CCCXCVI.—*Aminobenzthiazoles. Part VI. The Addition of Bromine to Nascent Tautomeric Systems of the Aminothiazole Type and the Mobility and Unsaturation of the 5-Bromo-1-alkylaminobenzthiazole System.*

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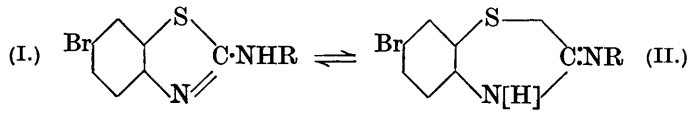
Of the two main experimental difficulties in determining the stability of the 1-alkylaminobenzthiazole bromides (preceding paper, p. 2952), that due to migration of bromine into the benzene nucleus can usually be prevented by introducing a bromine atom into this nucleus in the para-position to the reactive nitrogen atom (Fries, *Ber.*, 1904, **37**, 2388; *Annalen*, 1906, **346**, 128). In view of this and because the mobility of 5-bromo-1-aminobenzthiazole had already been established by the symmetry test (Hunter, this vol., p. 1389), it was decided to examine the mobility and unsaturation of the 5-bromo-1-alkylaminobenzthiazole system (I ⇌ II). The



choice of this system was a fortunate one, for the presence of the 5-bromo-substituent removed both difficulties referred to above and it was possible to isolate a series of dibromides of the required type and examine their stability. The physical properties of the 5-bromo-1-alkylaminobenzthiazole dibromides, however, made it impossible to extend the investigation beyond the *iso*butyl homologue.

The 5-bromo-1-alkylaminobenzthiazole bromides were obtained by brominating the corresponding *s*-*p*-bromophenylalkylthiocarbamides in chloroform (compare Hunter, J., 1925, **127**, 2023). These reacted much more slowly than the unbrominated thiocarbamides, owing to the effect of the substituent bromine and possibly also to the tendency to form the thiazole bromide (Hunter, *loc. cit.*).

The transformation of arylthiocarbamides into 1-aminobenzthiazole bromides doubtless occurs as follows : Bromine is added on at the double bond of the C:S group of the thiocarbamide, giving rise to an unstable dibromo-compound containing the CBr·SBr group; this then loses hydrogen bromide, and the nascent benzthiazole formed (Hugershoff, *Ber.*, 1903, **36**, 3121; compare also Hofmann, *Ber.*, 1880, **13**, 11) adds on bromine, giving the thiazole bromide

(Hunter, *loc. cit.*). This addition takes place in a mobile triad system, and from the 5-bromo-1-alkylaminobenzthiazole system either or both of the dibromides (III) and (IV) might be produced.

(III.) $C_6H_3Br<^{S}_{NBr_2}>C{\cdot}NHR$ $\qquad$ $C_6H_3Br<^{S}_{N[H]Br_2}>C{:}NR$ (IV.)

It is noteworthy that two forms of 2-β-naphthylamino-α-naphthathiazole have been isolated from the product of brominating *s*-di-β-naphthylthiocarbamide in chloroform under very slightly different conditions (J., 1925, **127**, 2271) and similar observations have been made on the tribromide of 1-amino-5-methylbenzthiazole (this vol., p. 1389).

By brominating *s*-ethyl-, *s*-*n*-propyl-, *s*-*n*-butyl-, and *s*-*iso*butyl-*p*-bromophenylthiocarbamides in chloroform under similar conditions, the dibromides of the corresponding 5-bromo-1-alkylaminobenzthiazoles were obtained. These were all coloured, crystalline compounds of the usual type which decomposed at the melting point and were reduced by sulphurous acid to the corresponding 5-bromo-1-alkylaminothiazoles; they displayed, however, somewhat unusual stability to moist air.

The dibromides differed considerably from one another in initial velocity of reduction by dilute hydriodic acid under similar conditions: 5-bromo-1-ethylaminobenzthiazole dibromide was quantitatively reduced, whereas reduction of the *iso*butyl homologue did not exceed 20% As the table shows, the stability of the compounds was in the expected order—ethyl<*n*-propyl<*n*-butyl<*iso*butyl—and thus the view expressed in the preceding paper is confirmed with regard to the effect of increasing atomic volume of the alkyl group on the unsaturation of the nuclear nitrogen atom.

Stability of the 5-Bromo-1-alkylaminobenzthiazole Dibromides.

Alkyl group.	% Bromine liberated.	% Labile bromine reacting.
Ethyl	38·0	98·9
n-Propyl	17·7	42·4
n-Butyl	15·1	37·3
*iso*Butyl	7·7	19·0

The great difference in stability between the *n*-butyl and the *iso*butyl compounds illustrates the very large effect produced by the *iso*butyl group, which is somewhat similar to a *gem*-dialkyl group (Ingold, J., 1921, **119**, 305, 951).

The bromination of *s*-*p*-bromophenylethylthiocarbamide under different conditions gave even more interesting results. When the labile 5-bromo-1-ethylaminobenzthiazole dibromide was boiled for some time with a mixture of bromine and chloroform, it was converted into an *isomeride* having the same chemical but different

physical properties and resembling 5-bromo-1-*iso*butylaminobenzthiazole dibromide in stability towards hydriodic acid. Both dibromides gave 5-bromo-1-ethylaminobenzthiazole on reduction with sulphurous acid, and therefore it appears highly probable that they are the dibromides (III and IV) of the tautomeric forms of 5-bromo-1-ethylaminobenzthiazole, the labile derivative (IV, R = Et) being formed from the iminodihydro-phase of the mobile triad system. Its conversion into the stable bromide appears, then, to involve merely a transference of the potentially mobile hydrogen atom and the necessary shifting of the double bond, and suggests the possibility of retarded mobility (Kon and Linstead, J., 1925, **127**, 813) between the bromides involving quinquevalent nitrogen—a possibility which the authors hope to investigate at a future time.

The percentage reductions of the 5-bromo-1-alkylaminobenzthiazole dibromides recorded in the table on p. 2959 are not a measure of the equilibrium of the symmetrical triad system, but, since the brominations and the reductions were both carried out under similar conditions, they do definitely indicate the shift of equilibrium in favour of the more unsaturated aminothiazole phase. The dibromides of *n*-propyl-, *n*-butyl-, and *iso*butyl-amino-5-bromobenzthiazoles probably contain appreciable quantities of the isomeric dibromides. The melting point is unfortunately no criterion of purity, because the compounds decompose rapidly on fusing (compare Reade, J., 1924, **125**, 150).

Bromination of 5-bromo-1-ethylaminobenzthiazole (as distinct from the nascent thiazole formed in the bromination of bromophenylethylthiocarbamide) yielded a bromide, m. p. 204° (decomp.), apparently consisting almost entirely of the labile dibromide obtained from the iminodihydro-form (II) of the base.

s-*p*-Bromophenylmethylthiocarbamide behaved abnormally on bromination, giving rise to the ***hexabromide*** of 5-bromo-1-methylaminobenzthiazole (V), one of the stablest of these hexabromides as yet isolated. Bromination of *s*-*p*-bromophenyl-*n*-amylthiocarbamide produced the *tetrabromide* of 5-bromo-1-*n*-amylaminobenzthiazole (VI), a difficultly crystallisable substance of the usual type.

$$C_6H_3Br\langle\begin{matrix}SBr_4\\NBr_2\end{matrix}\rangle C{\cdot}NHMe \qquad C_6H_3Br\langle\begin{matrix}SBr_2\\NBr_2\end{matrix}\rangle C{\cdot}NH{\cdot}C_5H_{11}$$

(V.) (VI.)

s-*n*-Hexyl-, *s*-*n*-heptyl-, and *s*-*iso*amyl-*p*-bromophenylthiocarbamides on bromination all gave rise to the corresponding 5-bromo-1-alkylaminobenzthiazole dibromides (III) or (IV). The difficulty of crystallising these prevented examination of their

quantitative reduction by hydriodic acid. They are compounds of the usual type and give the corresponding 5-bromo-1-alkylaminobenzthiazoles on reduction.

EXPERIMENTAL.

s-Di-*p*-bromophenylthiocarbamide was best prepared in quantity as follows: A solution of *p*-bromoaniline (500 g.) in a mixture of carbon disulphide (700 c.c.) and alcohol (600 c.c.) containing a little sulphur (compare Hugershoff, *Ber.*, 1899, **32**, 2245) was kept for several weeks; a large quantity of the dithiocarbamate then crystallised. A mixture (800 c.c.) of alcohol and carbon disulphide (4 : 1) was then added, and the whole refluxed for 3 hours. On cooling, the thiocarbamide crystallised in long, hard, shining needles, m. p. 184—185°. A further quantity was obtained by concentrating the mother-liquor. Yield, 480 g. (86%).

p-Bromophenylthiocarbimide was prepared by boiling a solution of *s*-di-*p*-bromophenylthiocarbamide (100 g.) in acetic anhydride (120 c.c.) (compare Werner, J., 1891, **59**, 396) for 15 minutes, pouring it into water (200 c.c.) at 60—80°, and steam-distilling the product. Yield, 40 g.; m. p. 60—61°.

The thiocarbamides described below were prepared by heating *p*-bromophenylthiocarbimide and the requisite amine in alcoholic solution and either crystallising the product from alcohol or extracting it with small quantities of ether until the m. p. was constant.

s-p-*Bromophenylmethylthiocarbamide* crystallises in shining needles, m. p. 148° (Found: Br, 33·2. $C_8H_9N_2BrS$ requires Br, 32·6%).

5-*Bromo*-1-*methylaminobenzthiazole Hexabromide.*—*p*-Bromophenylmethylthiocarbamide (1·1 g.) in chloroform (10 c.c.) was gradually treated with bromine (0·7 c.c.), and the mixture refluxed until the evolution of hydrogen bromide was inappreciable (5—10 minutes). The solution was cooled in a freezing mixture; a red gum then separated which, on scratching, solidified in small, orange-red crystals of the *hexabromide*. This was dried in a vacuum over potassium hydroxide, washed with a little chloroform, and again dried; m. p. 122—124° (decomp.) (Found: Br, 76·8. $C_8H_7N_2Br_7S$ requires Br, 77·8%). The hexabromide was almost unaffected by 50 hours' exposure to moist air [Found: Br (labile), 31·3%].

5-*Bromo*-1-*methylaminobenzthiazole* was obtained from the hexabromide (1 g.) by means of sulphurous acid (10 c.c.) and sulphur dioxide and subsequent treatment with hot 2*N*-sodium hydroxide. It crystallised from alcohol–ethyl acetate in white plates, m. p. 225°, but was contaminated with a dibromo-substitution derivative which could not be removed by crystallisation (compare the purification

of 5-bromo-1-methylaminobenzthiazole; this vol., p. 1393) (Found : Br, 43·6. $C_8H_7N_2BrS$ requires Br, 32·9%).

s-p-*Bromophenylethylthiocarbamide* forms small needles, m. p. 129° (Found : Br, 31·0. $C_9H_{11}N_2BrS$ requires Br, 30·9%).

5-*Bromo*-1-*ethylimino*-1 : 2-*dihydrobenzthiazole Dibromide* (IV; R = Et).—Prepared from the thiocarbamide (1 g.) and bromine (0·65 c.c.) by the method used in the preparation of the preceding hexabromide, this *dibromide* was obtained in small, yellowish-orange, microscopic crystals, which were washed with chloroform and dried in a vacuum over potassium hydroxide; m. p. 212° (with sintering) (Found : Br, 57·4. $C_9H_9N_2Br_3S$ requires Br, 57·4%).

Reduction. The dibromide (0·1 g.), dissolved in acetic acid (50 c.c.), was shaken with a saturated aqueous solution of potassium iodide (10 c.c.), and the liberated iodine titrated with *N*/10-sodium thiosulphate [Found : Br, 38·0. $C_9H_9N_2BrS(Br)_2$ requires (Br), 38·4%].

5-*Bromo*-1-*ethylaminobenzthiazole Dibromide* (III; R = Et).—*p*-Bromophenylethylthiocarbamide (1 g.) in chloroform (10 c.c.) was brominated as in the previous case with 1·3 c.c. of bromine, and the mixture refluxed for 12—15 minutes. The stable *dibromide* crystallised, on rubbing, in deep red prisms, m. p. 140° (decomp.) (Found : Br, 58·0. $C_9H_9N_2Br_3S$ requires Br, 57·4%). On reduction with hydriodic acid as described above, it gave immediately 7·6% of bromine, but more was liberated after a short time, showing that the stable dibromide is reduced more slowly than the labile isomeride.

5-*Bromo*-1-*ethylaminobenzthiazole* was obtained by reducing either of the preceding dibromides with sulphurous acid and sulphur dioxide and crystallised from alcohol–ethyl acetate in lustrous plates or needles, m. p. 256—258° (Found : Br, 31·2. $C_9H_9N_2BrS$ requires Br, 31·1%).

s-p-*Bromophenyl*-n-*propylthiocarbamide* crystallises in needles, m. p. 120° (Found : Br, 29·6. $C_{10}H_{13}N_2BrS$ requires Br, 29·3%).

5-*Bromo*-1-n-*propylaminobenzthiazole Dibromide.*—The thiocarbamide (1·1 g.) was brominated in chloroform (10 c.c.) in the usual way, and the small, yellow crystals finally obtained were washed with chloroform and dried in a vacuum; m. p. 146° (decomp.) (Found : Br, 55·7. $C_{10}H_{11}N_2Br_3S$ requires Br, 55·7%).

5-*Bromo*-1-n-*propylaminobenzthiazole* separates from alcohol–ethyl acetate in lustrous plates, m. p. 130° (Found : Br, 30·8. $C_{10}H_{11}N_2BrS$ requires Br, 29·5%).

s-p-*Bromophenyl*-n-*butylthiocarbamide* crystallises in needles, m. p. 111° (Found : Br, 27·6. $C_{11}H_{15}N_2BrS$ requires Br, 27·85%).

5-*Bromo*-1-n-*butylaminobenzthiazole Dibromide.*—This was pre-

pared in the usual way and slowly formed in microscopic, yellow crystals, m.p. 149° (decomp.) (Found: Br, 54·1. $C_{11}H_{13}N_2Br_3S$ requires Br, 54·0%).

5-*Bromo*-1-n-*butylaminobenzthiazole* is very soluble in the ordinary solvents and separates from concentrated solutions in tufts of lustrous needles, m. p. 118° (Found: Br, 28·6. $C_{11}H_{13}N_2BrS$ requires Br, 28·1%).

s-p-*Bromophenyl*iso*butylthiocarbamide* crystallises in silky plates, m. p. 119° (yield 70—80%) (Found: Br, 27·9. $C_{11}H_{15}N_2BrS$ requires Br, 27·9%).

5-*Bromo*-1-iso*butylaminobenzthiazole Dibromide*.—This was prepared from the thiocarbamide in the usual way and obtained in shining, orange prisms, m. p. 127° (decomp.) (Found: Br, 53·8. $C_{11}H_{13}N_2Br_3S$ requires Br, 54·0%). It is very soluble in chloroform.

5-*Bromo*-1-iso*butylaminobenzthiazole* separates from alcohol–ethyl acetate in microscopic crystals, m. p. 137° (Found: Br, 29·5. $C_{11}H_{13}N_2BrS$ requires Br, 28·1%).

s-p-*Bromophenyl*-n-*amylthiocarbamide* melts at 115° and is somewhat difficult to crystallise (Found: Br, 26·9. $C_{12}H_{17}N_2BrS$ requires Br, 26·6%).

5-*Bromo*-1-n-*amylaminobenzthiazole Tetrabromide*.—*p*-Bromophenyl-*n*-amylthiocarbamide (1·1 g. in chloroform, 10 c.c.) was brominated in the usual way (0·7 c.c. Br), the solvent distilled off in a vacuum at room temperature, and the product kept in a vacuum over potassium hydroxide for 2 days; the *tetrabromide* then crystallised in orange prisms, m. p. 86° (decomp.) (Found: Br, 64·3. $C_{12}H_{15}N_2Br_5S$ requires Br, 64·5%). Its stability in moist air was of the order of that of the tetrabromides of the 1-xylidinodimethylbenzthiazoles (this vol., p. 1401).

5-*Bromo*-1-n-*amylaminobenzthiazole* crystallises from alcohol–ethyl acetate in small plates, m. p. 105° (Found: Br, 27·6. $C_{12}H_{15}N_2BrS$ requires Br, 26·7%).

s-p-*Bromophenyl*iso*amylthiocarbamide* crystallises in needles, m. p. 120° (Found: Br, 26·4. $C_{12}H_{17}N_2BrS$ requires Br, 26·6%).

5-*Bromo*-1-iso*amylaminobenzthiazole Dibromide*.—This was prepared and purified like the preceding tetrabromide and was usually obtained in ill-defined crystals, m. p. 95° (decomp.) (Found: Br, 50·7. $C_{12}H_{15}N_2Br_3S$ requires Br, 52·3%). On one occasion, however, a beautifully crystalline *dibromide* was isolated, m. p. 111° (decomp.) (Found: Br, 51·5%).

5-*Bromo*-1-iso*amylaminobenzthiazole*, prepared by reducing the dibromide, was usually resinous and crystallised from alcohol–ethyl acetate with some difficulty. The crystals, m. p. 171°, were impure (Found: Br, 29·0. $C_{12}H_{15}N_2BrS$ requires Br, 26·7%).

s-p-*Bromophenyl*-n-*hexylthiocarbamide* crystallises in small prisms, m. p. 189° (Found : Br, 25·2. $C_{13}H_{19}N_2BrS$ requires Br, 25·4%).

5-*Bromo*-1-n-*hexylaminobenzthiazole Dibromide*.—*p*-Bromophenylhexylthiocarbamide (1·2 g. in chloroform, 10 c.c.) was brominated in the usual way, and the solution concentrated in a vacuum. The red gum obtained, after standing in a vacuum over potassium hydroxide, changed to a yellow solid which could not be crystallised (Found : Br, 49·5. $C_{13}H_{17}N_2Br_3S$ requires Br, 50·7%).

5-*Bromo*-1-n-*hexylaminobenzthiazole* was obtained as a white solid which was extremely difficult to purify; m. p. 156° (Found : Br, 27·7. $C_{13}H_{17}N_2BrS$ requires Br, 25·6%).

s-p-*Bromophenyl*-n-*heptylthiocarbamide* crystallises in shining plates, m. p. 100° (Found : Br, 24·5. $C_{14}H_{21}N_2BrS$ requires Br, 24·3%).

5-*Bromo*-1-n-*heptylaminobenzthiazole Dibromide*.—This was obtained in the same way as the tetrabromide of the *n*-amyl compound, in small, yellowish-orange needles, m. p. 118—120° (decomp.) (Found : Br, 48·2. $C_{14}H_{19}N_2Br_3S$ requires Br, 49·3%).

5-*Bromo*-1-n-*heptylaminobenzthiazole* was obtained impure and with some difficulty from alcohol–ethyl acetate in microscopic crystals which became yellow and melted at 86° (Found : Br, 29·7. $C_{14}H_{19}N_2BrS$ requires Br, 24·6%).

It is hoped to examine the chemotherapeutical properties of some of these bases at an early date.

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