312. *The Unsaturation and Tautomeric Mobility of Heterocyclic Compounds. Part X. The Effect of Ethoxyl Ions on the Methylation of 5-Substituted 1-Anilinobenzthiazoles, and the Ultra-violet Absorption Spectra of 5-Bromo-1-anilinobenzthiazole and of its N-Methyl Derivatives.*

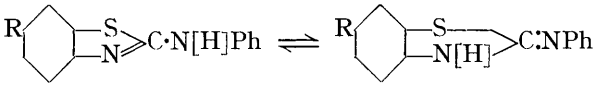
By Robert F. Hunter and M. A. Wali.

On methylation with methyl sulphate alone, 1-anilino-5-methylbenzthiazole, 5-bromo-1-anilinobenzthiazole, and its 5-chloro-analogue all react apparently exclusively in the amino-aromatic form, yielding 1-phenylimino-2-methyl-1 : 2-dihydrobenzthiazoles. The 5-nitro-derivative, however, gives rise to a mixture of isomeric methyl derivatives.

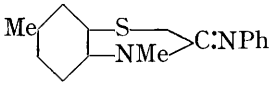
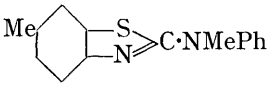
The presence of ethyl-alcoholic sodium ethoxide causes extensive methylation on the non-nuclear nitrogen atom in the 5-methyl-, 5-bromo-, and 5-chloro-bases, and in the case of the 5-nitro-derivative leads to exclusive alkylation at this position.

A comparison of the ultra-violet absorption spectrum of 5-bromo-1-anilinobenzthiazole with that of 5-bromo-1-phenylmethylaminobenzthiazole in ethyl alcohol indicates that the molecule has the amino-aromatic structure. In ethyl-alcoholic sodium ethoxide, there is a lowering of the first maximum, and a pronounced shift towards the region of longer wave-length.

The almost overwhelming tendency for 1-aminobenzthiazoles to react in the amino-aromatic form with methylating agents, giving rise to 1-imino-2-methyl-1 : 2-dihydrobenzthiazoles (Hunter and Styles, J., 1928, 3019; Hunter and Pride, J., 1929, 943) has been attributed (Hunter and Jones, J., 1930, 2190) to the greater stability of this form and to the fact that it permits the formation of the stable sextuple group (Armit and Robinson, J., 1925, **127**, 1605; Goss and Ingold, J., 1928, 1268) without calling on the lone pair of electrons of the nuclear nitrogen atom. The presence of the phenyl group of the anilino-substituent in 1-anilinobenzthiazole, however, enables the nitrogen atom to which it is attached to compete with the ring nitrogen atom during methylation, and a similar result has been observed in the cases of the oxazole (Desai, Hunter, and Khalidi, J., 1934, 1186) and selenazole analogues (Chiragh Hasan and Hunter, J., 1935, 1762). It was therefore of interest to examine the 5-substituted 1-anilinobenzthiazoles (I $\rightleftharpoons$ II) analogous to the 1-aminobenzthiazoles studied earlier (Hunter and Jones, *loc. cit.*), in which the 1-anilino-substituent might be expected to decrease the effect of the aromatic conjugation of the heterocyclic ring.

(I.)  (II.)

The methylation of 1-anilino-5-methylbenzthiazole (I $\rightleftharpoons$ II, R = Me), which was first investigated, led to an unexpected result in that the base reacted apparently exclusively in the form (I) with methyl sulphate, giving 1-*phenylimino*-2 : 5-*dimethyl*-1 : 2-*dihydrobenzthiazole* (III), unaccompanied by any detectable quantity of the isomeric 1-*phenylmethylamino*-base (IV), which was rationally synthesised from 1-chloro-5-methylbenzthiazole and methylaniline.

(III.)   (IV.)

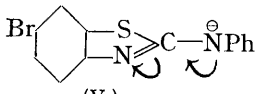
5-*Bromo*- and 5-*chloro*-1-*anilinobenzthiazole* (I $\rightleftharpoons$ II; R = Br and Cl, respectively) behaved similarly, although the halogen substituents are associated with strong polarisation in the sense opposite to that of the methyl group, and gave rise on methylation with methyl sulphate alone to derivatives of type (III), unaccompanied by those of type (IV).

The nitro-group in 5-*nitro*-1-*anilinobenzthiazole* (I $\rightleftharpoons$ II, R = NO_2), however, exhibited the depressing effect on the reactivity of the nuclear nitrogen atom to be anticipated on

account of the high dipole, and the methylation of this base gave rise to a mixture of 5-*nitro*-1-*phenylimino*-2-*methyl*-1 : 2-*dihydrobenzthiazole* and 5-*nitro*-1-*phenylmethylamino*-*benzthiazole*, in which the former slightly predominated.

Since the absorption spectra of 1-aminobenzthiazoles indicate that the molecules are present in the amino-aromatic form in alcoholic solutions, it was of interest to conduct the methylation of the 5-substituted 1-anilinobenzthiazoles in the presence of ethoxyl ions, whose catalytic influence in three-carbon prototropic changes is well known (Ingold and Shoppee, J., 1929, 447; Kon and Linstead, *ibid.*, p. 1269). It was found that the presence of alcoholic sodium ethoxide profoundly affects the course of methylation of 5-bromo-1-anilinobenzthiazole by methyl sulphate. The methyl derivative of type (IV), which could not even be detected in methylation with methyl sulphate alone, now occurred to the extent of about 74% in the methylation product.

The ultra-violet absorption of 5-bromo-1-anilinobenzthiazole in ethyl-alcoholic solution closely resembles that of 5-bromo-1-phenylmethylaminobenzthiazole. The absorption curve of 5-bromo-1-phenylimino-2-methyl-1 : 2-dihydrobenzthiazole, although belonging to the same family, lies to the left and exhibits a lower maximum and higher minimum than either of the former. In ethyl-alcoholic sodium ethoxide, however, 5-bromo-1-anilino-benzthiazole shows a lowering in the first maximum which is probably connected with the production of the ion (V), in which some distribution of anionic charge in the sense of the arrows might be anticipated. The curve also shows a pronounced shift towards the region of longer wave-length, which is probably due to deformation in the Fajans sense.



(V.)

The presence of sodium ethoxide exerted a similar influence on the methylation of 5-chloro-1-anilinobenzthiazole, leading to the production of a mixture containing about 65% of the phenylmethylamino-compound; and it caused 5-nitro-1-anilinobenzthiazole to undergo methylation apparently exclusively on the phenylated nitrogen atom.

The effect of ethoxyl ions was no less striking in the case of 1-anilino-5-methylbenzthiazole, which, under the conditions described in the experimental section, gave rise to a mixture of (IV) and (III) in which the former predominated to the extent of about 88%.

Experimental.

1-Anilino-5-methylbenzthiazole, prepared by condensation of 1-chloro-5-methylbenzthiazole (m. p. 48°) with aniline, crystallised in needles, m. p. 164° (previously recorded as m. p. 158°).

Methylation of 1-*Anilino*-5-*methylbenzthiazole*.—(i) A mixture of the anilino-base (2 g.) and methyl sulphate (6 c.c.) was heated on a water-bath under reflux for 3 hours, and the excess of the latter reagent was destroyed with aqueous ammonia (*d* 0·880). An alcoholic solution of the gum thus obtained, on being kept, deposited 1-*phenylimino*-2 : 5-*dimethyl*-1 : 2-*dihydrobenzthiazole* (1·5 g.), which on recrystallisation was obtained in needles, m. p. 107—108° (Found : C, 70·8; H, 5·5. $C_{15}H_{14}N_2S$ requires C, 70·8; H, 5·5%); its *picrate* separated from benzene in small yellow crystals, m. p. 180° (Found : S, 6·2. $C_{15}H_{14}N_2S,C_6H_3O_7N_3$ requires S, 6·6%). The alcoholic mother-liquors on concentration deposited unchanged 1-anilino-5-methylbenzthiazole (0·5 g.). A mixture of the above picrate with that of the 1-phenylmethylamino-isomer melted at 166°.

(ii) 1-Anilino-5-methylbenzthiazole (1·5 g.) was dissolved in alcoholic sodium ethoxide (prepared from 0·4 g. of sodium and 14 c.c. of absolute alcohol), and the mixture was heated with methyl sulphate (5 c.c.) and then treated with ammonia as above. On extraction with ether, a gum (1·55 g.) was obtained, which was converted into the picrate (2·75 g.), m. p. 156—168°. On recrystallisation from benzene this gave 0·13 g. of the picrate, m. p. 180—190°. The remainder (m. p. 158—164°) on fractional crystallisation from alcohol gave 0·06 g. of the picrate of unmethylated base, m. p. 228—232°, followed by 0·25 g. of the picrate of 1-phenylimino-2 : 5-dimethyl-1 : 2-dihydrobenzthiazole, m. p. 168—172°. The remainder (2·35 g.) had m. p. 180—190° and was identified as the picrate of 1-phenylmethylamino-5-methylbenzthiazole. The combined yield of this with the first fraction mentioned above, on decomposition with alkali, gave 1-phenylmethylamino-5-methylbenzthiazole (1·3 g.), m. p. 68—70° after recrystallisation from hexane.

Synthesis of 1-*Phenylmethylamino*-5-*methylbenzthiazole*.—A mixture of 1-chloro-5-methylbenzthiazole (2 g.) and methylaniline (1 c.c.) was gently heated until a violent reaction occurred.

The gum obtained on basification with ammonia was dried in a vacuum and recrystallised from cold dilute alcohol, the 1-*phenylmethylamino*-base being obtained in small crystals, m. p. 70—72° (Found : S, 12·3. $C_{15}H_{14}N_2S$ requires S, 12·6%). The *picrate* crystallised in small yellow needles, m. p. 192° (with previous blackening) (Found : S, 6·4. $C_{15}H_{14}N_3S,C_6H_3O_7N_3$ requires S, 6·6%).

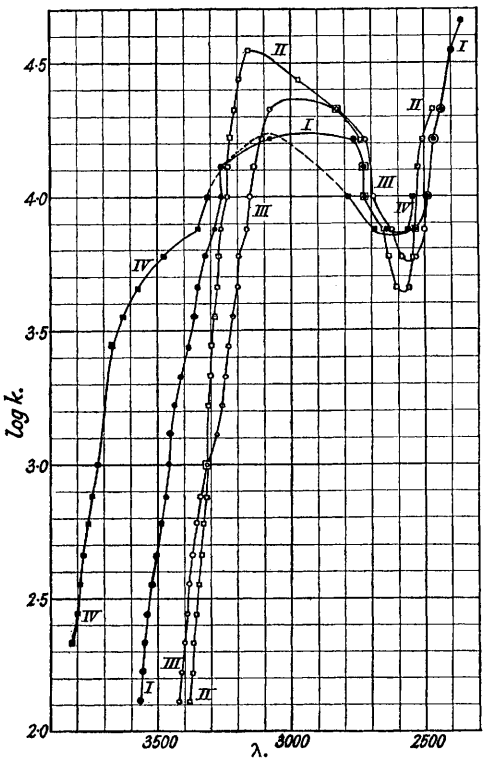
5-*Bromo*-1-*anilinobenzthiazole*.—A mixture of 1-chloro-5-bromobenzthiazole (5·7 g.) and aniline (5·7 c.c.) was heated until a vigorous reaction occurred, and the bluish-black product obtained on basification was recrystallised from alcohol (charcoal); the *base* formed small, colourless needles, m. p. 194° (Found : C, 51·3; H, 3·1; S, 10·3. $C_{13}H_9N_2BrS$ requires C, 51·1; H, 3·0; S, 10·4%). The *picrate* crystallised from benzene in short, yellow needles, m. p. 246—247° (Found : S, 6·2. $C_{13}H_9N_2BrS,C_6H_3O_7N_3$ requires S, 6·0%).

Methylation of 5-*Bromo*-1-*anilinobenzthiazole*.—(i) 2 G. of the base were methylated exactly as for the methyl analogue; the gum obtained gradually solidified on keeping, and on recrystallisation from benzene–hexane furnished 5-*bromo*-1-*phenylimino*-2-*methyl*-1 : 2-*dihydrobenzthiazole* (1 g.) in long needles, m. p. 114° (Found : C, 52·8; H, 3·5. $C_{14}H_{11}N_2BrS$ requires C, 52·6; H, 3·4%). The mother-liquors deposited a further quantity of this on keeping, but no evidence of the presence of the isomeric compound was obtained. The *picrate* crystallised from absolute alcohol in silky, yellow needles, m. p. 186—187° (Found : S, 5·8.

$C_{14}H_{11}N_2BrS,C_6H_3O_7N_3$

requires S, 5·8%).

(ii) In an experiment similar to the above, the crude methylation product was converted into the picrate, m. p. 178—184°. On fractional crystallisation from benzene, this gave a picrate, m. p. 246—247° (1·1 g.), identified as that of the unmethylated base, and the picrate of 5-bromo-1-phenylimino-2-methyl-1 : 2-dihydrobenzthiazole, m. p. 182—184° (1·7 g.). The mother-liquors furnished about 0·15 g. of a product, m. p. 150—205°, consisting mainly of the picrate of 5-bromo-1-anilinobenzthiazole contaminated by a certain amount of that of 5-bromo-1-phenylimino-2-methyl-1 : 2-dihydrobenzthiazole. No evidence was obtained of the presence of the picrate of 5-bromo-1-phenylmethylaminobenzthiazole.



I. 5-*Bromo*-1-*phenylimino*-2-*methyl*-1 : 2-*dihydrobenzthiazole*.
II. 5-*Bromo*-1-*anilinobenzthiazole*.
III. 5-*Bromo*-1-*phenylmethylaminobenzthiazole*.
IV. 5-*Bromo*-1-*anilinobenzthiazole* (*in alcoholic* NaOEt *solution*).

(iii) 5-Bromo-1-anilinobenzthiazole (2 g.) in alcoholic sodium ethoxide (prepared from 0·5 g. of sodium and 15 c.c. of absolute alcohol) was heated with methyl sulphate (6 c.c.), and the mixture treated as before. The gum so obtained was dissolved in alcohol and converted into picrate (3·2 g.), m. p. 172—180°. On fractional crystallisation from benzene, this gave 2·35 g. of 5-bromo-1-phenylmethylaminobenzthiazole picrate, m. p. 196—198°, identified by mixed m. p. determination and regeneration of the base, m. p. 81—82° (1·42 g.), undepressed by admixture with an authentic specimen of 5-bromo-1-phenylmethylaminobenzthiazole. The second fraction (0·65 g., m. p. 184—186°) was identified as 5-bromo-1-phenylimino-2-methyl-1 : 2-dihydrobenzthiazole picrate by mixed m. p. determination and by regeneration (by treatment with ammonia) of the base, m. p. 110—112° (0·37 g.), undepressed by admixture with the 5-bromo-1-phenylimino-2-methyl base. The third fraction (0·16 g., m. p. 174—180°) could not be purified by recrystallisation, and was therefore decomposed with ammonia, 0·08 g. of impure 5-bromo-1-phenylimino-2-methyl-1 : 2-dihydrobenzthiazole, m. p. 104—108°, being obtained.

Synthesis of 5-*Bromo*-1-*phenylmethylaminobenzthiazole*.—The gum obtained from 1-chloro-5-bromobenzthiazole (1 g.) and methylaniline (1 c.c.) was kept in a vacuum, triturated with

benzene, and recrystallised from dilute alcohol, the *base* being obtained in small needles, m. p. 82—83° (Found : C, 52·8; H, 3·7. $C_{14}H_{11}N_2BrS$ requires C, 52·6; H, 3·4%). The *picrate* crystallised from absolute alcohol in small yellow needles, m. p. 198° (Found : C, 43·8; H, 2·6; S, 6·0. $C_{14}H_{11}N_2BrS,C_6H_3O_7N_3$ requires C, 43·8; H, 2·6; S, 5·8%).

1 : 5-Dichlorobenzthiazole was prepared by heating diazotised 5-chloro-1-aminobenzthiazole with concentrated hydrochloric acid (Farooq and Hunter, *J. Indian Chem. Soc.*, 1933, **10**, 563), and isolated by distillation in steam. On recrystallisation from alcohol, it was obtained in needles, m. p. 100—101°.

5-Chloro-1-anilinobenzthiazole, obtained from 1 : 5-dichlorobenzthiazole and aniline, separated from alcohol in small needles, m. p. 192° (Found : C, 59·6; H, 3·4. $C_{13}H_9N_2ClS$ requires C, 59·8; H, 3·3%). The *picrate* separated from benzene in small yellow crystals, m. p. 238° (Found : S, 6·3. $C_{13}H_9N_2ClS,C_6H_3O_7N_3$ requires S, 6·5%).

Methylation of 5-Chloro-1-anilinobenzthiazole.—(i) The base (2 g.) was methylated with methyl sulphate (6 c.c.) in the usual way, and the crude product (2·2 g., m. p. 100—112°) treated with benzene. The sparingly soluble residue (0·38 g.) consisted of unchanged material. Fractional crystallisation of the benzene solution furnished *5-chloro-1-phenylimino-2-methyl-1 : 2-dihydrobenzthiazole* (1·3 g.), which on recrystallisation formed long glistening needles, m. p. 125—126° (Found : C, 61·1; H, 4·0. $C_{14}H_{11}N_2ClS$ requires C, 61·2; H, 4·0%); its *picrate* separated from benzene in small yellow cubes, m. p. 174° (Found : S, 6·1. $C_{14}H_{11}N_2ClS,C_6H_3O_7N_3$ requires S, 6·3%). The base remaining in the benzene mother-liquors was converted into picrate, and the solution was fractionally crystallised, 0·66 g. of crude 5-chloro-1-phenylimino-2-methyl-1 : 2-dihydrobenzthiazole picrate separating, m. p. 158—162°. A further 0·05 g. of this was obtained on further concentration, but no evidence was obtained of the presence of the picrate of the isomeric phenylmethylamino-derivative.

(ii) 2 G. of 5-chloro-1-anilinobenzthiazole in alcoholic sodium ethoxide were methylated with 6 c.c. of methyl sulphate in the usual way, and the mixture was treated with ammonia. The solid (0·34 g., m. p. 106—120°) which separated from the oil was dissolved in benzene and converted into picrate, affording 0·4 g. of 5-chloro-1-phenylimino-2-methyl-1 : 2-dihydrobenzthiazole picrate, m.p. 172—174° (regenerated base, m. p. 125—127°). The mother-liquors furnished a further 0·05 g. of this (m. p. 162—168°). The oil which constituted the bulk of the methylation product was converted into picrate (3·2 g., m. p. 160—190°), which was fractionally crystallised from benzene, yielding 2·2 g. of the sparingly soluble picrate of the 5-chloro-1-phenylmethylamino-base, m. p. 196—198° (regenerated base, 1·15 g., m. p. 72—74°). The mother-liquors furnished 0·9 g. of the picrate of the 5-chloro-1-phenylimino-2-methyl base, m. p. 160—164°, from which on recrystallisation and decomposition with alkali, 0·46 g. of this base was obtained. The original aqueous mother-liquors on extraction with ether and treatment of the product with benzene–hexane gave a small amount of unchanged 5-chloro-1-anilino-base (*ca.* 0·02 g.) and 0·15 g. of the base, m. p. 70—74°.

Synthesis of 5-Chloro-1-phenylmethylaminobenzthiazole.—The base obtained from 1 : 5-dichlorobenzthiazole and methylaniline formed a gum which could not be induced to solidify. It was therefore dissolved in benzene and converted into the *picrate*, which crystallised in small yellow needles, m. p. 196—198° (Found : S, 6·0. $C_{14}H_{11}N_2ClS,C_6H_3O_7N_3$ requires S, 6·3%). On decomposition with alkali, this gave the required *base*, which separated from alcohol in small glistening needles, m. p. 76—77° (Found : C, 61·0; H, 4·1. $C_{14}H_{11}N_2ClS$ requires C, 61·2; H, 4·0%).

5-Nitro-1-anilinobenzthiazole separated from benzene in small yellow needles, m. p. 248° (Found : C, 57·6; H, 3·4. $C_{13}H_9O_2N_3S$ requires C, 57·5; H, 3·3%).

Methylation of 5-Nitro-1-anilinobenzthiazole.—(i) The thiazole (2 g.) was methylated as in preceding cases. On crystallisation of the product from ethyl acetate, *5-nitro-1-phenylimino-2-methyl-1 : 2-dihydrobenzthiazole* (1 g.) was obtained, which formed glistening, silky, yellow needles, m. p. 210° (Found : C, 59·1; H, 3·8. $C_{14}H_{11}O_2N_3S$ requires C, 58·9; H, 3·8%), mixed m. p. with 5-nitro-1-anilinobenzthiazole 191°. The mother-liquors on concentration furnished 0·85 g. of crude 5-nitro-1-phenylmethylaminobenzthiazole, m. p. 136—140°, which could not be raised above 143° by recrystallisation. Pure *5-nitro-1-phenylmethylaminobenzthiazole*, prepared for comparison from 1-chloro-5-nitrobenzthiazole and methylaniline, crystallised from acetone in yellow plates, m. p. 152° (Found : C, 59·0; H, 4·05. $C_{14}H_{11}O_2N_3S$ requires C, 58·9; H, 3·8%); its *picrate* formed short yellow needles, m. p. 173° (Found : C, 46·6; H, 2·9; S, 6·2. $C_{14}H_{11}O_2N_3S,C_6H_3O_7N_3$ requires C, 46·7; H, 2·75; S, 6·2%).

(ii) A mixture of the 5-nitro-1-anilino-base (2 g.), alcoholic sodium ethoxide (prepared from 0·5 g. of sodium and 15 c.c. of absolute alcohol), and methyl sulphate (6 c.c.) was heated for 3

hours. On basification and recrystallisation from ethyl acetate, 1·25 g. of 5-nitro-1-phenylmethylaminobenzthiazole (m. p. 138—142°) and 0·27 g. of unchanged 5-nitro-1-anilinobenzthiazole (m. p. 247°) were obtained. The mother-liquors on concentration furnished a further 0·68 g. of the former, m. p. 140—144°, which was identified by mixed m. p. determination with the specimen already described.

Absorption Spectra Measurements.—The measurements were made with a medium Hilger E_2 spectrograph, quartz absorption cells (10 cm. thick) being used.

An $M/1000$-solution of 5-bromo-1-anilinobenzthiazole in absolute alcohol was first examined, and thereafter diluted ten-fold and then 100-fold with the same solvent. A similar procedure was observed with $M/1000$-solutions of 5-bromo-1-phenylmethylaminobenzthiazole and its isomer in alcohol. An $M/1000$-solution of 5-bromo-1-anilinobenzthiazole in $N/100$-ethyl-alcoholic sodium ethoxide was then examined, and the solution subsequently diluted to $M/10,000$ and $M/100,000$.

THE MUSLIM UNIVERSITY, ALIGARH, INDIA.

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