400. *Electrophilic Substitution in Benzothiazole. Part II.*[1] *The Bromination of the Aminobenzothiazoles*

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The bromination of 4-, 5-, 6-, and 7-aminobenzothiazoles in chloroform has been studied. Whilst the β-*ortho*-positions in 5- and 6-aminobenzothiazole appear to be more reactive than in the corresponding naphthalenes, quinolines, or 1,2,3-benzothiadiazoles, 4- and 7-aminobenzothiazole show decreased reactivity relative to 1-naphthylamine.

Improved methods are described for the preparation of 7-nitro- and 4-amino-benzothiazole.

Ring-opening of substituted benzothiazoles leads to substituted *o*-aminothiophenols, which can be further converted into bicyclic heterocycles, *e.g.*, 1,2,3-benzothiadiazoles, by diazotisation. Hence, studies of electrophilic substitution in benzothiazoles are not only of intrinsic interest in this system but also of considerable synthetic value in other directions. Products arising from such studies can often be orientated by conversion into known 1,2,3-benzothiadiazoles. Although much work has been carried out on electrophilic substitution in benzothiazoles little really worthwhile data, as judged by contemporary standards, exists. Furthermore, fundamental physical data required for useful theoretical interpretations was sadly lacking, *e.g.*, there are no reliable bond-length measurements for benzothiazoles. We have therefore embarked on a systematic study of electrophilic substitution in benzothiazoles, and measurements of relevant physical data.

We now report on the bromination of 4-, 5-, 6-, and 7-aminobenzothiazoles in chloroform, results being summarised in the Table.

Bromination of 4-, 5-, 6-, and 7-aminobenzothiazoles in chloroform at 20° *

NH_2 †	4	5	6	7
Br	7(24); 5, 7(69)	4(88); 4, 6(6)	5(86); 5, 7(7·5)	4(33); 4, 6(50)

* Using 1 mole of bromine. † Refers to the position of NH_2 and Br in the benzene ring of benzothiazole, figures in parentheses representing percentage yields of pure bromination products, calculated after allowance for recovered starting material. Similar results were obtained working in the presence of triethylamine, or in acetic acid (with or without the addition of sodium acetate).

5-Amino-4,6-dibromobenzothiazole and 6-amino-5,7-dibromobenzothiazole were also obtained either by reacting the amino-compounds with two moles bromine or by further bromination of 5-amino-4-bromo- and 6-amino-5-bromo-benzothiazoles.

Prior to this investigation, Boggust and Cocker [2] had obtained 6-amino-7-bromobenzothiazole and a compound, m. p. 146°, which they believed to be the 5-bromo-amine, by reacting 6-aminobenzothiazole with excess of bromine in chloroform. It now appears that the substance of m. p. 146° is 6-amino-5,7-dibromobenzothiazole.

It is well known that benzothiazole and its derivatives form addition complexes with bromine, probably involving attachment of the bromine molecule to the hetero-nitrogen atom, and such complexes could play an important role in nuclear substitutions (cf. Eisch and Jaseski [3] on the analogous quinoline–bromine adduct). Chawdri, Desai, and Hunter [4] found that addition of bromine to 2-aminobenzothiazole at 0° gave a labile perbromide which, in air, was rapidly converted into 2-amino-6-bromobenzothiazole. Hence, we attempted to isolate such complexes involving aminobenzothiazoles but without any definite results. Addition of 1 mole of bromine to 6-aminobenzothiazole in carbon tetrachloride at 0° gave an orange solid which, on exposure to air, rapidly lost its colour and was converted into the 7-bromo-derivative. Estimation of available bromine in the coloured solid gave low results but it could be a mixture of unchanged amine with such a complex. Since it is now known that the amino-nitrogen in the benzenoid aminobenzothiazoles is

[1] Part I, E. R. Ward and W. H. Poesche, *J.*, 1961, 2825.
[2] W. A. Boggust and W. Cocker, *J.*, 1949, 355.
[3] J. J. Eisch and B. Jaseski, *J. Org. Chem.*, 1963, **28**, 2865.
[4] N. A. S. Chawdri, R. D. Desai, and R. F. Hunter, *J. Indian Chem. Soc.*, 1934, **11**, 249.

more basic than the hetero-nitrogen atom,[5] then bromine addition might well occur at the former site.

Whilst the value of comparisons between different bicyclic systems is open to question, it is clear that the 5- and 6-aminobenzothiazoles, under the conditions described and in contrast to the corresponding derivatives of naphthalene,[6] quinoline,[7] and 1,2,3-benzothiadiazole,[8,9] are brominated in the β-*ortho*-positions as well as in the α-*ortho*-positions. This may be due to the higher π-electron density in the benzene ring of the benzothiazole, which is also inevitably associated with smaller differences in bond orders in this ring. The important issue of the extent of electronic interaction between the two rings of a bicyclic compound involving a benzene ring fused to a five- or six-membered heterocycle, and its effect on bond structure, has been explored by Efros [10] and by ourselves.[8,9]

The monobromoaminobenzothiazoles were orientated by diazotisation and deamination to the corresponding monobromobenzothiazoles (prepared by Sandmeyer reactions from diazotised aminobenzothiazoles). Deamination of the dibromo-amines from 4- and 6-aminobenzothiazole gave the same dibromobenzothiazole which must be 5,7-dibromobenzothiazole. This was confirmed by conversion of the latter, by ring-opening and subsequent diazotisation, into the known 5,7-dibromo-1,2,3-benzothiadiazole. Similarly, 5- and 7-aminodibromobenzothiazoles both gave 4,6-dibromobenzothiazole on deamination.

As already indicated [9] the most convenient route to 7-nitrobenzothiazole is by deamination of 6-amino-7-nitrobenzothiazole, for which we now report experimental details. 4-Aminobenzothiazole is best prepared from the mixed nitrobenzothiazoles arising from the nitration of benzothiazole.[1] Most of the 6-nitrobenzothiazole is removed by crystallisation from ethanol and the resulting mixed 4-, 5-, 6-, and 7-nitrobenzothiazoles reduced with stannous chloride and hydrochloric acid. Steam-distillation of the mixed crude amines gives 4-aminobenzothiazole only.

Experimental

7-Nitrobenzothiazole.—*6-p-Tolylsulphonamidobenzothiazole* was prepared and nitrated by the methods used for the corresponding derivatives of 1,2,3-benzothiadiazole.[8] The amide (92%) had m. p. 205—207° (from ethanol) (Found: C, 55·6; H, 4·0; N, 9·3; S, 21·0. $C_{14}H_{12}N_2O_2S_2$ requires C, 55·2; H, 3·9; N, 9·2; S, 21·2%) and gave an 85% yield of *7-nitro-6-p-tolylsulphonamidobenzothiazole*, yellow plates, m. p. 195° (from ethanol) (Found: C, 48·4; H, 2·6; N, 12·0. $C_{14}H_{11}N_3O_4S_2$ requires C, 48·2; H, 3·1; N, 12·0%). The nitro-amide (20 g.) was hydrolysed by warming a solution in sulphuric acid (*d* 1·84; 150 ml.) to 40°. After dilution with water (60 ml.) and cooling to 0°, diazotisation was achieved by addition of nitrosylsulphuric acid (2M; 30 ml.). After 15 min. hypophosphorus acid (50%; 100 ml.) was added and the mixture kept at 0° for 30 min. The next day an excess of aqueous ammonia (*d* 0·88) was added, the solids collected, dried at 60°, extracted with benzene (2 × 500 ml.) and the extract passed through a short alumina column. The column was eluted with more benzene and concentration of the eluate gave 7-nitrobenzothiazole (65%), m. p. 153°.

Reduction of Nitrobenzothiazoles to Aminobenzothiazoles.—This was performed with stannous chloride in hydrochloric acid as for the nitro-1,2,3-benzothiadiazoles.[11] 5-, 6-, and 7-Aminobenzothiazoles were obtained in 70% yield from the corresponding nitro-compounds, it being advantageous to saturate the reduction mixture with dry hydrochloric acid before isolation. 4-Aminobenzothiazole was prepared from the crude mixture of nitrobenzothiazoles obtained by the method of Ward and Poesche.[1] Most of the 6-nitrobenzothiazole was removed by crystallisation from ethanol and the residue (20 g.) obtained by evaporation of the ethanol was reduced as above. The mixture of crude amines so obtained was steam-distilled and the distillate (3 l.) saturated at 0° with sodium chloride when pure 4-aminobenzothiazole crystallised out (2·7 g.).

[5] C. H. Williams, *J.*, 1965, 2258.
[6] E. R. Ward and P. R. Wells, *J.*, 1961, 4866.
[7] R. R. Renshaw, H. L. Friedman, and F. J. Gajewski, *J. Amer. Chem. Soc.*, 1939, **61**, 3322.
[8] E. R. Ward and D. D. Heard, *J.*, 1963, 4794.
[9] E. R. Ward and D. D. Heard, *J.*, 1965, 1023.
[10] L. S. Efros, *Russ. Chem. Rev.*, 1960, **29**, 66.
[11] E. R. Ward, W. H. Poesche, D. Higgins, and (in part) D. D. Heard, *J.*, 1962, 2374.

The Monobromobenzothiazoles.—The aminobenzothiazole (1 g.) was diazotised by solution in hydrobromic acid (*d* 1·46; 6 ml.) and portionwise addition of sodium nitrite (0·45 g.) at 0°. The diazo-solution was then added to one of cuprous bromide (2 g.) in hydrobromic acid (*d* 1·46; 15 ml.) at 0°. After 1 hr. the mixture was diluted with water, made alkaline with aqueous ammonia (*d* 0·88), and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated, and the residue was crystallised from light petroleum (b. p. 80—100°). 4-*Bromobenzothiazole* (52%), m. p. 90° (Found: C, 39·2; H, 1·7; N, 6·7; Br, 37·0. C_7H_4BrNS requires C, 39·3; H, 1·9; N, 6·5; Br, 37·4%), 5-*bromobenzothiazole* (56%), m. p. 106° (Found: C, 40·1; H, 1·8; Br, 37·0; N, 6·6%), 6-bromobenzothiazole (55%), m. p. 54° (lit.,[2] 55°), and 7-*bromobenzothiazole* (34%), m. p. 82° (Found: C, 39·3; H, 2·1; Br, 37·7; N, 6·5%) were so prepared.

Bromination of the Aminobenzothiazoles.—A solution of the amine (1·5 g., 0·01 mole) in chloroform (35 ml.) was treated with bromine (1·6 g., 0·01 mole) in chloroform (5 ml.). After 15 min. the solids were collected, basified with ammonia, and the product dried (X). Further material (Y) was obtained by evaporating the original chloroform filtrate. All the reaction products were eventually crystallised from light petroleum (b. p. 80—100°).

(*a*) 4-*Aminobenzothiazole.* A solution of one third of the mixed bases (X) in chloroform was extracted with hydrochloric acid (0·2N; 25 ml.), the extract basified with ammonia and further extracted with chloroform. Evaporation of the dried ($MgSO_4$) extract gave starting material (0·23 g.). The acid-extracted chloroform was evaporated and the residue dissolved in benzene and chromatographed on alumina (30 × 2 cm.). After elution by benzene (750 ml.) 4-*amino*-5,7-*dibromobenzothiazole* began to appear in the eluate and was contained in the next 150 ml. (0·383 g.), colourless needles, m. p. 148° (Found: C, 27·6; H, 1·4; N, 8·6; Br, 51·3. $C_7H_4Br_2NS$ requires C, 27·3; H, 1·3; N, 9·1; Br, 51·9%). Further elution by ethyl acetate gave 4-*amino*-7-*bromobenzothiazole* (0·097 g.), colourless needles, m. p. 123° (Found: C, 36·7; H, 2·3; N, 12·2; Br, 34·5. C_7H_5BrNS requires C, 36·7; H, 2·2; N, 12·2; Br, 34·9%). The original chloroform extract gave no solids.

(*b*) 5-*Aminobenzothiazole.* Chromatography of material (X) (as above) gave first 5-*amino*-4-*bromobenzothiazole* (1·9 g.), colourless needles, m. p. 115° (Found: C, 36·5; H, 2·1; Br, 34·4; N, 12·1%) and then starting material (0·08 g.). (Y) gave 5-*amino*-4,6-*dibromobenzothiazole* (0·16 g.), m. p. 152° (Found: C, 26·3; H, 1·3; Br, 51·8; N, 8·7%).

(*c*) 6-*Aminobenzothiazole.* The procedure used in (*b*) gave starting materials (0·13 g.), 6-amino-7-bromobenzothiazole (1·8 g.), m. p. 123° (lit.,[2] 121°) (Found: Br, 34·5; N, 12·1%), and 6-*amino*-5,7-*dibromobenzothiazole* (0·21 g.), m. p. 149° (Found: C, 27·3; H, 1·3; Br, 51·7%).

(*d*) 7-*Aminobenzothiazole* (X) was dissolved in chloroform (50 ml.) and extracted successively with hydrochloric acid (0·1N, 3 × 15 ml. and then 3N, 2 × 12 ml.). The first extract yielded starting material (0·44 g.), basification of the second extract gave 7-*amino*-4-*bromobenzothiazole* (0·53 g.), m. p. 145° (Found: Br, 34·3; N, 12·7%). The solids from the residual chloroform were added to (Y), being 7-*amino*-4,6-*dibromobenzothiazole* (1·08 g.), m. p. 175° (Found: C, 26·8; H, 1·3; Br, 52·1; N, 9·2%).

(*e*) *Further bromination of monobromoaminobenzothiazoles.* 6-Amino-7-bromobenzothiazole was converted into 6-amino-5,7-dibromobenzothiazole (75%) by refluxing with one mole of bromine in chloroform, isolation being as described in the general procedure. 5-Amino-4,6-dibromobenzothiazole (70%) was similarly obtained from 5-amino-4-bromobenzothiazole.

Orientation of the Mono- and Di-bromoaminobenzothiazoles.—The monobromoaminobenzothiazole (1 g.) was dissolved in 50% v/v aqueous sulphuric acid (10 ml.) and diazotised at 0—5° by addition of aqueous sodium nitrite. After 15 min. hypophosphorous acid (50%, 4 ml.) was added and next day the bromobenzothiazole obtained by diluting with water (yields 50—70%). By a similar procedure 5,7-*dibromobenzothiazole* was obtained from either 4- or 6-amino-5,7-dibromobenzothiazole, m. p. 97° (from aqueous ethanol) (Found: Br, 52·8; N, 5·4. $C_7H_3Br_2NS$ requires Br, 54·6; N, 4·8). It was converted into the known 5,7-dibromo-1,2,3-benzothiadiazole by the ring-opening procedure of Boggust and Cocker,[2] followed by diazotisation of the intermediate 6-amino-2,4-dibromothiophenol and identified with an authentic specimen. 4,6-*Dibromobenzothiazole*, m. p. 141° (Found: Br, 54·5; N, 4·8%) was similarly obtained from 5- or 7-amino-4,6-dibromobenzothiazoles.

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