CCCC.—*The Synthesis of Four Amino-3-hydroxy-1 : 4-benz*iso*oxazines.*

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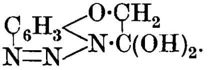
Of the four possible amino-3-hydroxy-1 : 4-benz*iso*oxazines in which the amino-group is in the benzene ring, only the 6-amino-derivative has hitherto been described (Howard, *Ber.*, 1897, **30**, 2103). As the characterisation of these isomerides was necessary for the orientation of certain of their arsinic acid derivatives, their synthesis from the corresponding nitro-2-aminophenols is here described.

6-Amino-3-hydroxy-1 : 4-benz*iso*oxazine obtained from 4-nitro-2-aminophenol by chloroacetylation, followed by ring closure by means of alkali and subsequent reduction, melted at 255°, whereas Howard (*loc. cit.*) gives 225°. The same product, m. p. 255°, was also obtained by the reduction of 2 : 4-dinitrophenoxyacetic acid.

The nitration of 4-acetamidophenoxyacetic acid, followed by hydrolysis, and the nitration of 4-aminophenoxyacetic acid by Howard's method gave the same nitro-4-aminophenoxyacetic acid. On reduction, 6-amino-3-hydroxy-1 : 4-benz*iso*oxazine, m. p. 255°, was obtained.

The basicity of 5-*amino*-3-*hydroxy*-1 : 4-*benz*iso*oxazine* is of a lower order than that of its isomerides; *e.g.*, $1\frac{1}{2}$ mols. of *N*/10-mineral acid are required for its solution, whereas the others dissolve in 1 mol. of *N*/10-acid to give salts which are neutral to Congo-red. The other isomerides diazotise normally, but the 5-isomeride forms with nitrous acid a *triazole* which crystallises with a molecule of water; this cannot be driven off at 120° and the triazole may therefore have the constitution 

$$\begin{array}{lcl} & & \mathrm{O\cdot CH_2} \\ \mathrm{C_6H_3} & < & \quad\;| \\ | & & \mathrm{N\cdot C(OH)_2.} \\ \mathrm{N{=}N} & \diagup & \end{array}$$

EXPERIMENTAL.

(A) 5-*Amino*-3-*hydroxy*-1 : 4-*benz*iso*oxazine*.—3-Nitro-2-aminophenol, obtained by Fourneau (*Bull. Soc. chim.*, 1927, **41**, 499) by the de-arsenication of 3-nitrobenzoxazolone-5-arsinic acid and by King (J., 1927, 1059) in small yield by nitration in acetic anhydride of *ON*-diacetyl-*o*-aminophenol (Ingold and Ingold, J., 1926, 1321), was obtained in improved yield by treating the crude nitration product as follows :

45 G. were boiled under reflux with hydrochloric acid (150 c.c.; *d* 1·16) for 45 minutes; 190 c.c. of 10*N*-sodium hydroxide were added to the cooled solution, which, still acid to Congo-red, was then boiled with charcoal and filtered. On cooling, 3-nitro-2-aminophenol (17 g., m. p. 217°) separated. The addition of a further 25 c.c. of 10*N*-sodium hydroxide gave a mixture (4·7 g., m. p. 180—185°). By rendering the liquor, which was still acid to Congo-red, neutral to litmus, 5-nitro-2-aminophenol (5·6 g., m. p. 200°) was obtained (total yield of nitro-2-aminophenols, 94%). The mixture of m. p. 180—185°, on similar fractional neutralisation of its solution in acid, gave 1·5 g. each of the above nitroaminophenols. The total yields isolated are thus 63·5 and 24·4% of the 3- and 5-nitro-2-aminophenols, respectively, which are considerably at variance with those estimated by Ingold and Ingold (*loc. cit.*).

The mother-liquors on extraction with ether gave a mixture of 5-nitro-2-aminophenol and *o*-aminophenol (m. p. 170°).

3-Nitro-2-aminophenol crystallised, on addition of water or sodium acetate to its solution in warm concentrated hydrochloric acid, in red needles changing to hexagonal plates, m. p. 212°. The mono- and di-acetyl derivatives agreed in m. p. with those described by Ingold and Ingold (*loc. cit.*).

3-*Nitro*-2-*chloroacetamidophenol.* To 3-nitro-2-aminophenol (10 g.) in acetone (80 c.c.), chloroacetyl chloride (8 c.c.) was added with shaking (temp. 25°). After 30 minutes, the bulk of the acetone was removed. The *chloroacetyl* derivative, which slowly separated (11·5 g.; 88%), crystallised from alcohol in yellow prisms, m. p. 153—154°, readily soluble in organic solvents but insoluble in water (Found: N, 12·0; Cl, 15·2. $C_8H_7O_4N_2Cl$ requires N, 12·1; Cl, 15·4%).

5-*Nitro*-3-*hydroxy*-1 : 4-*benz*iso*oxazine.* A paste of 3-nitro-2-chloroacetamidophenol (6 g.) and water (5 c.c.) was treated with 2*N*-sodium hydroxide (20 c.c.) and heated in a boiling water-bath for 30 minutes. On acidification, the *product* separated in orange prisms (4·9 g.; 98%), m. p. 115—116°. The solution in boiling water (50 parts) deposited, on cooling, long, prismatic needles of the same m. p. (Found: N, 14·2. $C_8H_6O_4N_2$ requires N, 14·4%).

5-*Amino*-3-*hydroxy*-1 : 4-*benz*iso*oxazine.* A mixture of the above nitro-compound (3 g.) with iron powder (6 g.) was added to boiling water (60 c.c.) containing glacial acetic acid (3 c.c.). After short boiling, the mixture was made faintly alkaline to litmus with 2*N*-sodium hydroxide and boiled with an equal volume of water. The *product* crystallised, on concentration of the filtered solution, in colourless prisms (1·6 g.; 73%), m. p. 236° after recrystallisation. It is moderately easily soluble in alcohol (Found: N, 16·9. $C_8H_8O_2N_2$ requires N, 17·1%). The *hydrochloride* formed characteristic rhombs, hydrolysed by boiling water (Found: N, 14·0; Cl, 17·3, $C_8H_8O_2N_2,HCl$ requires N, 13·9; Cl, 17·7%). The *acetyl* derivative (Found: N, 13·3. $C_{10}H_{10}O_3N_2$ requires N, 13·6%) crystallised from alcohol in colourless prisms, m. p. 255°. The *triazole*, made by addition of sodium nitrite (1 mol.) to a suspension of the hydrochloride in cold water, crystallised from boiling water in plates, m. p. 204° (Found: N, 21·7. $C_8H_5O_2N_3,H_2O$ requires N, 21·8%).

(B) 6-*Amino*-3-*hydroxy*-1 : 4-*benz*iso*oxazine.*—(a) When a mixture of 2 : 4-dinitrophenoxyacetic acid (Pratezi, *Gazzetta*, 1892, **21**, 402; m. p. 147—148°; 24 g.), iron filings (83 g.), water (100 c.c.), and hydrochloric acid (25 c.c.; *d* 1·16) was warmed, a vigorous reaction set in which was controlled when necessary by cooling. After a further 15 minutes' heating, the liquid was filtered and treated with a large excess of hydrochloric acid. The hydrochloride, together with a further amount obtained by extraction of the ferric oxide with boiling water, weighed 9·5 g. (47·5% yield) and crystallised in plates, m. p. 300° (decomp.) (Found : N, 13·7; Cl, 17·6%). The base (colourless prisms, m. p. 255° after crystallisation from alcohol) was obtained by treatment of the hydrochloride solution with sodium acetate (Found : N, 17·1%). The *acetyl* derivative (fine needles from water) melted at 298—299° (bath at 240°) (Found : N, 13·5%).

(b) 4-*Nitro*-2-*chloroacetamidophenol*, prepared from 4-nitro-2-aminophenol, crystallised from alcohol in stout hexagonal plates, m. p. 245° (decomp.). It was insoluble in water and ether and sparingly soluble in alcohol and acetone (Found : N, 12·0; Cl, 15·5%).

6-*Nitro*-3-*hydroxy*-1 : 4-*benz*iso*oxazine* formed almost colourless prisms from alcohol; m. p. 233—234°, depressed by admixture with the 7-nitro-compound, m. p. 232°. It was insoluble in water and sparingly soluble in alcohol and acetone (Found : N, 14·6%). On reduction with iron and boiling dilute acetic acid it gave the corresponding amino-derivative, m. p. 255°.

(c) 4-Acetamidophenoxyacetic acid (5·8 g.) mixed with potassium nitrate (2·9 g.) was added to sulphuric acid (30 c.c.) at 10°. After 1 hour the mixture was poured on ice; 2-*nitro*-4-*acetamidophenoxyacetic acid* (5·8 g.; 82%) then crystallised, and was obtained in yellow rhombic plates, m. p. 205—206°, by recrystallisation from water. It was readily soluble in alcohol and sparingly soluble in other organic solvents (Found : N, 10·7. $C_{10}H_{10}O_6N_2$ requires N, 11·0%). On hydrolysis with 7*N*-hydrochloric acid it gave 2-nitro-4-aminophenoxyacetic acid (m. p. 196°; yield, 92%), identical with that obtained by the nitration of 4-aminophenoxyacetic acid (Howard, *loc. cit.*). Both the nitroamino-acid and its acetyl derivative, on reduction by tin and hydrochloric acid, gave 6-amino-3-hydroxy-1 : 4-benz*iso*oxazine, m. p. 255°, not depressed by admixture with the products from (a) and (b).

(C) 7-*Amino*-3-*hydroxy*-1 : 4-*benz*iso*oxazine*.—5-*Nitro*-2-*chloroacetamidophenol*, prepared from 5-nitro-2-aminophenol, crystallised from alcohol in light yellow prisms or tetrahedra, m. p. 233° (decomp.). It was insoluble in cold water (Found : N, 12·1; Cl, 15·5%).

7-*Nitro*-3-*hydroxy*-1 : 4-*benz*iso*oxazine* formed yellow prisms, m. p. 232°, from alcohol (Found : N, 14·0%).

7-*Amino*-3-*hydroxy*-1 : 4-*benz*iso*oxazine* separated in colourless prisms, m. p. 220°, from boiling water. It is insoluble in cold water and ether, slightly soluble in chloroform, and moderately easily soluble in alcohol and acetone (Found : N, 17·3%).

Its *hydrochloride*, m. p. 275—278° (decomp.), formed colourless prisms, readily soluble in cold water to give a solution neutral to Congo-red (Found : N, 14·0; Cl, 17·5%).

7-*Acetamido*-3-*hydroxy*-1 : 4-*benz*iso*oxazine* was deposited from hot water in fine needles, m. p. 250°. It is insoluble in cold water, ether, and chloroform and moderately easily soluble in alcohol (Found : N, 13·3%).

(D) 8-*Amino*-3-*hydroxy*-1 : 4-*benz*iso*oxazine*.—The methods given in the literature for the formation of 6-nitro-2-aminophenol, *viz.*, the de-arsenication of 2-nitro-4-acetamido-3-hydroxyphenylarsinic acid (Benda, *Ber.*, 1914, **47**, 1010) and the nitration of *o*-acetamidophenol in acetic anhydride (King, *loc. cit.*), are not satisfactory for the preparation of large quantities. The following method was therefore used :

3 : 5-Dinitro-4-hydroxyphenylarsinic acid (120 g.) was refluxed for 1 hour with sodium bisulphite (60 g.) in water (400 c.c.); a further 60 g. of sodium bisulphite in water (100 c.c.) were then added, and the boiling continued for 3 hours. After cooling, the supersaturated solution of sodium sulphate decahydrate was decanted from the cake of 2 : 6-dinitrophenol, which was crystallised from 50% alcohol (m. p. 60°; yield, 54 g. or 75%). On reduction by ammonium sulphide (Post and Stuckenberg, *Annalen*, 1880, **205**, 85), and crystallisation from alcohol, a 45% yield of 6-nitro-2-aminophenol, m. p. 112—113° (Found : N, 17·9. Calc. : N, 18·2%), was obtained. The *acetyl* derivative was obtained as a monohydrate, m. p. 102—103°; the anhydrous substance melted at 122° (Found : N, 15·0. $C_8H_8O_4N_2$ requires N, 14·9%).

6-*Nitro*-2-*chloroacetamidophenol* crystallised from alcohol in rich yellow rhombs, m. p. 126°, insoluble in water and sparingly soluble in cold acetone (Found : N, 11·8; Cl, 15·6%).

8-*Nitro*-3-*hydroxy*-1 : 4-*benz*iso*oxazine* formed light yellow prisms, m. p. 255°, from alcohol (Found : N, 14·3%).

8-*Amino*-3-*hydroxy*-1 : 4-*benz*iso*oxazine* (Found : N, 17·0%) formed colourless prisms, m. p. 180°, from water. It formed a hydrochloride, m. p. 272° (decomp.), and an acetyl derivative, m. p. 257°. This compound and its derivatives were identical with those obtained previously by Dr. I. E. Balaban in this laboratory (p. 3070).

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