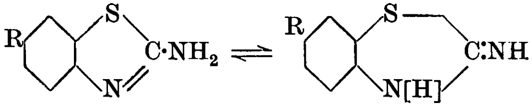
CLXIV.—*Aminobenzthiazoles. Part VIII. The Effect of Polar Substituents on the Formation and Stability of Nuclear-substituted* 1-*Aminobenzthiazole Bromides.*

By George Malcolm Dyson, Robert Fergus Hunter, and Richard William Morris.

It appeared probable that valuable evidence for the view that the bromine atoms in the benzthiazole dibromides are held to the nuclear nitrogen atom by means of single electrons (compare Ingold and Ingold, J., 1926, 1385) might be obtained by a study of the effect of different polar substituents on the formation and stability of these compounds. The examination of the bromides of the 5-substituted 1-aminobenzthiazoles (I $\rightleftharpoons$ II) was therefore undertaken.

(I.)  (II.)

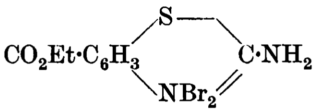
In accordance with the suggested electronic constitutions of these bromo-addition compounds, it was found that negative groups, such as the cyano- and the carbethoxy-group (R = CN, CO_2Et, etc.), tended to stabilise the NBr_2 complex in the bromides, whilst positive groups, such as the ethoxy- and the methoxy-group (R = OEt, OMe, etc.), had the reverse effect. The stability of the bromides could not be investigated quantitatively, but atmospheric decomposition of the compounds indicated that the effects of the substituents conform to " general polarity," the series being CN,$CO_2Et >$ Br,Cl $>$ OEt,OMe in order of decreasing stability of the bromide. This series is similar to that recorded by Rule and Paterson (J., 1924, **125**, 2155), and by Rule and Smith (J., 1925, **127**, 2188) denoting the relative influence of groups on acidic strengths of aliphatic acids and on velocity of reaction and molecular inductive capacity.

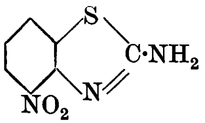
The 5-substituted 1-aminobenzthiazole bromides were obtained by bromination of the corresponding *p*-substituted phenylthiocarbamides in chloroform (Hunter, J., 1925, **127**, 2023, and later papers). These reacted much more slowly than phenylthiocarbamide and its homologues (J., 1926, 1385), resembling in this respect the *s*-*p*-bromophenylalkylthiocarbamides (Hunter and Soyka, J., 1926, 2958), owing possibly to the greater stability of the intermediate ·CBr·SBr compound (Hugershoff, *Ber.*, 1903, **36**, 3121; Hunter and Soyka, *loc. cit.*).

Under the usual conditions of bromination, *p*-cyanophenylthiocarbamide yielded a *tetrabromide* of 1-amino-5-cyanobenzthiazole, which on reduction gave the 5-cyano-base (I $\rightleftharpoons$ II; R = CN). 1-*Amino*-5-*cyanobenzthiazole*, however, on bromination in chloroform, gave a well-defined *hexabromide*, from which four labile bromine atoms were readily removed by ammonia (compare Macbeth and Hirst, J., 1922, **121**, 904; Macbeth, *ibid.*, p. 1116, and later papers).

Bromination of *p*-carbethoxyphenylthiocarbamide produced a *dibromide* (III) of 1-amino-5-carbethoxybenzthiazole, whereas bromination of 1-amino-5-carbethoxybenzthiazole itself (I $\rightleftharpoons$ II; R = CO_2Et) gave a *tribromide*, which is doubtless analogous to the tribromides of the 3-thiol-5-keto-2 : 4-dialkyltetrahydro-1 : 2 : 4-thiodiazoles (Freund and Asbrand, *Annalen*, 1895, **285**, 166; Freund and Bachrach, *ibid.*, p. 184).

(III.)





(IV.)

p-Chlorophenylthiocarbamide resembled *p*-carbethoxyphenylthiocarbamide in giving a *dibromide* (of 5-chloro-1-aminobenzthiazole; formula as III), but bromination in chloroform of 5-chloro-1-aminobenzthiazole gave rise to a *hexabromide* similar to that obtained from 1-amino-5-cyanobenzthiazole. Acetylation of the amino-group in 5-chloro-1-aminobenzthiazole, however, somewhat decreased the reactivity of the heterocyclic nucleus, for *5-chloro-1-acetamido-benzthiazole* yielded a *tetrabromide* on bromination under the usual conditions. Bromination of *p*-bromophenylthiocarbamide had previously been observed to give rise to a dibromide of 5-bromo-1-amino-benzthiazole (J., 1926, 1397); by using a higher concentration of bromine, a *tetrabromide*, analogous to the tetrabromide of 1-amino-5-cyanobenzthiazole, has now been isolated.

p-Ethoxyphenylthiocarbamide yielded, on bromination, a *penta-bromide* of 1-amino-5-ethoxybenzthiazole, which is probably the hydrobromide of the tetrabromo-addition compound; whereas *p*-methoxyphenylthiocarbamide, under similar conditions, gave rise to a *dibromide* of 1-amino-5-methoxybenzthiazole (formula as III).

1-Amino-5-methylbenzthiazole (I $\rightleftharpoons$ II; R = Me), on bromination, gave an unstable *tetrabromide*, which lost bromine on exposure to air, giving a more stable *tribromide*.

Several unsuccessful attempts were made to prepare 5-dimethyl-amino-1-aminobenzthiazole (I $\rightleftharpoons$ II; R = NMe_2) by bromination of *p*-dimethylaminophenylthiocarbamide. The formation of a thiazole ring on a benzene nucleus is clearly a case of ortho-substitution and therefore must depend on the *o* : *p*-directive influence of the nitrogen atom which becomes the nuclear nitrogen atom of the dicyclic system. The dimethylamino-group in *p*-dimethylamino-phenylthiocarbamide is considerably more basic than the amino-group, and the tendency is, therefore, towards *o* : *p*-substitution with respect to the dimethylamino-group, that is, towards hetero-cyclic ring formation in the meta-position to the thiocarbamide complex. Such formation is doubtless impossible (compare Perkin and Titley, J., 1922, **121**, 1562; Titley, J., 1926, 508), and benzthiazole ring formation in this case is therefore inhibited.

p-Acetylphenylthiocarbamide behaved anomalously on bromination, yielding a bromo-addition compound which, on reduction with sulphurous acid, gave a complex substance free from sulphur, the exact nature of which has not yet been ascertained.

In view of the low reactivity of 5-nitro-1-phenylbenzthiazole towards bromine (Hunter, J., 1926, 538), the effect of the nitro-group on the unsaturation of the heterocyclic nucleus in *3-nitro-1-amino-benzthiazole* (IV) was also examined. Under the usual conditions of bromination, *o*-nitrophenylthiocarbamide yielded what appeared to be a mixture of a tetrabromide and a tribromide of 3-nitro-1-aminobenzthiazole; on reduction in the usual way, this mixture yielded the base (IV). All attempts to brominate this nitroaminobenzthiazole led only to uncrystallisable bromides, which were not investigated.

EXPERIMENTAL.

The arylthiocarbimides required for this work were obtained by adding a solution of the corresponding nuclear-substituted aniline (1 mol.) in chloroform to a well-stirred suspension of thiocarbonyl chloride (1·3 mols.) in water, and isolating the product in the usual way (Dyson and Hunter, *J. Soc. Chem. Ind.*, 1926, **45**, 83T). The arylthiocarbimides were converted into the corresponding thiocarbamides by treatment with alcoholic ammonia (*loc. cit.*) and were usually recrystallised from alcohol.

Bromination.—The thiocarbamide or the benzthiazole was dissolved in chloroform and treated slowly with a solution of bromine in the same solvent. The benzthiazole bromide separated, in some cases at once, in others after the mixture had been heated under reflux, hydrogen bromide being evolved.

1-*Amino*-5-*cyanobenzthiazole tetrabromide* (prepared from *p*-cyanophenylthiocarbamide, 1 g.; chloroform, 15 c.c.; bromine, 1 c.c.; time of refluxing, 10—15 minutes) separated as a reddish-brown, crystalline mass, which was collected on porous earthenware and dried in a vacuum over potassium hydroxide. On heating, it became yellow at 60—70°, colourless at about 150°, and melted to a black, viscous liquid at 236° (Found: Br, 64·0. $C_8H_5N_3Br_4S$ requires Br, 64·6%). The compound lost bromine slowly on exposure to moist air, becoming colourless after some days. It liberated iodine from dilute hydriodic acid (Hunter and Soyka, J., 1926, 2962).

1-*Amino*-5-*cyanobenzthiazole.*—The tetrabromide was suspended in sulphurous acid and treated with sulphur dioxide, and the colourless solution was filtered and treated with ammonia (*d* 0·880); the *base* then separated in white flakes. It crystallised from 50% alcohol in tufts of silky needles, m. p. 196° (Found: S, 18·3. $C_8H_5N_3S$ requires S, 18·3%). This compound was hydrolysed only with difficulty by acids and was usually recovered unchanged after treatment with hydrochloric acid under the usual conditions, this behaviour recalling the similiar properties of 5-cyano-1-phenylbenzthiazole (Bogert and Abrahamson, *J. Amer. Chem. Soc.*, 1922, **44**, 826).

1-*Amino*-5-*cyanobenzthiazole hexabromide* (prepared from the aminocyanobenzthiazole, 0·3 g.; chloroform, 10 c.c.; bromine, 0·3 c.c.; time of refluxing, 1 minute) separated in golden-brown plates, which, after being dried in a vacuum, gradually lightened in colour on heating and charred at about 290° (Found: Br, 74·0. $C_8H_5N_3Br_6S$ requires Br, 73·2%). This compound had the usual properties and was relatively stable to air. On treatment with ammonia (*d* 0·880) it lost 2 mols. of bromine [Found : Br (labile), 48·4. $C_8H_5N_3Br_2S(Br_4)$ requires Br (labile), 48·9%].

1-*Amino*-5-*carbethoxybenzthiazole dibromide* (prepared from *p*-carbethoxyphenylthiocarbamide, 1 g.; chloroform, 20 c.c.; bromine, 1 c.c.; mixture refluxed) separated in small, red crystals which melted at 125° (decomp.) after being dried in a vacuum (Found : Br, 42·0. $C_{10}H_{10}O_2N_2Br_2S$ requires Br, 41·8%). The compound had the usual properties, but was relatively stable to air.

On one occasion, the bromination of *p*-carbethoxyphenylthiocarbamide gave rise to a red *tribromide*, m. p. 152° (decomp.) [Found : Br, 53·0. $(C_{10}H_{10}O_2N_2Br_3S)_2$ requires Br, 52·0%].

1-*Amino*-5-*carbethoxybenzthiazole*.—Either of the preceding bromides was suspended in sulphurous acid and treated with sulphur dioxide until the product was colourless when crushed. The product was then treated with ammonia (*d* 0·880), washed, dried, crystallised from alcohol, and recrystallised from alcohol–ethyl acetate (1 : 1); small, soft, glistening prisms, m. p. 242° (Found : S, 14·0. $C_{10}H_{10}O_2N_2S$ requires S, 14·4%), were thus obtained. On hydrolysis with hydrochloric acid, and extraction with ether, small crystals of 1-*amino*-5-*carboxybenzthiazole* were obtained, which did not melt on heating.

1-*Amino*-5-*carbethoxybenzthiazole tribromide* (prepared from the aminocarbethoxybenzthiazole, 0·2 g.; chloroform; bromine, 0·2 c.c.) separated as a red, crystalline mass. The dried substance turned yellow at 150—160°, became colourless on further heating, and melted at 247° (decomp.) [Found : Br, 51·7. $(C_{10}H_{10}O_2N_2Br_3S)_2$ requires Br, 51·9%]. This compound was relatively stable to air, and the labile bromine removed by ammonia (*d* 0·880) corresponded to 24%.

5-*Chloro*-1-*aminobenzthiazole dibromide* was prepared from *p*-chlorophenylthiocarbamide (1·5 g.) as a red, crystalline mass. After being dried, it became colourless at 135° and charred at 215° (Found : Br, 46·0. $C_7H_5N_2ClBr_2S$ requires Br, 46·5%). It had the usual properties and gradually lost bromine on exposure to air, becoming orange, yellow, and finally colourless.

5-*Chloro*-1-*aminobenzthiazole* was precipitated from the solution obtained from the reduction of the dibromide with sulphurous acid, by ammonia, in lustrous plates, m. p. 198°. On recrystallisation from 60% alcohol, it formed aggregates of small, glistening needles, m. p. 199° (Found : Cl, 19·0. $C_7H_5N_2ClS$ requires Cl, 19·2%). The *acetyl* derivative was obtained by boiling a solution of the base in acetic anhydride for a few minutes and pouring it into alcohol. It crystallised from alcohol–ethyl acetate (2 : 1) in small prisms, m. p. 225° (Found : Cl, 13·8. $C_9H_7ON_2ClS$ requires Cl, 15·7%).

5-*Chloro*-1-*aminobenzthiazole hexabromide* was obtained, by bromination of the base in chloroform with excess of bromine, in glistening, golden plates, which were unmelted at 270° (Found : Br, 73·0. $C_7H_5N_2ClBr_6S$ requires Br, 72·3%).

5-*Chloro*-1-*acetamidobenzthiazole tetrabromide* was obtained from 5-chloro-1-acetamidobenzthiazole in orange-yellow crystals, m. p. 215° (after drying) (Found : Br, 57·5. $C_9H_7ON_2ClBr_4S$ requires Br, 58·5%). It was relatively stable to moist air.

5-*Bromo*-1-*aminobenzthiazole tetrabromide*, prepared from *p*-bromophenylthiocarbamide by the method used in the case of 1-amino-5-cyanobenzthiazole tetrabromide, melted at 82—83° with effervescence, giving a yellow solid which became colourless at 170° and melted at 260—262° (decomp.; softening at 258°) (Found : Br, 73·0. $C_7H_5N_2Br_5S$ requires Br, 72·9%). On reduction with sulphurous acid, the tetrabromide yielded 5-bromo-1-aminobenzthiazole, m. p. 211° (Hunter, J., 1926, 1397).

1-*Amino*-5-*ethoxybenzthiazole tetrabromide hydrobromide*, prepared from 1 g. of *p*-ethoxyphenylthiocarbamide, separated in orange-coloured crystals. After being dried in a vacuum, it became colourless at 120—125° and charred at 200° (Found : Br, 67·8. $C_9H_{10}ON_2Br_4S,HBr$ requires Br, 67·3%).

1-*Amino*-5-*ethoxybenzthiazole*.—The preceding hydrobromide was dissolved in a large volume of sulphurous acid (saturated with sulphur dioxide at 15°), and the *base* precipitated with ammonia. After recrystallisation from alcohol–benzene (1 : 2) and from 50% alcohol, it was obtained in small, lustrous prisms, m. p. 174° (Found : S, 16·0. $C_9H_{10}ON_2S$ requires S, 16·5%).

1-*Amino*-5-*methoxybenzthiazole dibromide* (prepared from *p*-methoxyphenylthiocarbamide, 1 g.; chloroform, 20 c.c.; bromine, 1 c.c.) separated in dark brown granules. After drying in a vacuum, it became orange at 70—80°, colourless at 170°, and charred at 240° (Found : Br, 47·9. $C_8H_8ON_2Br_2S$ requires Br, 47·0%). It had the usual properties, but was very unstable and rapidly lost bromine on exposure to the atmosphere.

1-*Amino*-5-*methoxybenzthiazole* was obtained as in the case of the ethoxy-base, and crystallised from 50% alcohol in small, soft plates, m. p. 147° (Found : S, 17·5. $C_8H_8ON_2S$ requires S, 17·7%).

Bromination. The base (0·2 g.) was brominated in chloroform. A black, tarry mass was obtained which, on exposure to air for some days, yielded a violet solid. On heating, this substance became yellow, white and purple in turn and then melted at 220—225° (decomp.) (Found : Br, 48·1%).

1-*Amino*-5-*methylbenzthiazole Tetrabromide*.—One g. of 1-amino-5-methylbenzthiazole (m. p. 140°; Hunter, J., 1926, 1399) was dissolved in 10 c.c. of chloroform and treated with bromine (1 c.c.), a reddish-brown tar (which rapidly solidified) being precipitated. The filtered solution deposited the *tetrabromide* in chocolate-brown plates with a golden lustre. After drying in a vacuum, the tetrabromide lightened in colour at about 180—190°, but was unmelted at 275° (Found : Br, 66·1. $C_8H_8N_2Br_4S$ requires Br, 66·1%). The compound had the usual properties and liberated iodine from a solution of potassium iodide in pure acetic acid. On exposure to air, it lost bromine, leaving a brown, granular, microcrystalline *tribromide*, m. p. 295° (decomp.) [Found : Br, 58·0. $(C_8H_8N_2Br_3S)_2$ requires Br, 59·4%]. This substance was relatively stable to air.

Bromination of p-*Acetylphenylthiocarbamide.*—One g. of *p*-acetylphenylthiocarbamide in chloroform (20 c.c.) was brominated in the usual way; hydrogen bromide was evolved and a bromo-addition compound separated as a bright yellow, crystalline solid, m. p. 137—140° (decomp.). On reduction with sulphurous acid, this yielded a pale yellow, insoluble solid which did not melt below 300°. This substance was free from sulphur, but contained bromine (Found : Br, 20·6%).

3-*Nitro*-1-*aminobenzthiazole.*—One g. of *o*-nitrophenylthiocarbamide was brominated in the usual way, and the mixture refluxed; hydrogen bromide was slowly evolved. The bromo-addition compound formed glistening, orange-brown crystals, m. p. 288° (decomp.), whose composition corresponded most closely with that of a tribromide [Found : Br, 57·2. $(C_7H_5O_2N_3Br_3S)_2$ requires Br, 55·1. $C_7H_5O_2N_3Br_4S$ requires Br, 62·1%]. On reduction with sulphurous acid, the nitroaminobenzthiazole formed a yellow solid, which crystallised from alcohol–ethyl acetate in small, yellow plates which charred at 232° (Found : S, 15·9. $C_7H_5O_2N_3S$ requires S, 16·4%). Attempts to brominate this base led only to uncrystallisable bromides.

Bromination of *o*-bromophenylthiocarbamide in chloroform gave rise to a *tribromide* of 3-bromo-1-aminobenzthiazole which crystallised in glistening, orange plates, m. p. 155° (decomp.; charring at 285—290°) [Found : Br, 69·1. $(C_7H_5N_2Br_4S)_2$ requires Br, 68·2%].

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