *m*-tolylthiocarbamide (0·3 g.) and bromine (0·4 c.c.) in chloroform (5 c.c.) in the usual way, the *tetrabromide* was obtained, either spontaneously or by cooling the solution and scratching, in slender, orange-red needles which, after being dried, became yellow at 140°, soft at 160°, white at 180°, brown at 210°, and melted and decomposed at about 250° (Found : Br, 66·8. $C_8H_8N_2Br_4S$ requires Br, 66·1%). It had the usual properties of these bromides.

1-*Amino*-4-*methylbenzthiazole*.—The tetrabromide was reduced in the usual way. The base was precipitated by making the sulphurous acid solution alkaline and a further small quantity was obtained by extracting the filtrate with ether. The base crystallised from 50% alcohol in pearly plates, m. p. 145° (sintering at 135°), having the faint characteristic odour of these compounds (Found : S, 19·2. $C_8H_8N_2S$ requires S, 19·5%).

1-*Amino*-3 : 5-*dimethylbenzthiazole Tetrabromide*.—Prepared from 1 g. of *m*-xylylthiocarbamide and bromine (0·8 c.c.) in chloroform (10 c.c.), the *tetrabromide* separated from the cooled solution in red flakes which, after being dried in a vacuum, became colourless at

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80—90° and were unmelted at 250° (Found: Br, 63·8. $C_9H_{10}N_2Br_4S$ requires Br, 64·3%). It is very unstable, losing bromine and becoming colourless on exposure to air for ½ hour.

1-*Amino*-3 : 5-*dimethylbenzthiazole*, obtained from it in the usual way, crystallised from ether in needles and thereafter from dilute alcohol in silvery plates, m. p. 116° (softening at about 100°), having the usual faint odour of these compounds (Found: S, 16·8. $C_9H_{10}N_2S$ requires S, 17·9%).

2-*Amino*-β-*naphthathiazole Tetrabromide*.—Prepared from α-naphthylthiocarbamide (0·5 g.) and bromine (0·5 c.c.) in chloroform, the *tetrabromide* was obtained as an orange, microcrystalline powder which, after drying in a vacuum, began to lighten in colour at 130° and was unmelted at 260° (Found: Br, 60·9. $C_{11}H_8N_2Br_4S$ requires Br, 61·6%).

2-*Amino*-β-*naphthathiazole*, obtained by reducing the tetrabromide, crystallised from alcohol–ethyl acetate in small, odourless crystals, m. p. 235—237° after sintering at about 220° (Found: S, 16·1. $C_{11}H_8N_2S$ requires S, 16·0%).

2-*Amino*-α-*naphthathiazole Tetrabromide*.—β-Naphthylthiocarbamide (0·5 g.) was brominated as in the case of the α-compound. The *tetrabromide* was obtained as a yellow, microcrystalline powder, m. p. 165° (decomp.) (Found: Br, 60·8%).

2-*Amino*-α-*naphthathiazole* crystallised from alcohol–ethyl acetate in small prisms, m. p. 249—251°, after sintering at about 230° (Found: S, 16·2. $C_{11}H_8N_2S$ requires S, 16·0%).

The 1-*Aminobenzthiazole Dibromide* ⟶ 5-*Bromo*-1-*aminobenzthiazole Hydrobromide Transformation.*

1-Aminobenzthiazole dibromide (obtained by Hugershoff's method, *loc. cit.*; after being dried in the usual way, it turned red at 105—110°, melted at 112—114°, and charred at 206°) (36 g.) was added to 200 c.c. of nearly boiling water. A colourless solution was at once produced which on evaporation on the steam-bath left 32 g. of crude 5-bromo-1-aminobenzthiazole hydrobromide (a certain amount of the dibromide undergoes decomposition, giving the hydrobromide of 1-aminobenzthiazole). Thirty g. of the product, after treatment with ammonia and recrystallisation from alcohol, yielded 15—16 g. of 5-bromo-1-aminobenzthiazole.

In view of the curious physiological action of certain benzthiazole derivatives (J., 1925, **127**, 911), the alleged immunity to certain swamp fevers conferred by "thiazole dermatitis" (private communication from Dr. G. M. Dyson), and the clinical use of substances such as *o*-aminophenyl sulphide in syphilis, a series of

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experiments has been commenced in collaboration with Dr. Dyson on the trypanocidal effect of water-soluble aminobenzthiazoles.

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