## 254. *The Unsaturation and Tautomeric Mobility of Heterocyclic Compounds. Part IV. The Methylation and Bromination of a Series of* 2-p-*Substituted Anilinothiazoles.*

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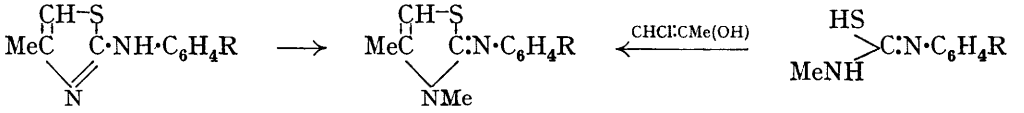
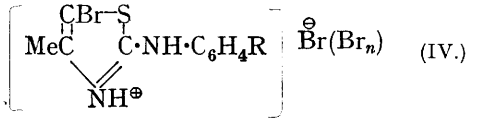
It has been shown (Hunter and Jones, J., 1930, 2190) that the phenyl group of the anilino-substituent in 1-anilinobenzthiazole competes with the aromatic conjugation of the heterocyclic nucleus for the proximity of the αβ-double bond of the semi-cyclic amidine system during methylation, leading to the production of a considerable proportion of 1-phenylmethylaminobenzthiazole in addition to the isomeric imino-dihydro-derivative. This effect is further enhanced by the presence of a *p*-bromine substituent in the anilino-grouping, since 4'-bromo-1-anilinobenzthiazole yields solely the methyl derivative corresponding to the latter form on methylation.

It has now been found that 2-anilino-, and 2-p-*chloro-*, *-bromo-*, *-iodo-*, *-ethoxy-*, *-hydroxy-*, and *-nitro-anilino-4-methylthiazoles* (I; R = H, Cl, Br, I, OEt, OH, or $NO_2$) react apparently exclusively in the amino-aromatic form on methylation, yielding 2-p-*substituted-phenylimino-3 : 4-dimethyl-2 : 3-dihydrothiazoles* (II) identical with the products of condensation of monochloroacetone with the corresponding *s*-arylmethylthiocarbamides (III).




On bromination under conditions in which benzthiazoles usually give rise to bromo-addition compounds (Hunter, J., 1930, 125), the 2-arylamino-4-methylthiazoles underwent substitution with the production of *hydro-tri-* or *-penta-bromides* of bases which are evidently 5-bromothiazoles (IV; $n = 2$ or 4) (cf. Dyson, Hunter, Jones, and Styles, *J. Indian Chem. Soc.*, 1931, **8**, 147).




When the double bond (4 : 5) of the thiazole ring is reduced as in 2-anilino-5-methyl-4 : 5-dihydrothiazole, however, the phenyl group becomes once more capable of attracting the double bond of the amidine system, with the production of the methyl derivatives obtained from the 2-arylimino-2 : 3 : 4 : 5-tetrahydro-phase on methylation (Young and Crookes, J., 1906, **89**, 59).

### Experimental.

*Synthesis of* 2-p-*Chloroanilino-4-methylthiazole* (I, R = Cl).—The following condensation is typical of the series. A mixture of *p*-chlorophenylthiocarbamide (10 g.) and monochloroacetone ( 6 c.c.) was gently heated until a violent reaction took place, the resulting gum was extracted with boiling 20% hydrochloric acid (100 c.c.), and the extract basified with ammonia (*d* 0·880). The *thiazole* was extracted with chloroform and recrystallised from methyl alcohol (charcoal), separating in glistening needles (4 g.), m. p. 147° (Found : Cl, 16·0; S, 14·3. $C_{10}H_9N_2ClS$ requires Cl, 15·8; S, 14·2%).

*Methylation of* 2-p-*Chloroanilino-4-methylthiazole, and Synthesis of* 2-p-*Chlorophenylimino-3 : 4-dimethyl-2 : 3-dihydrothiazole.*—The following experiments are typical of the series. (i) A mixture of the chloro-anilino-base (1·5 g.) and methyl iodide (2 c.c.) was heated in a sealed tube at 100° for 5—6 hours, and the product was basified with hot 20% potassium hydroxide and extracted with chloroform. The gum (1·6 g.) so obtained was dissolved in acetone (10 c.c.) and treated with picric acid (1·6 g. in 10 c.c. of acetone). The *picrate* of 2-p-chlorophenylimino-3 : 4-dimethyl-2 : 3-dihydrothiazole thereby obtained was recrystallised from acetone, separating in large yellow prisms, m. p. 138—139° (slight softening at 120°) (Found : Cl, 7·5; S, 7·0.

$C_{11}H_{11}N_2ClS,C_6H_3O_7N_3$ requires Cl, 7·6; S, 6·8%). (ii) 2 G. of *s*-*p*-chlorophenylmethylthiocarbamide were condensed with monochloroacetone (1·2 c.c.) as above, and the gum isolated by extraction with chloroform was converted into picrate as before. On recrystallisation, this picrate had m. p. 138—139° (slight softening at 120°) alone, and when mixed with the preceding specimen.

*Bromination of* 2-p-*Chloroanilino*-4-*methylthiazole*.—The solution obtained by treating the thiazole (2 g.) in chloroform (20 c.c.) with bromine (2 c.c.) at 0° was concentrated in a vacuum at room temperature, and a *hydropentabromide* of 5-bromo-2-*p*-chloroanilino-4-methylthiazole separated in small orange-red prisms, which were dried in a vacuum, m. p. 128—129° (decomp.) [Found : Br (total), 67·4; Br (labile), 45·4. $C_{10}H_8N_2ClBrS,HBr(Br_4)$ requires Br (total), 68·2; Br (labile), 45·4%]. On being kept in a vacuum over potassium hydroxide for 48 hours, they lost bromine, yielding a *hydrotribromide*, m. p. 124—126° (decomp.) [Found : Br (total), 58·5; Br (labile), 29·6. $C_{10}H_8N_2ClBrS,HBr(Br_2)$ requires Br (total), 58·8; Br (labile), 29·4%]. On treatment with a large volume of sulphurous acid, basification of the colourless product with ammonia, and recrystallisation from cold alcohol, either bromo-compound yielded 5-*bromo*-2-p-*chloroanilino*-4-*methylthiazole*, m. p. 126—127° (decomp.) (Found : Br, 26·7. $C_{10}H_8N_2ClBrS$ requires Br, 26·3%).

2-p-*Bromoanilino*-4-*methylthiazole* (I, R = Br), prepared from *p*-bromophenylthiocarbamide, separated from methyl alcohol (charcoal) in fine needles, m. p. 162° (Found : Br, 29·6; S, 12·1. $C_{10}H_9N_2BrS$ requires Br, 29·7; S, 11·9%). An attempt to methylate this base (1 g.) with methyl sulphate (4 c.c.) in alcohol (10 c.c.) (cf. Hunter and Jones, *loc. cit.*) proved unsuccessful, the base (0·9 g.) being recovered unchanged. The *picrate* obtained from the gum formed by methylation with methyl iodide, as in the previous case, crystallised in glistening yellow prisms, m. p. 154° alone, and when mixed with the picrate (m. p. 154—155°) obtained from the gum formed by condensation of *s*-*p*-bromophenylmethylthiocarbamide with monochloroacetone (Found : C, 39·75; H, 2·8; N, 13·7; S, 6·3; Br, 15·7. $C_{11}H_{11}N_2BrS,C_6H_3O_7N_3$ requires C, 39·8; H, 2·7; N, 13·6; S, 6·25; Br, 15·6%).

5-*Bromo*-2-p-*bromoanilino*-4-*methylthiazole*.—The *hydropentabromide* of this thiazole, obtained by bromination of 2-*p*-bromoanilino-4-methylthiazole, formed orange-red prisms, m. p. 114—115° (decomp.) [Found : Br (total), 73·6; Br (labile), 40·8. $C_{10}H_8N_2Br_2S,HBr(Br_4)$ requires Br (total), 74·7; Br (labile), 42·7%], and yielded a *hydrotribromide*, m. p. 118—119°, on standing over potassium hydroxide for 48 hours [Found : Br, 67·6. $C_{10}H_8N_2Br_2S,HBr(Br_2)$ requires Br, 67·9%]. On reduction with sulphurous acid, both hydrobromides yielded 5-*bromo*-2-p-*bromoanilino*-4-*methylthiazole*, which separated from cold alcohol in small needles, m. p. 137° (Found : Br, 45·9. $C_{10}H_8N_2Br_2S$ requires Br, 46·0%). On reduction with tin and hydrochloric acid, however, this base lost one atom of bromine, regenerating 2-*p*-bromoanilino-4-methylthiazole, m. p. 160—161° alone, and when mixed with the original specimen.

2-op-*Dibromoanilino*-4-*methylthiazole*, synthesised from 2 : 4-dibromophenylthiocarbamide and monochloroacetone, separated from alcohol in needles, m. p. 136—137° (Found : Br, 46·1. $C_{10}H_8N_2Br_2S$ requires Br, 46·0%). Mixed with 5-bromo-2-*p*-bromoanilino-4-methylthiazole, it melted at 115°.

2-p-*Iodoanilino*-4-*methylthiazole* crystallised in snow-white needles, m. p. 168—169° (Found : S, 9·9. $C_{10}H_9N_2IS$ requires S, 10·1%). The *picrate* of the gum obtained on methylation had m. p. 154—155° alone and when mixed with the picrate of 2-*p*-iodophenylimino-3 : 4-dimethyl-2 : 3-dihydrothiazole (m. p. 156°), obtained from *s*-*p*-iodophenylmethylthiocarbamide (Found : C, 36·2; H, 2·6; N, 12·5; S, 5·6; I, 22·5. $C_{11}H_{11}N_2IS,C_6H_3O_7N_3$ requires C, 36·5; H, 2·5; S, 5·7; N, 12·5; I, 22·7%).

2-p-*Ethoxyanilino*-4-*methylthiazole* separated from methyl alcohol in small plates, m. p. 135—136° (Found : S, 13·9. $C_{12}H_{14}ON_2S$ requires S, 13·7%). The gum obtained by heating this base (1 g.) with methyl iodide (0·4 c.c.) at 100° solidified on keeping, and separated from methyl alcohol in small plates, m. p. 114—115°, alone, and when mixed with a specimen of 2-p-*ethoxyphenylimino*-3 : 4-*dimethyl*-2 : 3-*dihydrothiazole* prepared from *s*-*p*-ethoxyphenylmethylthiocarbamide (Found : S, 13·0. $C_{13}H_{16}ON_2S$ requires S, 12·9%).

5-*Bromo*-2-p-*ethoxyanilino*-4-*methylthiazole*.—The *hydrotribromide* of this thiazole formed red prisms, m. p. 119—120° [Found : Br (total), 58·2; Br (labile), 27·6. $C_{12}H_{13}ON_2BrS,HBr(Br_2)$ requires Br (total), 57·8; Br (labile), 28·9%]. The *base*, obtained by grinding this salt with cold sulphurous acid, separated from cold alcohol in needles, m. p. 136—137° (Found : Br, 25·8. $C_{12}H_{13}ON_2BrS$ requires Br, 25·6%). On reduction with tin and hydrochloric acid, it lost bromine, with regeneration of 2-*p*-ethoxyanilino-4-methylthiazole (m. p. and mixed m. p.).

2-p-*Hydroxyanilino*-4-*methylthiazole* had m. p. 220° (Found : S, 15·4. $C_{10}H_{10}ON_2S$ requires

S, 15·4%). 2-p-*Hydroxyphenylimino*-3 : 4-*dimethyl*-2 : 3-*dihydrothiazole*, obtained by methylation of the anilino-base, had m. p. 189—190° (Found : S, 14·5. $C_{11}H_{12}ON_2S$ requires S, 14·5%).

s-p-*Hydroxyphenylmethylthiocarbamide*, prepared from *p*-hydroxyphenylthiocarbimide (Dyson and George, J., 1924, **125**, 1702) and methylamine in alcohol, separated from alcohol in prisms, m. p. 186° (Found : S, 17·6. $C_8H_{10}ON_2S$ requires S, 17·6%). The dihydrothiazole obtained from this had m. p. 189° alone and when mixed with the specimen obtained by methylation of 2-*p*-hydroxyanilino-4-methylthiazole.

2-p-*Nitroanilino*-4-*methylthiazole* crystallised from alcohol–ethyl acetate in red needles, m. p. 181—182° (Found : S, 13·8. $C_{10}H_9O_2N_3S$ requires S, 13·6%). The *iminodimethyldihydrothiazole*, obtained by methylation of this, crystallised from alcohol–ethyl acetate in long, orange-red needles, m. p. 151° (Found : S, 13·0. $C_{11}H_{11}O_2N_3S$ requires S, 12·85%).

s-p-*Nitrophenylmethylthiocarbamide*, prepared from *p*-nitrophenylthiocarbimide and methylamine, crystallised from alcohol in small yellow prisms, m. p. 183—184° (Found : S, 15·0. $C_8H_9O_2N_3S$ requires S, 15·2%). Its condensation product with monochloroacetone had m. p. 150° alone and when mixed with the foregoing specimen.

5-*Bromo*-2-p-*nitroanilino*-4-*methylthiazole hydropentabromide* formed red-brown crystals, m. p. 113—114° (decomp.) [Found : Br (total), 65·5; Br (labile), 43·6. $C_{10}H_8O_2N_3BrS,HBr(Br_4)$ requires Br (total), 67·1; Br (labile), 44·7%]. The *base* separated from alcohol in orange-yellow crystals, m. p. 162° (decomp.) (Found : Br, 25·3. $C_{10}H_8O_2N_3BrS$ requires Br, 25·5%).

*Methylation and Bromination of* 2-*Anilino*-4-*methylthiazole*.—Methylation of the base (Young and Crookes, *loc. cit.*) yielded 2-phenylimino-3 : 4-dimethyl-2 : 3-dihydrothiazole, m. p. 71—72°, alone and when mixed with a specimen synthesised from *s*-phenylmethylthiocarbamide (Found : S, 15·5. Calc. : S, 15·7%). The isomeric 2-phenylmethylamino-4-methylthiazole, prepared from *as*-phenylmethylthiocarbamide, formed a gum which did not solidify on keeping in a vacuum for several days; its *picrate* had m. p. 113—114° (Found : S, 7·2. $C_{11}H_{12}N_2S,C_6H_3O_7N_3$ requires S, 7·4%).

Bromination of 2-anilino-4-methylthiazole yielded a red unstable *hydropentabromide* of 5-bromo-2-anilino-4-methylthiazole, m. p. 121—122° [Found : 69·7. $C_{10}H_9N_2BrS,HBr(Br_4)$ requires Br, 71·6%]. The *base*, obtained by reduction with sulphurous acid, had m. p. 131—132° (decomp.) (Found : Br, 29·3. $C_{10}H_9N_2BrS$ requires Br, 29·7%); its mixture with 2-*p*-bromoanilino-4-methylthiazole melted at 124°, after sintering at 118°.

5-*Bromo*-2-*phenylimino*-3 : 4-*dimethyl*-2 : 3-*dihydrothiazole hydrotribromide* formed small red crystals, m. p. 127—128° [Found : Br (total), 61·4; Br (labile), 29·0. $C_{11}H_{11}N_2BrS,HBr(Br_2)$ requires Br (total), 61·1; Br (labile), 30·5%]; the *base* formed needles, m. p. 123° (Found : Br, 28·4. $C_{11}H_{11}N_2BrS$ requires Br, 28·3%).

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