CCCXCV.—*Aminobenzthiazoles. Part V. Stability of the 1-Alkylaminobenzthiazole Bromides.*

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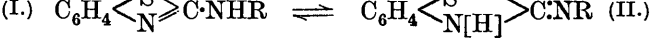
Recently, as the fourth object of this investigation (see footnote, this vol., p. 1385), the study of the relation between unsaturation and mobility in triad systems of the aminothiazole type was commenced. Since the tautomerism of 1-aminobenzthiazole with the

corresponding 1-imino-1 : 2-dihydro-derivative had already been established (*loc. cit.*), the 1-alkylaminobenzthiazole system appeared to be suitable for the examination of the effect of diminishing mobility of the hydrogen atom [H] on the unsaturation of the nitrogen atom of the thiazole nucleus.

On the basis of Ingold's modified strain theory (J., 1921, **119**, 305, 951; Deshapande and Thorpe, J., 1922, **121**, 1432; compare also Bains and Thorpe, J., 1923, **123**, 1206; Lanfear and Thorpe, *ibid.*, p. 2865) it seems probable that increasing the atomic volume of the alkyl group R in the 1-alkylaminobenzthiazole system (I $\rightleftharpoons$ II) would increase the stability of the two-membered, heterocyclic ring, N=C, of the aminothiazole phase (I) and thus would enhance this phase of the tautomeric system (compare Packer and Thorpe, this vol., p. 1203). Consequently, on ascending the homologous series of 1-alkylaminobenzthiazoles, a gradual shift of the equilibrium in favour of the phase (I) is to be expected.



(I.) $C_6H_4<^{S}_{N}>C\cdot NHR \rightleftharpoons C_6H_4<^{S\text{——}}_{N[H]}>C{:}NR$ (II.)

The nuclear nitrogen atom of the aminothiazole phase (I) has more residual affinity than the corresponding nitrogen atom of the iminodihydro-phase (II), since it has free affinity due to the nuclear double bond in addition to its own residual affinity. The nuclear nitrogen atom in the phase (I) is, then, more unsaturated than that in the phase (II) and hence, on increasing the bulk of the alkyl group R, a corresponding increase in the unsaturation of the thiazole nucleus should ensue, leading to an increase in the stability of the bromo-addition compound of the alkylaminothiazole. Experiments on the stability of the bromides of 1-alkylaminobenzthiazoles (R = Me up to *n*-heptyl) have therefore been made with the view of testing this point and obtaining some knowledge of the effect on the carbon tetrahedral angle of the hitherto unstudied butyl, amyl, and hexyl groups (Hunter, footnote, this vol., p. 1401).

The bromo-addition compounds of the 1-alkylaminobenzthiazoles obtained from the corresponding *s*-phenylalkylthiocarbamides were first examined. In view of the remarkable instability of 1-aminobenzthiazole dibromide, which rapidly loses bromine on exposure to the atmosphere (*loc. cit.*), it seemed that the stability of the bromides could be most conveniently tested by measuring the decrease in labile bromine content produced by exposing them to air under similar conditions. Unfortunately, owing to the tendency of the thiazole nucleus in the 1-alkylaminobenzthiazoles to add on more than two bromine atoms, the difficulties attending the iodometric estimation of the labile bromine (due to a part of the labile

bromine entering the benzene nucleus, giving rise to bromo-substitution derivatives), and to the physical properties of the compounds, a stability curve could not be obtained. Greater success, however, has attended the study of the 5-bromo-1-alkylaminobenzthiazole system, and experiments are described in the following paper which confirm the view here suggested regarding the increase in unsaturation of the nuclear nitrogen atom produced by an increase in the volume of R.

With the exception of the *n*-propyl compound, all the *s*-phenylalkylthiocarbamides, on bromination in chloroform, readily passed either into the *dibromides* (III) of the corresponding 1-alkylaminobenzthiazoles or into the *hydrobromides* of these (IV or V). Thus

(III.) $C_6H_4\langle{}^{S}_{NBr_2}\rangle C{\cdot}NHR$ $\quad$ $C_6H_4\langle{}^{S}_{NBr_2}\rangle C{\cdot}NHR,HBr$ (IV.)

(V.) $C_6H_4\langle{}^{S}_{NBr_2(HBr)}\rangle C{\cdot}NHR$ $\quad$ $C_6H_4\langle{}^{SBr_2}_{NBr_2}\rangle C{\cdot}NHPr^{\alpha}$ (VI.)

s-phenylethylthiocarbamide readily yielded the *dibromide* of 1-ethylaminobenzthiazole (III, R = Et), a bright red compound of the usual type which gradually lost bromine on exposure to air, liberated iodine from dilute hydriodic acid, yielded a bromo-substitution derivative on treatment with dilute alcohol, and was reduced to 1-ethylaminobenzthiazole (I or II, R = Et) by sulphurous acid and sulphur dioxide in the usual way (*loc. cit.*). Similarly, *s*-phenyl-*n*-butylthiocarbamide and *s*-phenyl-*n*-hexylthiocarbamide gave the *dibromides* of 1-*n*-butylamino- and 1-*n*-hexylamino-benzthiazoles (III, R = *n*-C_4H_9 and *n*-C_6H_{13}, respectively). On the other hand, *s*-phenyl*iso*butylthiocarbamide, *s*-phenyl-*n*-amylthiocarbamide, and *s*-phenyl-*n*-heptylthiocarbamide yielded *tribromo*-addition compounds of 1-*iso*butylamino-, 1-*n*-amylamino-, and 1-*n*-heptylamino-benzthiazoles (IV or V, R = *iso*-C_4H_9, *n*-C_5H_{11}, and *n*-C_7H_{15}, respectively) similar to the tribromide of 5-methyl-1-aminobenzthiazole (this vol., p. 1389).

s-Phenyl*iso*amylthiocarbamide yielded the *tribromo*-addition compound of 1-*iso*amylaminobenzthiazole, a compound of the usual type which could not be obtained crystalline. This difficulty was experienced with 5-bromo-1-*iso*amylaminobenzthiazole tribromide also (Hunter and Soyka, following paper) and appears to be associated with the *iso*amylamino-group.

s-Phenyl-*n*-propylthiocarbamide gave a red *tetrabromide* of 1-*n*-propylaminobenzthiazole (VI) which, on exposure to air, rapidly lost bromine with the formation of a yellow, stable *dibromide*. Both bromides had the usual properties and gave 1-*n*-propylaminobenzthiazole on treatment with sulphurous acid.

By bromination under the conditions described in this paper, *s*-phenylmethylthiocarbamide has been converted directly into the stable yellow dibromide of 1-methylaminobenzthiazole previously obtained from the unstable tetrabromide (this vol., p. 1393). This dibromide, which is remarkably stable in moist air, resembles the stable tribromides of the 1-arylaminobenzthiazoles (J., 1925, **127**, 2025) and is quite distinct from the red dibromo-addition compounds of 1-ethylamino- and 1-*n*-butylamino-benzthiazoles. Since it is formed from the unstable tetrabromide by exposure to air, it may be produced by loss of bromine across the heterocyclic nucleus of (VI, with Me in place of Pr$^{\alpha}$) and may contain the ·S·Br·NBr complex. This suggestion applies also to the stable yellow dibromide of 1-*n*-propylaminobenzthiazole.

The results of the experiments on the stability of the 1-alkylaminobenzthiazole bromides are tabulated below.

Alkyl group.	Bromide.	Labile halogen (initial) %.	Labile halogen (final) %.	Exposure in hours.
Methyl.	Dibromide.	24·8	24·4	46
Ethyl.	,,	45·4	30·4	44
n-Propyl.	Tetrabromide.	51·3	27·7	,,
n-Butyl.	Dibromide.	32·8	32·6	,,
*iso*Butyl.	Tribromide.	32·3	17·9	48

EXPERIMENTAL.

1-*Methylaminobenzthiazole Dibromide.*—A solution of *s*-phenylmethylthiocarbamide (1 g.) in chloroform (6 c.c.) was slowly treated with bromine (0·8 c.c.) and heated under reflux for 2—5 minutes; hydrogen bromide was then copiously evolved. On slight concentration, cooling and scratching, the dibromide separated in small, yellow crystals, which were collected on porous earthenware and dried in a vacuum over potassium hydroxide. They turned brownish-orange at 105—106°, crumbled slightly at about 120°, and sintered and decomposed at 144—146° (Found: Br, 50·5. Calc. for $C_8H_8N_2Br_2S$: Br, 49·4%). The compound was reduced by sulphurous acid to 1-methylaminobenzthiazole (this vol., p. 1394) and liberated iodine from dilute hydriodic acid. After exposure to air at 17°/770 mm. for 46 hours, it sintered and decomposed at 134—137°, but the labile bromine content was almost unaltered (see table).

1-*Ethylaminobenzthiazole dibromide* was obtained in a similar way from 2 g. of *s*-phenylethylthiocarbamide (Weith, *Ber.*, 1875, **8**, 1524) in chloroform (10 c.c.) and bromine (1·5 c.c.), a labile dibromo-addition compound of the thiocarbamide (?) (compare Hugershoff, *Ber.*, 1903, **36**, 3121) being precipitated and redissolving before the solution was heated. The red gum obtained solidified in glistening,

red needles, which were dried in a vacuum over potassium hydroxide; m. p. 76—78° (decomp.) (Found: Br, 47·2. $C_9H_{10}N_2Br_2S$ requires Br, 47·3%). This compound has the usual properties of the dibromides. After 44 hours' exposure to air, it melted at 48°, becoming red and soft at 40—45°, and the labile bromine content decreased by 15%.

1-*Ethylaminobenzthiazole* was obtained by treating the dibromide, suspended in sulphurous acid, with sulphur dioxide, and the filtered solution with ammonia (*d* 0·880). It crystallised from alcohol in small, glistening prisms, m. p. 87—88° (Found: S, 18·1. $C_9H_{10}N_2S$ requires S, 17·9%).

1-n-*Propylaminobenzthiazole Tetrabromide*.—*s*-Phenyl-*n*-propylthiocarbamide (Hecht, *Ber.*, 1890, **23**, 286) (1·5 g.) in chloroform (6 c.c.) was slowly treated with bromine (0·9 c.c.) and the mixture was refluxed for 2 minutes, concentrated, and cooled; a red gum separated slowly which could not be crystallised. This was dissolved in chloroform containing bromine, and the solution evaporated slowly in a vacuum; the *tetrabromide* then crystallised in small, vermilion prisms which melted at 54—56° (decomp.) after being dried in the usual way (Found: Br, 63·1. $C_{10}H_{12}N_2Br_4S$ requires Br, 62·5%). The compound lost bromine appreciably in ½ hour, and after 44 hours' exposure, it was yellowish-orange and melted at 65°, softening at 59—61°.

1-n-*Propylaminobenzthiazole dibromide* was obtained in small, orange prisms by exposing a thin layer of the tetrabromide to air for 5 days. After being washed with ether and dried in a vacuum, it melted at 80—82° (decomp.) (Found: Br, 47·5. $C_{10}H_{12}N_2Br_2S$ requires Br, 45·7%).

1-n-*Propylaminobenzthiazole* was obtained from either of the preceding bromides in the usual way and separated from alcohol in small prisms, m. p. 68° (Found: S, 17·0. $C_{10}H_{12}N_2S$ requires S, 16·7%).

s-*Phenyl*-n-*butylthiocarbamide*.—*n*-Butylamine (2 g.) was condensed with phenylthiocarbimide (4 g.) in alcohol in the usual way. The *thiocarbamide*, after being washed with light petroleum (b. p. 40—60°), was obtained in shining, flat prisms, m. p. 65° (Found: S, 15·4. $C_{11}H_{16}N_2S$ requires S, 15·4%).

1-n-*Butylaminobenzthiazole Dibromide*.—When phenyl-*n*-butylthiocarbamide (2 g.) in chloroform (8 c.c.) was slowly treated with 1·3 c.c. of bromine a violent reaction took place, the solution boiling spontaneously with evolution of hydrogen bromide. The mixture was refluxed, concentrated, and cooled in a freezing mixture; the *dibromide* then suddenly crystallised in small, glistening, orange prisms which, after drying, became soft and red at 80° and melted

at 86° (decomp.) (Found: Br, 42·4. $C_{11}H_{14}N_2Br_2S$ requires Br, 43·7%). The compound had the usual properties. After 44 hours' exposure to air, it became soft and red at 79—80° and melted at 82—84°, but the labile bromine content was almost unaltered. After several weeks' exposure, however, it lost bromine and became almost colourless.

1-n-*Butylaminobenzthiazole*, obtained from the dibromide, on recrystallisation from alcohol separated in small, glistening plates, m. p. 87° (Found: S, 15·8. $C_{11}H_{14}N_2S$ requires S, 15·5%).

1-iso*Butylaminobenzthiazole Dibromide Hydrobromide.*—*s*-Phenyl-*iso*butylthiocarbamide (Hecht, *Ber.*, 1892, **25**, 813; Dixon, J., 1893, **63**, 320) was treated like the *n*-butyl compound. Cooling having failed to induce crystallisation, the solution was treated with bromine–chloroform, and the solvent removed in a vacuum. The red gum obtained, after being kept in a vacuum over potassium hydroxide for 18 hours, changed to small, orange-red prisms on being rubbed. These were very soluble in chloroform and were resinified by ether or petroleum, and therefore they were crushed and again dried in a vacuum. The substance became red at about 50°, softened at 60°, and melted at 66—68° (decomp.) (Found: Br, 52·5. $C_{11}H_{14}N_2Br_2S$,HBr requires Br, 53·7%). After 48 hours' exposure to air, it melted at 50° and the labile bromine content decreased by more than 14%.

1-iso*Butylaminobenzthiazole* separated from alcohol in small, shining needles, m. p. 103—104° (Found: S, 15·6. $C_{11}H_{14}N_2S$ requires S, 15·5%).

s-*Phenyl*-n-*amylthiocarbamide* was obtained from *n*-amylamine and phenylthiocarbimide in the usual way and crystallised from alcohol in glistening plates, m. p. 69—71° (Found: S, 14·2. $C_{12}H_{18}N_2S$ requires S, 14·5%).

1-n-*Amylaminobenzthiazole Dibromide Hydrobromide.*—A solution of phenyl-*n*-amylthiocarbamide (1 g.) in chloroform (6 c.c.) was slowly treated with 0·7 c.c. of bromine, heated under reflux, and concentrated in a vacuum over potassium hydroxide. The *tribromide* was thus obtained in small, vermilion-orange crystals, m. p. 90° (decomp.; reddening at 60°) (Found: Br, 52·6. $C_{12}H_{16}N_2Br_2S$,HBr requires Br, 52·4%).

1-n-*Amylaminobenzthiazole* crystallised from alcohol in rosettes of glistening needles, m. p. 68—69° (Found: S, 14·2. $C_{12}H_{16}N_2S$ requires S, 14·6%).

1-iso*Amylaminobenzthiazole Dibromide Hydrobromide.*—Treatment of phenyl*iso*amylthiocarbamide (Dixon, J., 1893, **63**, 324) (1·5 g.) in the usual way (chloroform, 6 c.c.; bromine, 1 c.c.) produced a red gum. This was freed from solvent in a vacuum and agitated

with a current of air; the orange-red resin thus obtained would not crystallise (Found: Br, 47·8. $C_{12}H_{16}N_2Br_2S$,HBr requires Br, 52·4%).

1-iso*Amylaminobenzthiazole*, prepared from the bromide in the usual way, crystallised from alcohol in aggregates of needles, m. p. 69—71° (Found: S, 14·7. $C_{12}H_{16}N_2S$ requires S, 14·6%).

s-*Phenyl*-n-*hexylthiocarbamide* was obtained from *n*-hexylamine and phenylthiocarbimide in the usual way and crystallised from alcohol in small prisms, m. p. 103—104° (Found: S, 13·5. $C_{13}H_{20}N_2S$ requires S, 13·6%).

1-n-*Hexylaminobenzthiazole Dibromide*.—This was prepared from *s*-phenyl-*n*-hexylthiocarbamide (0·5 g.), chloroform (5 c.c.), and bromine (0·5 c.c.). The crude product, a red gum, after being kept in a vacuum over potassium hydroxide for 24 hours, changed to orange prisms of the *dibromide*, m. p. 100—102° (decomp.; sintering at 90°) (Found: Br, 41·2. $C_{13}H_{18}N_2Br_2S$ requires Br, 40·6%).

1-*n*-*Hexylaminobenzthiazole*, prepared from the dibromide in the usual way, crystallised from alcohol in small, glistening prisms, m. p. 57° (Found: S, 13·8. $C_{13}H_{18}N_2S$ requires S, 13·7%).

s-*Phenyl*-n-*heptylthiocarbamide*, prepared from *n*-heptylamine and phenylthiocarbimide in alcohol, crystallised from this solvent in small prisms, m. p. 70—71° (Found: S, 13·0. $C_{14}H_{22}N_2S$ requires S, 12·8%).

1-n-*Heptylaminobenzthiazole Dibromide Hydrobromide*.—A solution of phenyl-*n*-heptylthiocarbamide (1·5 g.) in chloroform (8 c.c.) was treated with bromine (0·9 c.c.), refluxed for 3 minutes, and concentrated in a vacuum; the *tribromide* then crystallised in small, orange-yellow, glistening prisms, m. p. 79—81° (after drying) (Found: Br, 48·2. $C_{14}H_{20}N_2Br_2S$,HBr requires Br, 49·1%).

1-n-*Heptylaminobenzthiazole* was prepared by keeping the tribromide in contact with sulphurous acid for a week and boiling the product with 10% sodium hydroxide solution. The colourless oil obtained solidified in glistening plates on cooling and then crystallised from alcohol in shining needles, m. p. 55° (Found: S, 13·0. $C_{14}H_{20}N_2S$ requires S, 12·9%).

In view of the trypanocidal activity of 1-aminobenzthiazole the chemotherapy of its alkyl derivatives will be examined.

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