258. *The Unsaturation and Tautomeric Mobility of Heterocyclic Compounds. Part V. Benzoxazoles.*

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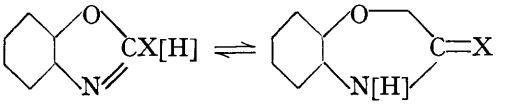
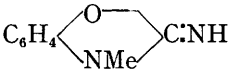
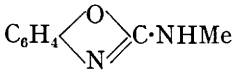
It appeared of interest from the point of view of the theory of sextuple valency-group stability (Armit and Robinson, J., 1925, **127**, 1605; Goss and Ingold, J., 1928, 1268; Hückel, *Z. Physik*, 1931, **70**, 204) to compare the behaviour of semi-cyclic triad systems containing an oxazole ring (I $\rightleftharpoons$ II) with that of benzthiazole derivatives (Hunter, J., 1926, 1385; 1930, 125; Hunter and Jones, *ibid.*, p. 2190). It has been found that these compounds exhibit a striking resemblance to their thiazole analogues with regard to behaviour towards alkylating agents and bromine, but nevertheless retain certain distinctive features of the oxazole ring system.

(I.)  (II.)

1-Aminobenzoxazole (I $\rightleftharpoons$ II; X = NH) could not be obtained from phenylcarbamide and bromine under the usual conditions of thiazole cyclisation of arylthiocarbamides; nuclear substitution occurred, with the production first of *p*-bromo- and then of 2 : 4-dibromo-phenylcarbamide. The base was obtained by the action of mercuric oxide on *o*-hydroxyphenylthiocarbamide, and also by treatment of 1-thiol-

benzoxazole (I ⇌ II; X = S) with ammonia. The presence of the μ-amino-group was established by the formation of a diazonium chloride which coupled with alkaline β-naphthol to give an azo-dye, and was converted into 1-*chlorobenzoxazole* by the Sandmeyer reaction. On methylation, it yielded 1-*imino*-2-*methyl*-1 : 2-*dihydrobenzoxazole* (III), whose constitution follows from its hydrolysis to *o*-methylaminophenol; no evidence was obtained of the formation of the isomeric 1-*methylaminobenzoxazole* (IV), which was synthesised from 1-thiolbenzoxazole and methylamine. Bromination of the amino-base

(III.)   (IV.)

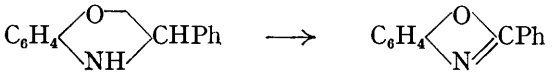
in chloroform at low temperatures also gave a bromo-addition compound, which could not be isolated but readily passed into the *hydrobromide* of 5(?)-bromo-1-aminobenzoxazole.

Substitution of a hydrogen atom of the 1-amino-group by phenyl, however, stabilises the iminodihydro-form of the triad system, and the methylation of 1-anilinobenzoxazole (I ⇌ II, X = NPh) gave rise to a mixture of 1-phenylimino-2-methyl-1 : 2-dihydrobenzoxazole and 1-phenylmethylaminobenzoxazole, in which the former isomeride, derived from the amino-aromatic form (Burtles and Pyman, J., 1923, **123**, 362; Hunter and Styles, J., 1928, 3019), was present in larger amount. Both were isolated as *picrates*.

1-Hydroxybenzoxazole (I ⇌ II, X = O) was obtained by the action of carbonyl chloride upon *o*-aminophenol, from the hydrolysis of 1-chlorobenzoxazole (cf. Hunter, *loc. cit.*), and also from the condensation of *o*-aminophenol and chloroformic ester (Bender, *Ber.*, 1886, **19**, 2269). On methylation in alkaline medium, it behaved similarly to the 1-hydroxybenzthiazoles and yielded 1-*keto*-2-*methyl*-1 : 2-*dihydrobenzoxazole*, and on bromination in chloroform it underwent nuclear substitution, presumably at the carbon atom para to the nuclear nitrogen atom.

1-Thiolbenzoxazole (I ⇌ II, X = S) was obtained by pyrolysis of *o*-hydroxyphenylthiocarbamide, by the action of sodium hydrosulphide on 1-chlorobenzoxazole (cf. Hofmann, *Ber.*, 1887, **20**, 1778), and by the interaction both of thiocarbonyl chloride and carbon disulphide with *o*-aminophenol (Dunner, *Ber.*, 1876, **9**, 465). Methylation failed to yield a well-defined compound, but a mercuric chloride *compound* was isolated. 1-*Thio*-2-*methyl*-1 : 2-*dihydrobenzoxazole*, however, was synthesised from the corresponding ketomethyldihydro-derivative and phosphorus pentasulphide. On bromination in chloroform the thiolbenzoxazole gave rise to bromo-addition products which were evidently mixtures, since they yielded the original thiol derivative, a bromo-substitution derivative of this, and 1 : 1-benzoxazyl disulphide on reduction with sulphurous acid.

In the course of the present investigation, unsuccessful attempts were also made to convert benzylidene-*o*-aminophenol into 1-phenylbenzoxazole by oxidation with both hydrogen peroxide and potassium ferricyanide. The phenyloxazole (VI) was, however, obtained by heating a mixture of *o*-aminophenol and benzaldehyde for several hours, a reaction which most probably takes place by way of the 1 : 2-dihydro-derivative (V) (cf. Bogert and Stull, *J. Amer. Chem. Soc.*, 1925, **47**, 3078).

(V.)  (VI.)

Experimental.

Bromination of Phenylcarbamide.—(i) A solution of phenylcarbamide (1 g.) in chloroform (20 c.c.) was treated with bromine (1 c.c. in 2 c.c. of the same solvent) at 0°, and kept over-night. The product which crystallised did not contain labile halogen, and on treatment with sulphurous acid and then with ammonia yielded *p*-bromophenylcarbamide, identified by m. p. (278°) and by hydrolysis to *p*-bromoaniline. (ii) A repetition of this experiment at 40—50° yielded 2 : 4-dibromophenylcarbamide, m. p. 200° (Bertram, *Ber.*, 1892, **25**, 48) (Found: Br, 54·9. Calc. for $C_7H_6ON_2Br_2$: Br, 54·4%), which was hydrolysed to 2 : 4-dibromoaniline.

1-*Aminobenzoxazole.*—*o*-Hydroxyphenylthiocarbamide, prepared by heating a mixture of

o-aminophenol (15 g.), potassium thiocyanate (15 g.), and 10% hydrochloric acid (70 c.c.) at 100° for 6 hours, separated in 60% yield from alcohol in needles, m. p. 162°. A solution of this thiocarbamide (5 g.) in alcohol (50 c.c.) was treated with freshly precipitated mercuric oxide (15 g.), and the mixture heated on a water-bath under reflux for 8—10 hours. On recrystallisation from hot water, the aminobenzoxazole formed long flattened needles, m. p. 130° (Bendix, *Ber.*, 1878, **11**, 2262). The acetyl derivative separated from alcohol in needles, m. p. 172°. The *picrate* (formed in benzene solution) crystallised from acetone in prismatic needles, m. p. 224° (sintering at 200°) (Found: C, 42·8; H, 2·6. $C_7H_6ON_2,C_6H_3O_7N_3$ requires C, 43·0; H, 2·5%).

Methylation of 1-*Aminobenzoxazole*.—A mixture of 1-aminobenzoxazole (1 g.) and methyl iodide (1 c.c.) was heated in a sealed tube at 100° for 8 hours, and the product was basified with alkali, extracted with chloroform, and the chloroform removed on a water-bath; the methylation product solidified, and on recrystallisation from benzene–petroleum, 1-*imino*-2-*methyl*-1 : 2-*dihydrobenzoxazole* was obtained in small plates, m. p. 96° (Found: C, 64·6; H, 5·7. $C_8H_8ON_2$ requires C, 64·9; H, 5·4%). On being heated with concentrated hydrochloric acid for 2 hours and basified with ammonia, it yielded *o*-methylaminophenol, m. p. 129°. Its *picrate* separated from benzene in yellow needles, m. p. 189—190° (Found: C, 44·4; H, 3·2. $C_8H_8ON_2,C_6H_3O_7N_3$ requires C, 44·6; H, 2·9%); and its *acetyl* derivative formed plates from dilute alcohol, m. p. 92° (Found: C, 63·1; H, 5·4. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3%).

Synthesis of 1-*Methylaminobenzoxazole*.—A mixture of 1-thiolbenzoxazole (1 g.) and methylamine (1 c.c. of 30% aqueous solution) was heated in a sealed tube at 100° for 8 hours, the mixture extracted with ether, the extract well washed with 10% sodium hydroxide to remove unchanged thiolbenzoxazole, dried, and the ether removed on a steam-bath; the methylaminobenzoxazole formed a gum which showed little tendency to crystallise, but its acetyl derivative crystallised in small prisms, m. p. 91° (Found: C, 63·0; H, 5·45%). A mixture of this with the isomeric 1-acetylimino-2-methyl-1 : 2-dihydro-derivative melted at 55—60°.

Bromination of 1-*Aminobenzoxazole*.—(i) A solution of 1-aminobenzoxazole in chloroform (1 g. in 20 c.c.) was treated with bromine (0·5 c.c. in 2 c.c. of chloroform) at 0°, and kept for 3—4 hours in a freezing mixture; the *hydrobromide* of 5(?)-*bromo*-1-*aminobenzoxazole* then separated in white needles, m. p. 245° (Found: Br, 54·5. $C_7H_5ON_2Br,HBr$ requires Br, 54·4%). A further quantity (m. p. 245°) was obtained from the yellow gum afforded by evaporation of the chloroform mother-liquors in a vacuum at room temperature. On basification with ammonia, the hydrobromide yielded 5(?)-*bromo*-1-*aminobenzoxazole*, which separated from dilute alcohol in prismatic needles, m. p. 194—195° (Found: Br, 37·45. $C_7H_5ON_2Br$ requires Br, 37·5%). (ii) In a similar experiment in which twice the quantity of bromine was employed, an oil was obtained, which on keeping yielded yellow needles of a *hydrodibromide*, m. p. 232° (decomp.; sintering at about 180°), after drying in a vacuum [Found: Br (total), 64·3; Br (labile), 19·6. $C_7H_5ON_2Br,HBr(Br)$ requires Br (total), 64·2; Br (labile), 21·4%]. On reduction with sulphurous acid and basification with ammonia, the bromo-addition compound yielded the bromobenzoxazole, m. p. 194—195°.

1-Anilinobenzoxazole was prepared both by the desulphurisation of *o*-hydroxy-*s*-diphenylthiocarbamide in alcoholic solution by means of mercuric oxide, and, better, by a general method, *viz.*, heating a mixture of 1-thiolbenzoxazole and aniline for 6 hours at 180° (Kalckhoff, *Ber.*, 1883, **16**, 1825; Young and Dunstan, J., 1908, **93**, 1052). On recrystallisation from dilute alcohol, it formed needles, m. p. 194°. The *picrate* separated from benzene in yellow needles, m. p. 188° (Found: C, 51·7; H, 2·8. $C_{13}H_{10}ON_2,C_6H_3O_7N_3$ requires C, 51·8; H, 2·95%).

1-p-*Toluidinobenzoxazole*, prepared by the second method above, separated from dilute alcohol in cubic crystals, m. p. 178° (Found: C, 74·8; H, 5·5. $C_{14}H_{12}ON_2$ requires C, 75·0; H, 5·3%).

Methylation of 1-*Anilinobenzoxazole*.—A mixture of 1-anilinobenzoxazole (1 g.) and methyl iodide (2 c.c.) was heated in a sealed tube at 100° for 12 hours, and the product was basified with warm alkali, and extracted with ether. The resulting gum showed little tendency to crystallise and was therefore dissolved in acetone and treated with picric acid (1·2 g.) in the same solvent, 0·8 g. of the *picrate* of 1-phenylimino-2-methyl-1 : 2-dihydrobenzoxazole being obtained; on recrystallisation it formed yellow needles, m. p. 156° (Found: C, 52·7; H, 3·6. $C_{14}H_{12}ON_2,C_6H_3O_7N_3$ requires C, 53·0; H, 3·3%), unaffected by further recrystallisation but depressed by admixture with the following picrate. The first acetone mother-liquors, on evaporation and recrystallisation of the product from benzene, yielded yellow needles of the *picrate* of 1-phenylmethylaminobenzoxazole, m. p. 176° (Found: C, 52·8; H, 3·5%).

Synthesis of 1-*Phenylaminobenzoxazole Picrate.*—A mixture of 1-thiolbenzoxazole (1 g.) and methylaniline (1 g.) was heated in a hard-glass tube at 170—180° for 6 hours, hydrogen sulphide then being no longer evolved; the product was extracted with ether, and the extract washed with dilute sodium hydroxide, dilute hydrochloric acid, and dried. The gum obtained by removal of ether was dissolved in benzene and treated with the theoretical quantity of picric acid in the same solvent, whereupon the picrate of 1-phenylmethylaminobenzoxazole was obtained, m. p. 175—176° alone and when mixed with the specimen obtained as above.

Synthesis of 1-*Hydroxybenzoxazole.*—(i) 1-*Chlorobenzoxazole.* An unsuccessful attempt was made to obtain this compound by heating phenylcarbimide and phosphorus pentachloride together in a sealed tube at 165—170° for 6 hours (cf. Hofmann, *Ber.*, 1879, **12**, 1126; 1880, **13**, 8), but the main product was *s*-diphenylcarbamide, long prismatic needles, m. p. 236—237°. The chlorobenzoxazole was therefore prepared from 1-aminobenzoxazole (cf. Hunter and Jones, J., 1930, 2190). A solution of 1-aminobenzoxazole (1 g.) in dilute hydrochloric acid (10 c.c.) was cooled to 0°, treated with sodium nitrite (0·6 g. in 6 c.c. of water), and kept in a freezing mixture for ½ hour. 5 C.c. of concentrated hydrochloric acid were then added, and the mixture was warmed and distilled in steam, whereupon 0·3 g. of 1-chlorobenzoxazole was obtained as a yellow oil, which was heated on a water-bath with an alcoholic solution of sodium ethoxide (from 0·1 g. Na) for 4 hours. After removal of alcohol on a water-bath, the product was heated with concentrated hydrochloric acid, and afforded 1-hydroxybenzoxazole, m. p. 142°, identified by mixed m. p.

(ii) A mixture of *o*-aminophenol (3 g.), 12% solution of carbonyl chloride in toluene (12 c.c.), and dry toluene (50 c.c.) was heated on a water-bath under reflux for 2 hours, and the precipitated hydrochloride of *o*-aminophenol was removed by filtration. On removal of the toluene, and recrystallisation of the residue from petroleum, 1-hydroxybenzoxazole, m. p. 142°, was obtained in prismatic needles. The mother-liquors on keeping yielded another product, small plates, m. p. 106°, which was not investigated.

(iii) 1-Hydroxybenzoxazole was most conveniently prepared from *o*-aminophenol, sodium ethoxide, and chloroformic ester by Bender's method (*Ber.*, 1886, **19**, 2269), and separated from hot water in needles, m. p. 140°, raised to 144° after sublimation.

Methylation of 1-*Hydroxybenzoxazole.*—A solution of 1-hydroxybenzoxazole (1 g.) in chloroform (10 c.c.) was treated with 30% potassium hydroxide solution (10 c.c.), and then with methyl sulphate (4 c.c.). The mixture was kept at room temperature for ½ hour and then heated on a water-bath under reflux for a further ½ hour. The product obtained after destruction of the excess of methyl sulphate with alkali and removal of chloroform was recrystallised from methyl alcohol, 1-*keto*-2-*methyl*-1 : 2-*dihydrobenzoxazole* being obtained in long silky needles, m. p. 87—88° (Found: C, 64·4; H, 4·9. $C_8H_7O_2N$ requires C, 64·6; H, 4·7%). On hydrolysis with concentrated hydrochloric acid, it yielded *o*-methylaminophenol, m. p. 129°.

Bromination of 1-*Hydroxybenzoxazole.*—A solution of the hydroxy-compound in chloroform (0·5 g. in 10 c.c.) was gradually treated with bromine (0·5 c.c. in 2 c.c. of chloroform) at 0°; a *hydrobromide* of 5(?)-bromo-1-hydroxybenzoxazole gradually separated, which showed no reaction for labile bromine (potassium iodide) after being dried in a vacuum (Found: Br, 54·1. $C_7H_4O_2NBr,HBr$ requires Br, 54·2%).

5(?)-*Bromo*-1-*hydroxybenzoxazole*, obtained by decomposition of the hydrobromide with water or dilute ammonia, separated from alcohol in long, flattened needles, m. p. 190° (Found: Br, 37·15. $C_7H_4O_2NBr$ requires Br, 37·2%).

Synthesis of 1-*Thiolbenzoxazole.*—(i) A mixture of 1-chlorobenzoxazole (0·2 g.), sodium hydrosulphide (0·3 g.), and alcohol (15 c.c.) was heated under reflux for 2 hours, and the product obtained by removal of the alcohol on a water-bath was extracted with dilute sodium hydroxide. On acidification, 1-thiolbenzoxazole was obtained, which crystallised from dilute alcohol in long needles, m. p. 194°. (ii) The same compound was also obtained from *o*-aminophenol and thiocarbonyl chloride in chloroform (cf. Hunter, J., 1930, 125). (iii) 1 G. of *o*-hydroxyphenylthiocarbamide was heated in a dry tube at 170—180° for 3 hours, and the cold melt was extracted with ammonia. On acidification 1-thiolbenzoxazole (0·2 g.) was obtained. (iv) The thiolbenzoxazole was, however, most conveniently prepared by heating a mixture of *o*-aminophenol (10 g.), carbon disulphide (30 c.c.), potassium hydroxide (5 g.), and alcohol (20 c.c.) under reflux for 6 hours (Dunner, *Ber.*, 1876, **9**, 465). On recrystallisation from dilute alcohol, it formed long, flattened needles, m. p. 196°. The *mercuric* salt, prepared by heating the thiolbenzoxazole in alcohol with yellow mercuric oxide and filtering the hot solution, crystallised in lustrous plates, m. p. 204° (Found: S, 13·05. $C_{14}H_8O_2N_2S_2Hg$ requires S,

12·8%). This salt was also obtained by treating an alcoholic solution of the thiolbenzoxazole with aqueous mercuric chloride.

Attempted Methylation of 1-*Thiolbenzoxazole.*—A mixture of 1-thiolbenzoxazole (1 g.), methyl alcohol (3 c.c.), and methyl sulphate (3 c.c.) was heated on a water-bath, under reflux, for an hour. The excess of methyl sulphate was destroyed with ammonia (*d* 0·880), and the mixture extracted with chloroform. The syrup obtained by removal of chloroform did not solidify in a vacuum, and was therefore dissolved in alcohol and treated with aqueous mercuric chloride; the *compound* of mercuric chloride with 1-methylthiolbenzoxazole separated, and on recrystallisation from benzene was obtained in needles, m. p. 162° (Found : S, 7·55. $C_8H_7ONS,HgCl_2$ requires S, 7·33%). A similar result was obtained by methylating the thiolbenzoxazole with methyl iodide in the presence of methyl-alcoholic sodium methoxide, although in this case the syrup obtained after removal of chloroform solidified in a freezing-mixture, but melted again at laboratory temperature.

Synthesis of 1-*Thio*-2-*methyl*-1 : 2-*dihydrobenzoxazole.*—A mixture of 1-keto-2-methyl-1 : 2-dihydrobenzoxazole (0·3 g.) and phosphorus pentasulphide (0·6 g.) was heated at 120—130° for ½ hour, and the melt was extracted with benzene. On concentration of the extract, the required *compound* separated; it crystallised from alcohol in long needles, m. p. 134—135° (Found : S, 20·9. C_8H_7ONS requires S, 20·6%).

Bromination of 1-*Thiolbenzoxazole.*—(i) Bromine (0·5 c.c. in 2 c.c. of chloroform) was added to a solution of 1-thiolbenzoxazole (0·5 g.) in chloroform (20 c.c.) at 0°; the red bromo-addition product which separated had m. p. 138° (decomp.) after being dried in a vacuum [Found : Br (total), 37·5; Br (labile), 17·0%]. This consisted probably of a mixture of a hydrodibromide of 1-thiolbenzoxazole and a hydrobromide of the disulphide, since on reduction with sulphurous acid it yielded the original thiolbenzoxazole, accompanied by benzoxazyl 1 : 1-disulphide, m. p. 110°.

(ii) In a similar experiment, with double the amount of bromine, a crystalline, vermilion bromo-addition *compound* was obtained, m. p. 128° (decomp.) after drying in a vacuum [Found : Br (total), 53·5; Br (labile), 30·0. $C_7H_5ONS,HBr(Br)$ requires Br (total), 51·3; Br (labile), 25·7%]. This yielded the original thiolbenzoxazole on reduction with sulphurous acid, accompanied by only traces of the disulphide. Concentration of the chloroform mother-liquors of the original bromination, however, yielded a solid, which on treatment with sulphurous acid and basification with ammonia gave 5(?)-*bromo*-1-*thiolbenzoxazole*, which separated from dilute alcohol in long, flattened needles, m. p. 200° (Found : Br, 34·9. C_7H_4ONBrS requires Br, 34·8%).

Synthesis of 1-*Phenylbenzoxazole.*—Benzylidene-*o*-aminophenol, prepared by heating a mixture of *o*-aminophenol (1 g.) and benzaldehyde (1 g.) in dry benzene (20 c.c.) for 3 hours, crystallised in pale yellow needles, m. p. 89° (Pictet and Ankersmit, *Annalen*, 1891, **266**, 138). Attempts to oxidise it to 1-phenylbenzoxazole led, however, to tarry materials. A mixture of *o*-aminophenol (2 g.), benzaldehyde (4 g.), and glacial acetic acid was therefore heated on a water-bath for 4 hours; the mixture darkened, and as nothing crystalline was obtained on dilution with water, it was distilled in steam for 3—4 hours, benzaldehyde and acetic acid passing over, followed by a white substance which solidified in the receiver. On re-crystallisation from alcohol, this separated in needles, m. p. 103° alone and when mixed with a specimen of 1-phenylbenzoxazole prepared by Ladenburg's method (*Ber.*, 1876, **9**, 1524).

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