LXV.—*Aminobenzthiazoles. Part XI. The Synthesis of* 5 : 4′-*Disubstituted* 1-*Anilinobenzthiazoles from Nuclear-substituted Thiocarbanilides.*

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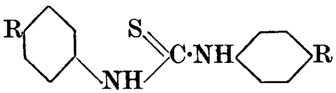
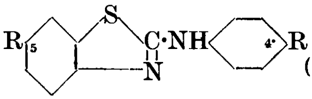
One of the original objects of this investigation (J., 1925, **127**, 2023), *viz.*, the bromination of di-*p*-substituted *s*-diphenylthiocarbamides (I) and of the corresponding 5 : 4′-disubstituted 1-anilinobenzthiazoles (II) has now been studied.

(I.)

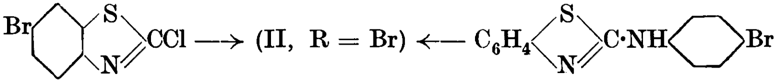




(II.)

On account of the retarding effect of nuclear bromine on the closure of the thiazole ring (Hunter and Soyka, J., 1926, 2958), the bromination of *s*-di-*p*-bromophenylthiocarbamide (I, R = Br) was first examined.

On treatment with bromine in chloroform, this thiocarbamide yielded a *perbromide* which may be a derivative of the hypothetical $(R{\cdot}NH)_2CBr{\cdot}SBr$ addition compound, since it changed into a *hydropentabromide* of 5 : 4′-dibromo-1-anilinobenzthiazole when the solution was heated. On reduction, the hydropentabromide yielded 5 : 4′-*dibromo*-1-*anilinobenzthiazole* (II, R = Br), which was also prepared by condensation of 1-*chloro*-5-*bromobenzthiazole* (III) with *p*-bromoaniline, and by decomposition with hydroxylic solvents of the bromo-addition compounds obtained by treating 1-anilinobenzthiazole (II, R = H) and 4′-*bromo*-1-*anilinobenzthiazole* (IV) with bromine in chloroform.



(III.) (IV.)

By brominating *s*-di-*p*-chloro- and *s*-di-*p*-fluoro-phenylthiocarbamide, *hydrotribromides* of the corresponding dichloro- and difluoro-anilinobenzthiazoles were obtained, and all attempts to prepare higher bromo-addition compounds were unsuccessful. *s*-Di-*p*-carbethoxyphenylthiocarbamide (I, R = CO_2Et), however, gave rise to an unstable *hydropentabromide* of ethyl 1-anilinobenzthiazole-5 : 4′-dicarboxylate.

The fact that the hydrotribromides and hydropentabromides can also be prepared by bromination of the hydrobromides of the anilinobenzthiazoles themselves in inert solvents suggests that the compounds are best formulated as polyhalide-ion derivatives (Base, $\overset{+}{H}$) $\overset{-}{Br_3}$ and (Base, $\overset{+}{H}$) $\overset{-}{Br_5}$, analogous to the tribromides and pentabromides of the alkali metals (Wells and Wheeler, *Amer. J. Sci.*, 1892, **43**, 476; Ephraim, *Ber.*, 1917, **50**, 1069) and to the ammonium pentabromide described by Roozeboom (*Ber.*, 1881, **14**, 2398).

In the course of these experiments we were led to re-examine the bromination of acetyldiphenylthiocarbamide. Hugershoff and König (*Ber.*, 1901, **34**, 3136) described the formation of a tribromide, $NPhBr{\cdot}CS(Br_2){\cdot}NPhAc$, which yielded a curiously stable "sulphoxide" on treatment with sulphurous acid; subsequently, Hugershoff (*Ber.*, 1903, **36**, 3121) discovered that the alleged sulphoxide was identical with Hofmann's acetanilidobenzthiazole (*Ber.*, 1879, **12**, 1126; 1880, **13**, 11). The tribromide is actually a *hydrotribromide* of 1-acetanilidobenzthiazole, and the formation of such a compound by an acetyl derivative is worthy of note, arising doubtless from the residual basicity of the nuclear nitrogen atom of the amidine system.

The bromination of the anilinobenzthiazoles themselves in chloroform gives rise to unstable bromo-addition compounds which differ strikingly from the Hugershoff bromides, particularly in the ease with which they change into bromo-substitution derivatives.

The effect of a single nuclear halogen substituent on the bromination of thiocarbanilides was also examined. It was found that *s*-*p*-bromo- and *s*-*p*-chloro-diphenylthiocarbamides,

$$NHPh{\cdot}CS{\cdot}NH{\cdot}C_6H_4X,$$

which might conceivably give rise either to 5-substituted 1-anilinobenzthiazoles or to 4′-substituted derivatives, actually yielded bases of the latter type (IV), which were identical with those obtained by condensation of 1-chlorobenzthiazole with the corresponding *p*-halogenated anilines.

The tendency of the substituent to seek the *pp'*-positions in 1-anilinobenzthiazole was also observed in cases other than bromination : nitration of this base by fuming nitric acid and iodination by iodine monochloride both produced 5 : 4'-disubstituted 1-anilinobenzthiazoles, identical with those obtained by bromination of the corresponding di-*p*-substituted *s*-diphenylthiocarbamides—observations which suggest that the equivalence of the aromatic nuclei in the *s*-diarylthiocarbamides is partly maintained in the corresponding anilinobenzthiazoles.

EXPERIMENTAL.

5 : 4'-*Dibromo*-1-*anilinobenzthiazole* (II, R = Br).—(A) *Synthesis from* s-*di*-p-*bromophenylthiocarbamide by way of the hydropentabromide, and the isolation of the intermediate perbromide of the thiocarbamide.* A suspension of 2 g. of *s*-di-*p*-bromophenylthiocarbamide in 30 c.c. of chloroform was treated with a solution of bromine (4 c.c.) in the same solvent (4 c.c.), and the mixture heated under reflux on a steam-bath for ½ hour. The perbromide of the thiocarbamide which first separated dissolved, and hydrogen bromide began to be evolved after an inhibition period of some 10 minutes. The *hydropentabromide* crystallised from the hot solution in orange-red needles, which were collected on porous earthenware and dried rapidly in a vacuum for analysis. Because of the instability of the compound, the crystals were kept in the vacuum until the actual moment of weighing [Found : Br (total), 71·8, 71·4, 71·6; Br (labile) (iodometrically in purified acetic acid), 42·5, 42·0; (iodometrically in chloroform containing a few drops of acetic acid), 41·5, 41·0. $C_{13}H_8N_2Br_2S,HBr(Br_4)$ requires Br (total), 71·4; Br (labile), 40·8%]. The hydropentabromide melted with decomposition at 170°, and rapidly lost bromine on exposure to moist air; no lower bromide could, however, be isolated.

The hydropentabromide, suspended in sulphurous acid, was treated with sulphur dioxide until the solid was colourless when crushed. The mixture was basified with ammonia (*d* 0·880) and the product was washed with boiling water and twice recrystallised from alcohol–ethyl acetate, 5 : 4'-*dibromo*-1-*anilinobenzthiazole* being obtained in silky needles, m. p. 221° (Found : N, 7·3; Br, 41·5; S, 8·5. $C_{13}H_8N_2Br_2S$ requires N, 7·3; Br, 41·7; S, 8·3%). The *acetyl* derivative, prepared by boiling a solution of the base in acetic anhydride for a few minutes and diluting the solution with absolute alcohol, separated from alcohol–ethyl acetate in needles, m. p.

205—206° (Found : Br, 37·5. $C_{15}H_{10}ON_2Br_2S$ requires Br, 37·6%). The *hydrobromide*, prepared by saturating a warm suspension of the base in chloroform (0·5 g. in 40 c.c.) with dry hydrogen bromide and concentrating the resulting solution (after filtration) under reduced pressure at laboratory temperature, crystallised in small needles, m. p. 250° (decomp. with charring at 247°), which retained a small quantity of solvent and gave a high value for bromine (Found : Br, 52·9. $C_{13}H_8N_2Br_2S,HBr$ requires Br, 51·6%). Recrystallisation from ethyl acetate and similar solvents led to decomposition into the original components ; the hydrobromide was also completely decomposed by cold water, and therefore could not be prepared by concentrating solutions of the dibromo-base in hydrobromic acid, even of *d* 1·45.

By treating a solution of the hydrobromide in chloroform, prepared as described above, with 5 c.c. of bromine and concentrating the resulting solution at 15°/30 mm., orange-red needles of the hydropentabromide were obtained which, after drying, had m. p. 170° (decomp.), alone and when mixed with a specimen prepared by brominating *s*-di-*p*-bromophenylthiocarbamide. The identity was further confirmed by analysis [Found : Br (total), 71·7 ; Br (labile), 41·5%].

A mixture of 3 g. of *s*-di-*p*-bromophenylthiocarbamide and 3 c.c. of bromine in 50 c.c. of chloroform was well shaken and kept for a short time; the perbromide of the thiocarbamide formed orange needles, m. p. 164° (decomp.) (Found : Br, 71·1%). On treatment of the perbromide with sulphurous acid, the thiocarbamide was regenerated; it was identified by its properties, m. p., and the m. p. of a mixture with a genuine specimen. On treatment with 20% potassium hydroxide solution, the perbromide yielded a product which separated from alcohol–ethyl acetate in colourless flakes, m. p. 275° (decomp. with charring) (Found : Br, 41·3%).

(B) *Synthesis from* p-*bromophenylthiocarbimide by way of* 1-*chloro*-5-*bromobenzthiazole.* A mixture of 30 g. of *p*-bromophenylthiocarbimide (purified by melting on a steam-bath with fused calcium chloride and redistillation under reduced pressure) and 30 g. of phosphorus pentachloride was heated for 30—40 hours in a sealed tube at 170—180°. The product was fractionated under reduced pressure and the fraction, b. p. 157—159°/18 mm., was redistilled. 1-*Chloro*-5-*bromobenzthiazole* formed small white crystals, m. p. 89°, from ether (yield, 0·8 g.) (0·0953 g. gave 0·1280 g. of mixed silver halides. $C_7H_3NClBrS$ requires 0·1270 g.).

A mixture of 0·3 g. of 1-chloro-5-bromobenzthiazole and 0·25 g. of *p*-bromoaniline was gently warmed. Recrystallisation of the product from alcohol–ethyl acetate gave needles of slightly impure

5 : 4′-dibromo-1-anilinobenzthiazole (m. p. 213°, mixed m. p. 218°), from which the pure acetyl derivative (m. p. and mixed m. p. 205—206°) was prepared.

(C) *Synthesis of* 4′-*bromo*-1-*anilinobenzthiazole from* s-*phenyl*-p-*bromophenylthiocarbamide and from* 1-*chlorobenzthiazole and* p-*bromoaniline, and its conversion into the* 5 : 4′-*dibromo-base.* (i) The *hydrotribromide*, m. p. 148° (decomp.) [Found : Br (total), 58·5; Br (labile), 30·0. $C_{13}H_9N_2BrS,HBr(Br_2)$ requires Br (total), 58·6; Br (labile), 29·3%], which crystallised after the solution obtained from 1·3 g. of phenyl-*p*-bromophenylthiocarbamide (in 25 c.c. of chloroform) and bromine (2·5 c.c. in 3 c.c. of chloroform) had been refluxed for 5 minutes, was reduced in the usual way. The 4′-*bromo*-1-*anilinobenzthiazole* separated from alcohol–ethyl acetate in feathery needles, m. p. 214—215° (Found : Br, 26·5; S, 10·2. $C_{13}H_9N_2BrS$ requires Br, 26·2; S, 10·5%). (ii) The condensation of a mixture of 0·3 g. of 1-chlorobenzthiazole with 0·3 g. of *p*-bromoaniline was carried out exactly as described under (B) and the product obtained after basification and recrystallisation was identified with 4′-bromo-1-anilinobenzthiazole by m. p. and mixed m. p. determination.

A suspension of 0·5 g. of 4′-bromo-1-anilinobenzthiazole in 20 c.c. of chloroform was treated with 0·9 c.c. of bromine, the bromo-addition compound which separated from the resulting solution was dissolved in boiling absolute alcohol, and the product obtained by concentrating this solution was basified. The 5 : 4′-dibromo-1-anilinobenzthiazole obtained, after recrystallisation from alcohol–ethyl acetate (animal charcoal), had m. p. 217° and mixed m. p. 219° (acetyl derivative, m. p. 203°, mixed m. p. 204°).

A similar experiment to this with 1·5 g. of 1-anilinobenzthiazole yielded a *hexabromide*, m. p. 140° (Found : Br, 68·3. $C_{13}H_{10}N_2Br_6S$ requires Br, 68·0%), which gave 5 : 4′-dibromo-1-anilinobenzthiazole, m. p. 220°, mixed m. p. 221° (Found : Br, 41·5%), on being dissolved in boiling absolute alcohol.

Hugershoff's dibromoanilinobenzthiazole (*Ber.*, 1903, **36**, 3121) was still ill-defined after several recrystallisations and usually had m. p. 195° (on one occasion a specimen, m. p. 200°, was obtained). It appears to consist mainly of 5 : 4′-dibromo-1-anilinobenzthiazole, since a mixture of the 195° product (Found : Br, 41·0%) with the 5 : 4′-dibromo-base melted at 198—200°. Moreover, the 195° product yielded an acetyl derivative which melted at 191°, and at 199° when mixed with 5 : 4′-dibromo-1-acetanilidobenzthiazole.

Bromination of 5 : 4′-*Dibromo*-1-*anilinobenzthiazole.*—By treatment of the dibromo-base (1·4 g.) in chloroform (25 c.c.) with bromine (2·5 c.c.), an unstable orange *hexabromide* was obtained, m. p. 254° (Found : Br, 73·6. $C_{13}H_8N_2Br_8S$ requires Br, 74·1%). From a hot absolute alcoholic solution of this, a slightly impure *tetrabromo*-substitution derivative was obtained which separated from alcohol–ethyl acetate in colourless flakes, m. p. 196—198° (Found: Br, 57·7. $C_{13}H_6N_2Br_4S$ requires Br, 59·0%). Attempts to purify this substance further by recrystallisation were unsuccessful.

5 : 4′-*Dichloro*-1-*anilinobenzthiazole* (II, R = Cl).—The *hydrotribromide* separated, during the refluxing of the solution obtained from *s*-di-*p*-chlorophenylthiocarbamide (1·4 g.), chloroform (18 c.c.), and bromine (1·6 c.c.), in orange needles, m. p. 165—167° (decomp.; sintering at 158°) [Found: Br (total), 44·6; Br (labile), 30·0. $C_{13}H_8N_2Cl_2S,HBr(Br_2)$ requires Br (total), 44·8; Br (labile), 29·9%]. This compound, which is remarkably stable, was also produced in all attempts to prepare a hydropentabromide of the dichloroanilinobenzthiazole by using a high concentration of bromine. On reduction, it yielded 5 : 4′-*dichloro*-1-*anilinobenzthiazole*, which separated from alcohol–ethyl acetate in silky white plates, m. p. 224° (Found: N, 9·6; Cl, 23·8; S, 10·6. $C_{13}H_8N_2Cl_2S$ requires N, 9·5; Cl, 24·1; S, 10·85%). The *acetyl* derivative formed needles, m. p. 186—187° (Found: Cl, 21·2. $C_{15}H_{10}ON_2Cl_2S$ requires Cl, 21·1%). The *hydrobromide*, prepared as in the case of the 5: 4′-dibromo-compound, formed yellowish plates, m. p. 217° (sintering at 212°) (0·1399 g. gave 0·1780 g. of silver halides. $C_{13}H_8N_2Cl_2S,HBr$ requires 0·1771 g.).

The hydrotribromide was also prepared by saturating a suspension of 0·5 g. of the dichloro-base in 40 c.c. of chloroform with hydrogen bromide, adding 5 c.c. of bromine to the solution, and concentrating it under reduced pressure at laboratory temperature. It crystallised in orange needles, which melted at 165—167° alone and when mixed with a specimen of the Hugershoff bromide [0·1278 g. gave 0·2022 g. of silver halides. Calc. 0·2027 g. Found: Br (labile), 29·5%].

By concentrating the solution obtained from 0·25 g. of the dichloro-base and 0·7 c.c. of bromine in chloroform at 15°/30 mm., a *hexabromide* was obtained which crystallised in orange prisms, m. p. 253° (decomp.) (0·1770 g. gave 0·3238 g. of silver halides. $C_{13}H_8N_2Cl_2Br_6S$ requires 0·3233 g.).

Synthesis of 4′-*Chloro*-1-*anilinobenzthiazole from* s-*Phenyl*-p-*chlorophenylthiocarbamide and from* 1-*Chlorobenzthiazole*.—(i) The bromo-addition compound obtained by refluxing a mixture of 1·3 g. of the chlorodiphenylthiocarbamide, chloroform (15 c.c.), and bromine (1·3 c.c.) for 6 minutes and concentrating the solution at 15°/30 mm. crystallised in orange needles, m. p. 130° (decomp.) (0·2238 g. gave 0·3435 g. of silver halides). 4′-*Chloro*-1-*anilinobenzthiazole* separated from alcohol–ethyl acetate in silky needles, m. p. 196° (Found: Cl, 14·0; S, 12·5. $C_{13}H_9N_2ClS$ requires Cl, 13·6; S, 12·3%). (ii) 0·3 G. of 1-chlorobenzthiazole was condensed with *p*-chloroaniline as in the previous case. The base obtained had m. p. 198° after recrystallisation and melted at 197° when mixed with the specimen prepared in (i).

5 : 4′-*Di-iodo*-1-*anilinobenzthiazole.*—(A) On refluxing a mixture of *s*-di-*p*-iodophenylthiocarbamide (1 g.), chloroform (15 c.c.), and bromine (1·5 c.c.), a red bromide separated, m. p. 185°. Concentration of the mother-liquor yielded another bromide, which crystallised in yellow needles, m. p. 211°.

On reduction, both bromides yielded 5 : 4′-*di-iodo*-1-*anilinobenzthiazole*, which crystallised in glistening needles, m. p. 193° (decomp.), from alcohol–ethyl acetate (Found : I, 53·0; S, 6·9. $C_{13}H_8N_2I_2S$ requires I, 53·1 ; S, 6·7%).

(B) The 5 : 4′-di-iodo-base was also obtained by treating 1-anilinobenzthiazole (1·5 g.) in glacial acetic acid (15 c.c.) with iodine monochloride (1·5 g.), warming the resulting solution, and diluting it with water (200 c.c.). The product was identified by m. p. and mixed m. p. determination.

5 : 4′-*Difluoro*-1-*anilinobenzthiazole.*—The solution obtained by refluxing 2 g. of *s*-di-*p*-fluorophenylthiocarbamide, 30 c.c. of chloroform, and 3 c.c. of bromine for 20 minutes was concentrated under reduced pressure; a *hydrotribromide* then crystallised in orange needles, m. p. 150—152° (decomp.; sintering at 148°) [Found : Br (total), 48·0; Br (labile), 32·0. $C_{13}H_8N_2F_2S,HBr(Br_2)$ requires Br (total), 47·7; Br (labile), 31·8%]. This compound was also prepared from the difluoro-base, hydrogen bromide, and bromine in chloroform.

5 : 4′-*Difluoro*-1-*anilinobenzthiazole* crystallises from methyl alcohol–ethyl acetate in needles, m. p. 227—228° (Found : S, 12·6. $C_{13}H_8N_2F_2S$ requires S, 12·2%). It is much more soluble than the dichloro-, dibromo-, and dicyano-bases in ordinary solvents.

5 : 4′-*Dinitro*-1-*anilinobenzthiazole.*—(A) The red solid obtained by refluxing 1 g. of *s*-di-*p*-nitrophenylthiocarbamide with bromine (1 c.c.) and chloroform (12 c.c.) was reduced by sulphurous acid. The *dinitro-base* separated from alcohol–ethyl acetate in brilliant yellow plates, m. p. 280° (Found : N, 17·5; S, 10·15. $C_{13}H_8O_4N_4S$ requires N, 17·7 ; S, 10·1%).

(B) *Nitration of* 1-*anilinobenzthiazole.* 1 G. of the anilino-base was treated with 5 c.c. of nitric acid (*d* 1·5) at laboratory temperature, a further 5 c.c. of the same acid were then added, and the solution was kept at 15° for an hour. On addition of water (300 c.c.), the dinitro-base was precipitated; after recrystallisation it melted at 280°, alone and when mixed with the specimen already described.

5 : 4′-*Dicyano*-1-*anilinobenzthiazole.*—The bromo-addition *compound* obtained from the dicyanodiphenylthiocarbamide (1·6 g.),

chloroform (20 c.c.), and bromine (2 c.c.) crystallised during refluxing in golden plates, m. p. 159—160° (decomp.) (Found: Br, 66·5. $C_{15}H_8N_4Br_6S,HBr$ requires Br, 66·9%). The *dicyano-base* separated from alcohol–ethyl acetate in small needles, m. p. 222° (Found: S, 11·2. $C_{15}H_8N_4S$ requires S, 11·6%). On hydrolysis with 25% hydrochloric acid for 30—40 hours, it gave 1-anilinobenzthiazole-5 : 4′-dicarboxylic acid, which was more conveniently prepared from *s*-di-*p*-carbethoxyphenylthiocarbamide.

Ethyl 1-*Anilinobenzthiazole*-5 : 4′-*dicarboxylate*.—The solution obtained by refluxing 1·1 g. of *s*-di-*p*-carbethoxyphenylthiocarbamide, chloroform (18 c.c.), and bromine (1·5 c.c.) for 40 minutes was concentrated under reduced pressure at laboratory temperature; a *hydropentabromide* then separated in small orange crystals, m. p. 110° (decomp.; softening at 97°) [Found: Br (total), 52·6; Br (labile), 44·0. $C_{19}H_{18}O_4N_2S,HBr(Br_4)$ requires Br (total), 51·9; Br (labile), 41·5%]. On reduction, *ethyl* 1-*anilinobenzthiazole*-5 : 4′-*dicarboxylate* was obtained which, after two recrystallisations from alcohol–ethyl acetate, formed small white plates, m. p. 190—192° (Found: S, 8·8. $C_{19}H_{18}O_4N_2S$ requires S, 8·65%). The analysis of this compound for nitrogen by Dumas's method gave consistently high results due to the formation of methane and we therefore analysed the acid. *Hydrolysis*. The ethyl ester (0·5 g.) was hydrolysed by refluxing it with 50 c.c. of 25% hydrochloric acid for 30—40 minutes. 1-*Anilinobenzthiazole*-5 : 4′-*dicarboxylic acid* formed small white plates from alcohol, which were unmelted at 290° (Found: N, 9·0; S, 10·1. $C_{15}H_{10}O_4N_2S$ requires N, 8·9; S, 10·2%).

Bromination of s-*Di*-p-*anisylthiocarbamide*.—A suspension of 1·3 g. of the dianisylthiocarbamide in chloroform (10 c.c.) was treated with bromine (1·5 c.c.), and the mixture refluxed for 10 minutes. On cooling, brick-red crystals of a bromide separated, m. p. 137° (decomp.) (Found: Br, 62·2%), which yielded a *dibromo*-5 : 4′-*dimethoxy*-1-*anilinobenzthiazole*, m. p. 240°, on reduction (Found: Br, 35·9; S, 7·15. $C_{15}H_{12}O_2N_2Br_2S$ requires Br, 36·0; S, 7·2%).

Bromination of Acetyldiphenylthiocarbamide and of 1-*Acetanilidobenzthiazole*.—(i) The hydrotribromide prepared from 1·2 g. of acetyldiphenylthiocarbamide and bromine (2 c.c.) in chloroform (30 c.c.) crystallised in orange needles, m. p. 167° (decomp.) [Found: Br (total), 47·5; Br (labile), 31·0. Calc. for $C_{15}H_{12}ON_2S,HBr(Br_2)$: Br (total), 47·2; Br (labile), 31·4%]. (ii) The hydrotribromide prepared from 1 g. of 1-acetanilidobenzthiazole, 30 c.c. of chloroform, excess of dry hydrogen bromide, and bromine (2·5 c.c.) had the same appearance as the above and melted at 166°, and at 167° when mixed with Hugershoff's compound [Found: Br (total), 47·5; Br (labile), 32·0%]. (iii) Concentration under reduced pressure of the solution obtained from 1 g. of acetanilidobenzthiazole, 20 c.c. of chloroform and 2 c.c. of bromine yielded a *hexabromo-addition compound*, which crystallised in orange needles, m. p. 163° (decomp.) (Found : Br, 63·8. $C_{15}H_{12}ON_2Br_6S$ requires Br, 64·2%).

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