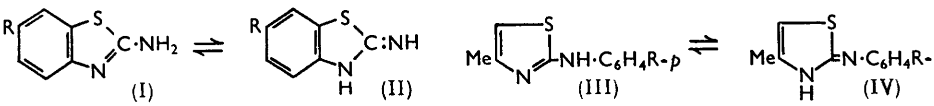
157. *The Unsaturation and Tautomeric Mobility of Heterocyclic Compounds. Part XIII.* The Methylation of Some Amino-thiazole Derivatives.*

By R. F. Hunter, E. R. Parken, and Eileen M. Short.

6-Substituted 2-aminobenzothiazoles [1] and 2-(*p*-substituted anilino)-4-methylthiazoles [2] which apparently react wholly in the amino-aromatic form with dimethyl sulphate and methyl iodide alone, to give iminomethylthiazoline derivatives, yield mixtures of methyl isomers corresponding to both tautomeric forms in the presence of ethanolic sodium ethoxide. 2-Anilinonaphtho-[2,1]- and -[1,2]-thiazole similarly give greatly enhanced proportions of the methylaminothiazole derivatives formed in small amount with methyl iodide alone.

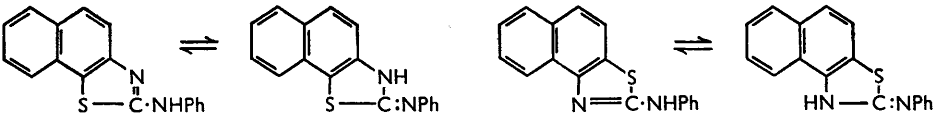
The methylation of representative 6-substituted 2-aminobenzothiazoles [1] (I $\rightleftharpoons$ II) and 2-(*p*-substituted anilino)-4-methylthiazoles [2] (III $\rightleftharpoons$ IV), which apparently react exclusively in the amino-aromatic form to give 2-imino-3-methyl- and 2-arylimino-3 : 4-dimethyl-thiazolidine derivatives, have been re-examined in respect of the influence of ethoxide ions. As might be expected from the results obtained with 6-substituted, 6 : 4′-disubstituted, and 4′-substituted 2-anilinobenzothiazoles,[3] ethoxide ions cause substantial methylation on the non-nuclear nitrogen atom of the semicyclic amidine system, leading to pairs of isomeric methyl derivatives in accordance with " classical tautomerism."

Methylation of 2-amino-6-methylbenzothiazole (I $\rightleftharpoons$ II; R = Me) in ethanolic sodium ethoxide in the presence of a large excess of dimethyl sulphate gave a 2 : 3 mixture of 2-methylamino-6-methylbenzothiazole and 2-imino-3 : 6-dimethylbenzothiazoline. The 6-chloro- and the 6-bromo-derivative (I $\rightleftharpoons$ II; R = Cl or Br) gave respectively 1 : 2 and 1 : 4 mixtures of the corresponding isomers.



(I) (II) (III) (IV)

4-Methyl-2-*p*-toluidinothiazole (III $\rightleftharpoons$ IV; R = Me) with methyl iodide and an excess of ethanolic sodium ethoxide gave a mixture of 2-*p*-tolylimino-3 : 4-dimethyl- and 2-*p*-tolylmethylamino-4-methyl-thiazole (the ratio could not be estimated on account of gum-formation). 2-*p*-Chloro- and 2-*p*-bromo-anilino-4-methylthiazole (III $\rightleftharpoons$ IV; R = Cl and Br) gave respectively 4 : 1 and 5 : 2 mixtures in which the 3 : 4-dimethylthiazolines predominated.



(V) (VI) (VII) (VIII)

2-Anilinonaphtho[2,1]thiazole (V $\rightleftharpoons$ VI) with methyl iodide alone, which was previously reported [4] to yield solely the 3-methyl-2-phenyliminonaphthothiazoline, gives actually ~12% of 2-*N*-methylanilino-isomer, but in the presence of ethanolic sodium ethoxide this slightly predominated.

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* Part XII, *J.*, 1958, 1561.

[1] Hunter and Jones, *J.*, 1930, 2190; Dyson, Hunter, Jones, and Styles, *J. Indian Chem. Soc.*, 1931, **8**, 147.

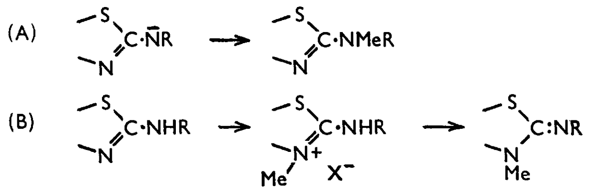
[2] Hunter and Parken, *J.*, 1934, 1175.

[3] Hunter, Parken, and Short, *J.*, 1958, 1561.

[4] Chowdhury, Desai, and Hunter, *J. Indian Chem. Soc.*, 1933, **10**, 637.

2-Anilinonaphtho[1,2]thiazole (VII $\rightleftharpoons$ VIII) with methyl iodide alone was also found to give more (*ca.* 10%) 2-methylanilino-isomer than was originally reported.[5] In the presence of ethanolic sodium ethoxide, the ratio of isomers was reversed in favour of the 2-methylanilino-derivative.

The effect of ethoxide ions in causing the appearance of methylamino-isomers, or in greatly enhancing their proportion, is interpreted as resulting mainly from superposition of an " amide " mechanism (A) of methylation of the ion derived from the amino-aromatic form by deprotonation on the " ammonium " mechanism (B) pictured for methylation of the base itself in the presence of methyl iodide or dimethyl sulphate alone. It appears feasible, however, that the formation of pairs of isomeric methyl derivatives in methylation by methyl iodide alone may arise from methylation by the " ammonium " mechanism of actual tautomerides as pictured by Hunter and Styles in 1928 [6] on the basis of Pyman's experiments on the addition of methyl iodide to " mobile " and " static " amidines.[7] The iminothiazoline tautomer which gives rise to the methylamino-isomer is derived from the original single individual which has the amino-aromatic structure (ultraviolet spectroscopical evidence) by a mechanism involving prototropy under the influence of solvating methyl iodide molecules which are present in substantial excess.



[*Added, November* 30*th*, 1958.—Distribution of charge will of course cause production to some extent of the isomeric ion having an exocyclic imino-group and a negative charge on the ring nitrogen atom. This should, however, be small since the stability will be lower on account of the use of an electron of the aromatic sextet for the αβ double bond, which therefore breaks the aromatic resonance. It is not suggested that the ions of the tautomers necessarily exist as actual entities; the deprotonated system is probably best symbolised by a sharing of the negative charge between the two nitrogen atoms.]

EXPERIMENTAL

2-*Amino*-6-*methylbenzothiazole*.—The base, m. p. 142°, prepared from *N*-*p*-tolylthiourea and bromine,[8] gave a pale yellow *picrate* in acetone which, crystallised from ethyl acetate, had m. p. 280—281° (Found: S, 7·9. $C_8H_8N_2S,C_6H_3O_7N_3$ requires S, 8·1%).

Methylation by dimethyl sulphate in ethanolic sodium ethoxide. The base (2 g.) in ethanolic sodium ethoxide (prepared from 2·3 g. of sodium in 50 ml. of ethanol) was heated with dimethyl sulphate (10 ml.) under reflux for 4 hr., treated with excess of ammonia (*d* 0·880) after removal of the bulk of the alcohol, and extracted with chloroform. The gum recovered from an ethanolic solution of the product by concentration under reduced pressure at room temperature was stirred with cold acetone. The residue (0·5 g.), when washed with ether and recrystallised from boiling water, gave 2-amino-6-methylbenzothiazole (0·2 g.), m. p. and mixed m. p. 141—142°. The gum (1·1 g.) recovered from the acetone extraction was converted into a mixture of picrates which on fractional crystallisation furnished 6-methyl-2-methylaminobenzothiazole picrate (0·7 g.) which after recrystallisation from ethyl acetate (charcoal) had m. p. 255° and 255—256° on admixture with a specimen prepared from the synthetic base, and 2-*imino*-3 : 6-*dimethylbenzothiazoline picrate* (1·1 g.), m. p. 221° (from ethyl acetate; charcoal) and 219—220° when mixed with a specimen prepared from the synthetic base (Found: S, 7·65. $C_9H_{10}N_2S,C_6H_3O_7N_3$ requires S, 7·9%). 2-Imino-3 : 6-dimethylbenzothiazoline, prepared from

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[5] Desai, Hunter, and Kureishy, *J.*, 1936, 1668.

[6] Hunter and Styles, *J.*, 1928, 3019.

[7] Burtles and Pyman, *J.*, 1923, **123**, 362; Pyman, *ibid.*, pp. 367, 3359.

[8] Hunter, *J.*, 1926, 1385.

N-methyl-*N*-*p*-tolylthiourea and bromine, gave a *picrate*, yellow needles, m. p. 220—221° (from ethyl acetate) (Found: S, 7·7%). 2-Methylamino-6-methylbenzothiazole, m. p. 152°,[1] prepared from *N*-methyl-*N'*-*p*-tolylthiourea and bromine, gave a *picrate*, yellow needles, m. p. 256—257° (from ethyl acetate) (Found: S, 7·7%).

2-*Amino*-6-*chlorobenzothiazole*.—The *picrate* of this base crystallised from ethyl acetate in pale yellow needles, m. p. 271° (Found: S, 7·65. $C_7H_5N_2ClS,C_6H_3O_7N_3$ requires S, 7·7%). The base (2 g.) was methylated in ethanolic sodium ethoxide (50 ml.) with dimethyl sulphate (10 ml.). A residue (0·2 g.) remaining after extraction with chloroform was unchanged base (m. p. and mixed m. p. 196°). The gum was converted into mixed picrates which on crystallisation from ethyl acetate gave the picrate of unchanged base (1 g.; m. p. and mixed m. p. 271°), 6-chloro-2-imino-3-methylbenzothiazoline picrate (1·55 g.) (which on recrystallisation had m. p. 239—240° and 239° when mixed with a specimen prepared from the synthetic base), and 6-chloro-2-methylaminobenzothiazole picrate (0·8 g.) (which on recrystallisation had m. p. 230° and 229—230° when mixed with a specimen prepared from the synthetic base).

N-p-*Chlorophenyl*-N-*methylthiourea*, prepared from *p*-chloro-*N*-methylaniline (3·5 g.), potassium thiocyanate (2·5 g.), and hydrochloric acid (3 ml.) in aqueous ethanol, crystallised from ethanol in prisms, m. p. 125° (1·7 g.) (Found: S, 16·1. $C_8H_9N_2ClS$ requires S, 16·0%). 6-Chloro-2-imino-3-methylbenzothiazoline obtained by heating the thiourea (1 g.) with bromine (1 ml.) in chloroform (12 ml.) under reflux for 10 min., crystallised from methanol in plates, m. p. 79°. The yellow *picrate*, prepared in acetone and crystallised from ethyl acetate, had m. p. 239° (Found: Cl, 8·4; S, 7·3. $C_8H_7N_2ClS,C_6H_3O_7N_3$ requires Cl, 8·3; S, 7·4%).

6-*Chloro*-2-*methylaminobenzothiazole*, m. p. 214°, prepared from *N*-*p*-chlorophenyl-*N'*-methylthiourea and bromine,[1] gave a *picrate*, needles (from ethyl acetate), m. p. 230—231° (Found: S, 7·3. $C_8H_7N_2ClS,C_6H_3O_7N_3$ requires S, 7·4%).

2-Amino-6-bromobenzothiazole, prepared by bromination of 2-aminobenzothiazole in chloroform,[9] gave a *picrate*, m. p. 273° (from ethyl acetate) (Found: S, 6·9. $C_7H_5N_2BrS,C_6H_3O_7N_3$ requires S, 7·0%). The base (2 g.) was treated in ethanolic sodium ethoxide (40 ml.) with dimethyl sulphate (10 ml.), and the gum was converted into a mixture of picrates. Fractionation from acetone and then from ethyl acetate yielded picrate of unchanged base (0·6 g.; m. p. 272°; mixed m. p. 272—273°), 6-bromo-2-imino-3-methylbenzothiazoline picrate (3 g.) (on recrystallisation from ethyl acetate, m. p. 240° and 239—240° when mixed with a specimen obtained from the synthetic base), and 6-bromo-2-methylaminobenzothiazole picrate (0·6 g.) (after recrystallisation, m. p. and mixed m. p. 236°).

6-Bromo-2-imino-3-methylbenzothiazoline, m. p. 110°, prepared by bromination of the 2-imino-3-methyl base, gave a *picrate*, yellow needles, m. p. 240° (from ethyl acetate) (Found: S, 6·9. $C_8H_7N_2BrS,C_6H_3O_7N_3$ requires S, 6·8%).

6-Bromo-2-methylaminobenzothiazole, prepared from *N*-*p*-bromophenyl-*N'*-methylthiourea and bromine, crystallised from ethanol in needles, m. p. 224°. The *picrate*, prepared in acetone, crystallised from ethyl acetate in pale yellow needles, m. p. 231° (Found: S, 6·7%).

2-Anilinonaphtho[2,1]thiazole, prepared from *N*-β-naphthyl-*N'*-phenylthiourea and bromine,[10] had m. p. 211—212°. The *picrate*, prepared in benzene, crystallised from alcohol in pale yellow needles, m. p. 253° (Found: S, 6·5. $C_{17}H_{12}N_2S,C_6H_3O_7N_3$ requires S, 6·3%). (i) The base (5 g.) was heated with methyl iodide (7·5 ml.) at 100° for 12 hr., the product digested with hot 33% aqueous potassium hydroxide and extracted with chloroform, and the gummy base was stirred with cold absolute ethanol. The residue of 3-methyl-2-phenyliminonaphtho[2,1]-thiazoline (4 g.) had m. p. 183° (185—186° on recrystallisation from ethanol) and at 186° when mixed with a specimen synthesised from *N*-methyl-*N*-β-naphthyl-*N'*-phenylthiourea. A solution of the gum (0·9 g.) recovered from the alcoholic extract in benzene gave 1·1 g. of 1-*N*-methylanilinonaphtho[2,1]thiazole picrate in four fractions which after recrystallisation had m. p. 184° alone and when mixed with a specimen prepared from the synthetic base. (ii) The gum obtained by heating the base (4 g.), methyl iodide (6 ml.), and ethanolic sodium ethoxide (6 ml.) under the same conditions gave on stirring with cold absolute ethanol 3-methyl-2-phenyliminonaphtho[2,1]thiazoline (1·45 g.) which after recrystallisation had m. p. 184—185° and mixed m. p. 185°. The picrate from the recovered gum yielded a total of 3·15 g. of 1-*N*-methylanilinonaphtho[2,1]thiazole picrate which on recrystallisation from ethanol (charcoal) had m. p. and mixed m. p. 186—187°.

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[9] Hunter, *J.*, 1930, 125.

[10] Hunter and Jones, *J.*, 1930, 941.

N-*Methyl*-N-*β-naphthyl*-N′-*phenylthiourea*, prepared from phenylthiocarbimide and *N*-methyl-β-naphthylamine, had m. p. 108—109° (from ethanol; charcoal) (Found: S, 11·0. $C_{18}H_{16}N_2S$ requires S, 11·0%).

3-Methyl-2-phenyliminonaphtho[2,1]thiazoline, obtained by cyclisation of the thiourea (2 g.) with bromine (0·8 ml.) and crystallised from ethanol, had m. p. 186—187°. The *picrate*, prepared in benzene, had m. p. 217—218° (Found: S, 6·0. $C_{18}H_{14}N_2S,C_6H_3O_7N_3$ requires S, 6·2%).

2-Anilinonaphtho[1,2]thiazole was conveniently prepared from a solution of *N*-α-naphthyl-*N′*-phenylthiourea (6 g.) and bromine (2·4 ml.) in chloroform (68 ml.) and crystallised from ethanol in needles, m. p. 143° alone and when mixed with a specimen prepared from 2-chloronaphtho[1,2]thiazole and aniline (yield, 5 g.). (i) The base (4 g.) was heated with methyl iodide (6 ml.) at 100° for 12—15 hr. Fractionation of the picrate obtained from the gum gave 4 g. of crude 3-methyl-2-phenyliminonaphtho[1,2]thiazoline, m. p. 184° (3·3 g. of m. p. and mixed m. p. 202—203° after extraction with boiling ethyl acetate), and 0·6 g. of 2-*N*-methylanilinonaphtho[1,2]thiazole picrate (m. p. 152—154° and 155—156°; m. p. and mixed m. p. 156° after recrystallisation), and picrate of unmethylated base. (ii) The gum obtained by heating the base (5 g.), methyl iodide (7·5 ml.), and ethanolic sodium ethoxide (7·5 ml.) at 100° for 12 hr. gave with cold absolute ethanol 2-methylanilinonaphtho[1,2]thiazole (3·2 g.), m. p. 113—114° (114—115° after recrystallisation). The recovered gum (1·2 g.) yielded 1·2 g. of 3-methyl-2-phenyliminonaphtho[1,2]thiazoline picrate (m. p. 190; 203° after recrystallisation) and 0·6 g. of 2*N*-methylanilinonaphtho[1,2]thiazole picrate (m. p. and mixed m. p. 154—155° after recrystallisation).

N-*Methyl*-N-*α-naphthyl*-N′-*phenylthiourea*, prepared from phenylthiocarbimide and *N*-methyl-α-naphthylamine, crystallised from ethanol in prisms, m. p. 158—159° (Found: S, 11·0. $C_{18}H_{16}N_2S$ requires S, 11·0%). 3-*Methyl*-2-*phenyliminonaphtho*[1,2]*thiazoline* obtained by cyclisation of the thiourea (2 g.) with bromine (0·8 ml.), crystallised from ethanol (charcoal) in needles, m. p. 152° (Found: S, 11·1. $C_{18}H_{14}N_2S$ requires S, 11·0%). The picrate prepared in benzene solution had m. p. 203°.

4-Methyl-2-*p*-toluidinothiazole, m. p. 127—128°, prepared from *p*-tolylthiourea and monochloroacetone, gave a *picrate*, needles, m. p. 193—194° (from ethanol) (Found: S, 7·4. $C_{11}H_{12}N_2S,C_6H_3O_7N_3$ requires S, 7·4%).

The base (5 g.), methyl iodide (7·5 ml.), and ethanolic sodium ethoxide (10 ml.) were heated at 100° for 6 hr., the product was digested with 33% aqueous potassium hydroxide, and the mixture diluted with water and extracted with chloroform. When stirred with cold ethanol, the resulting gum gave 3 : 4-dimethyl-2-*p*-tolyliminothiazoline (0·2 g.), m. p. and mixed m. p. 108° (after recrystallisation). The uncrystallisable gum was converted in acetone into a picrate which with benzene gave 1·9 g. of 3 : 4-dimethyl-2-*p*-tolyliminothiazoline picrate (after recrystallisation, m. p. 138°; 138—139° when mixed with a synthetic specimen) and 1·1 g. of 4-methyl-2-*N*-methyl-*p*-toluidinothiazole picrate (after recrystallisation, m. p. and mixed m. p. 176°). The *picrate* obtained from 3 : 4-dimethyl-2-*p*-tolyliminothiazoline which had been prepared from *N*-methyl-*N′*-*p*-tolylthiourea and monochloroacetone, on crystallisation from benzene and then ethanol, formed pale yellow needles, m. p. 139° (Found: S, 7·2. $C_{12}H_{14}N_2S,C_6H_3O_7N_3$ requires S, 7·2%). The *picrate* obtained from 4-methyl-2-*N*-methyl-*p*-toluidinothiazole which had been prepared from *N*-methyl-*N*-*p*-tolylthiourea, crystallised in yellow prisms, m. p. 176° (Found: S, 7·3%).

2-*p*-Chloroanilino-4-methylthiazole, m. p. 147°, gave a *picrate*, m. p. 218° (Found: S, 7·2. $C_{10}H_9N_2ClS,C_6H_3O_7N_3$ requires S, 7·1%). A mixture of the base (5 g.), ethanolic sodium ethoxide (7·5 ml.) and methyl iodide (7·5 ml.) was heated at 100° for 6 hr., then basified with 33% aqueous potassium hydroxide, and the gum (5·1 g.) extracted with chloroform, which showed no signs of crystallisation after 2 days *in vacuo*, converted into a mixture of gummy picrates which were washed with cold ethanol. The residue (6 g.) on fractional crystallisation from ethanol furnished 2-*p*-chlorophenylimino-3 : 4-dimethylthiazoline picrate (4·2 g.) and 2-*p*-chlorophenylmethylamino-4-methylthiazole picrate (1·4 g.) which had m. p. 159—160° unaltered by recrystallisation from ethanol and admixture with a specimen prepared from the synthetic base. The original ethanolic extract furnished a further 0·4 g. of 2-*p*-chlorophenylimino-3 : 4-dimethylthiazoline picrate (m. p. 138—139° and 132—135° after fractionation from benzene; total, 0·35 g.), and the gum (3·2 g.) obtained by evaporation of the mother-liquors was washed repeatedly with cold ethanol, giving a further 1·5 g. of the picrate, m. p. 134—135°.

The united fractions of 2-*p*-chlorophenylimino-3 : 4-dimethylthiazoline picrate on recrystallisation from ethanol formed needles, m. p. and mixed m. p. 138—139°. 2-*p*-Chlorophenylmethylamino-4-methylthiazole, prepared by condensation of *N*-*p*-chlorophenyl-*N*-methylthiourea (0·8 g.) and monochloroacetone (0·4 ml.), formed a gum (1 g.) whose *picrate*, prepared in acetone, crystallised from ethanol (charcoal) in orange-brown needles, m. p. 159° (Found: Cl, 7·8; S, 6·7. $C_{11}H_{11}N_2ClS,C_6H_3O_7N_3$ requires Cl, 7·6; S, 6·8%).

2-*p*-Bromoanilino-4-methylthiazole, m. p. 162°, gave a *picrate*, m. p. 219° (Found: S, 6·4. $C_{10}H_9N_2BrS,C_6H_3O_7N_3$ requires S, 6·4%).

The gum obtained from the base (5 g.), methyl iodide (7·5 ml.), and ethanolic sodium ethoxide (7·5 ml.) was converted into a mixture of picrates. The first crop consisted of 2-*p*-bromophenylimino-3 : 4-dimethylthiazoline picrate (5·3 g.) which on recrystallisation from benzene gave fractions, m. p. 154—155° (3·7 g.) and m. p. 150—152° (1·4 g.). The mother-liquors, on concentration, furnished crops which on refractionation from ethanol gave 2-*p*-bromophenylmethylamino-4-methylthiazole picrate (2·1 g.), m. p. 161—162° after recrystallisation (Found: Br, 15·8; S, 6·3. $C_{11}H_{11}N_2BrS,C_6H_3O_7N_3$ requires Br, 15·6; S, 6·3%), and the picrate of unchanged base (0·3 g.), m. p. and mixed m. p. 219°.

One of the authors thanks Professor Sir Christopher Ingold, F.R.S., for helpful discussions.

THE TECHNICAL COLLEGE, BRIGHTON.
THE MUSLIM UNIVERSITY, ALIGARH, INDIA.

[*Received, May* 1*st*, 1958.]