233. 4-*Aminosalicylic Acid and Its Derivatives. Part II.* The Synthesis of* 4-*Amino*-2 : 5- *and* 4-*Amino*-2 : 3-*dihydroxybenzoic Acid.*

By S. C. Bhattacharyya and D. E. Seymour.

Persulphate oxidation of 4-nitrosalicylic acid is shown to give 4-nitro-2 : 5- and 4-nitro-2 : 3-dihydroxybenzoic acid. Reduction of the nitrodihydroxy-acids gives the corresponding amino-acids, various derivatives of which have been prepared for biological study.

With the object of making certain oxidation products of 4-aminosalicylic acid available for biological study, 4-amino-2 : 5- and 4-amino-2 : 3-dihydroxybenzoic acid have been synthesised.

Oxidation of 4-nitrosalicylic acid with alkaline potassium or ammonium persulphate gives 4-nitro-2 : 5-dihydroxybenzoic acid together with a smaller amount of a more soluble isomer which has been shown to be 4-nitro-2 : 3-dihydroxybenzoic acid. 4-Nitro-2 : 5-dihydroxybenzoic acid was reduced to 4-amino-2 : 5-dihydroxybenzoic acid (isolated as its hydrochloride) which on deamination yielded 2 : 5-dihydroxybenzoic acid (gentisic acid). This establishes the structure of the parent nitrodihydroxybenzoic acid; it was confirmed by conversion of the amino-acid into 4-chloro-2 : 5-dihydroxybenzoic acid which was also obtained by persulphate oxidation of 4-chlorosalicylic acid.

The structure of the minor oxidation product was established by its reduction to the corresponding aminodihydroxybenzoic acid, deamination of which yielded 2 : 3-dihydroxybenzoic acid.

The isomeric aminodihydroxybenzoic acids were obtained by catalytic reduction of the corresponding nitro-compounds and, as was expected, they are unstable in air and were isolated as their hydrochlorides or as their acetyl derivatives.

The acids described are being examined as possible tuberculostatic agents, and the results of this examination will be described elsewhere. French and Freedlander (*J. Amer. Pharm. Assoc.*, 1949, **38**, 343) have suggested that 4-amino-2 : 5-dihydroxybenzoic acid or the corresponding quinone may be responsible for the tuberculostatic activity of aminosalicylic acid.

Experimental.

4-*Nitro*-2 : 5-*dihydroxybenzoic Acid.*—A solution of 4-nitrosalicylic acid (10 g.) and sodium hydroxide (16 g.) in water (200 ml.) was treated with a solution of potassium persulphate (11 g.) in water (400 ml.). After 48 hours at room temperature, the solution was just acidified (Congo-red) with dilute sulphuric acid with ice cooling, and the mixture was extracted with ether to remove unchanged 4-nitrosalicylic acid (6 g.). The solution was then made strongly acid with sulphuric acid, boiled for 20 minutes, and cooled to room temperature. The crystalline precipitate was removed and the mother-liquor retained for further treatment. On recrystallisation of this precipitate from hot water (charcoal) 4-*nitro*-2 : 5-*dihydroxybenzoic acid* was obtained as brown needles (2·3 g.) m. p. 242°, becoming orange on drying (Found : C, 42·6; H, 2·65; N, 7·15. $C_7H_5O_6N$ requires C, 42·3; H, 2·55; N, 7·05%). The acid sublimes without decomposition; it gives a violet colour with ferric chloride solution, and an intense violet colour with alkali.

4-*Nitro*-2 : 3-*dihydroxybenzoic Acid.*—The mother-liquor obtained as described above was extracted with ether, and the extract was washed with water. After removal of the ether the residue was crystallised twice from hot water (charcoal) to give golden needles of 4-*nitro*-2 : 3-*dihydroxybenzoic acid* (0·6 g.), m. p. 194° (Found : C, 42·55; H, 2·5; N, 6·7%). The acid gives colour reactions similar to those described for 4-nitro-2 : 5-dihydroyxbenzoic acid.

4-*Nitro*-2 : 5-*diacetoxybenzoic Acid.*—A solution of 4-nitro-2 : 5-dihydroxybenzoic acid (2 g.) in acetic anhydride (6 ml.) was heated at 100° for 3½ hours. The cold solution was poured into water (25 ml.), and the mixture was filtered. The solid, after being washed with water, was crystallised from alcohol giving 4-*nitro*-2 : 5-*diacetoxybenzoic acid* (1·8 g.), m. p. 194° (Found : C, 46·3; H, 3·4; N, 5·2. $C_{11}H_9O_8N$ requires C, 46·65; H, 3·2; N, 4·95%). The product does not give a coloration with ferric chloride solution.

4-*Nitro*-2 : 3-*diacetoxybenzoic Acid.*—This was obtained in 70% yield by a similar acetylation of 4-nitro-2 : 3-dihydroxybenzoic acid. When crystallised from alcohol, 4-*nitro*-2 : 3-*diacetoxybenzoic acid* was obtained as plates, m. p. 186° with softening at 160—170° (Found : C, 46·8; H, 3·2; N, 4·75%).

4-*Amino*-2 : 5-*dihydroxybenzoic Acid Hydrochloride.*—A solution of 4-nitro-2 : 5-dihydroxybenzoic acid (4 g.) in ethyl acetate (200 ml.) was shaken with hydrogen in the presence of Adams's platinum catalyst (70 mg.) for 30 minutes; gas absorption was then complete. The solution was filtered in an atmosphere of carbon dioxide and, after a stream of anhydrous hydrogen chloride had been passed through the filtrate, the insoluble hydrochloride (3·8 g.) separated as a microcrystalline powder. This was collected, washed with ethyl acetate, and dried at room temperature over sulphuric acid. 4-*Amino*-2 : 5-*dihydroxybenzoic acid hydrochloride*, m. p. 212° (decomp.), is unstable, and aqueous solutions of the salt darken rapidly on being kept (Found : C, 40·6; H, 4·0; N, 6·5; Cl, 16·9. $C_7H_8O_4NCl$ requires C, 40·9; H, 3·9; N, 6·8; Cl, 17·25%). The free amino-acid in one instance was precipitated directly

* Part I, *J.*, 1949, 1498.

from the ethyl acetate solution (obtained on reduction) by the addition of light petroleum; it rapidly darkens on exposure to air.

4-*Amino*-2 : 3-*dihydroxybenzoic Acid Hydrochloride*.—Reduction of 4-nitro-2 : 3-dihydroxybenzoic acid as described above gave 4-*amino*-2 : 3-*dihydroxybenzoic acid hydrochloride* as a white microcrystalline powder, m. p. 180° (yield, 95%) (Found: C, 40·65; H, 4·1; N, 6·7; Cl, 17·8%).

4-*Chloro*-2 : 5-*dihydroxybenzoic Acid*.—(*a*) A solution of 4-nitro-2 : 5-dihydroxybenzoic acid and sodium carbonate (1 g.) in water (150 ml.) was shaken with hydrogen in the presence of Adams's platinum oxide catalyst (70 mg.). After reduction was complete the catalyst was removed and the solution was acidified with hydrochloric acid and diazotised at 0° by the addition of 10% sodium nitrite (10 ml.). The solution was stirred for 15 minutes and poured into a freshly prepared solution of cuprous chloride (5 g.) in concentrated hydrochloric acid (100 ml.). After being kept at room temperature overnight the solution was extracted with ether and the reaction product isolated. 4-*Chloro*-2 : 5-*dihydroxybenzoic acid* (1·5 g.) separated from water as plates, m. p. 222° (Found: C, 44·6; H, 2·6; Cl, 20·0. $C_7H_5O_4Cl$ requires C, 44·6; H, 2·7; Cl, 18·8%).

(*b*) A solution of 4-chlorosalicylic acid (10 g.) in water (300 ml.) containing sodium hydroxide (25 g.) was treated with a solution of ammonium persulphate (11 g.) in water (200 ml.) with cooling. After 48 hours at room temperature the solution was acidified with dilute sulphuric acid with cooling, and the unchanged 4-chlorosalicylic acid was removed by extraction with ether. The aqueous solution was made strongly acid by the addition of concentrated sulphuric acid (50 g.) and after boiling for 20 minutes and cooling 4-*chloro*-2 : 5-*dihydroxybenzoic acid* (3·4 g.) was isolated by extraction with ether. Crystallisation of the product from water (charcoal) yielded the acid as plates, m. p. 222° undepressed in admixture with the specimen obtained by method (*a*).

4-*Chloro*-2 : 3-*dihydroxybenzoic Acid*.—A solution of 4-amino-2 : 3-dihydroxybenzoic acid hydrochloride (1·2 g.) in hydrochloric acid (50 ml.; 15%) was diazotised with sodium nitrite (0·5 g.). The diazo-solution was poured into a solution of cuprous chloride (4 g.) in concentrated hydrochloric acid (50 ml.). After 12 hours at room temperature the solution was extracted with ether. The product was isolated and crystallised from water (charcoal) to give 4-*chloro*-2 : 3-*dihydrobenzoic acid* (0·55 g.), m. p. 226° (Found: C, 44·9; H, 2·6; Cl, 19·0%). The acid gives a deep-blue colour with ferric chloride solution.

2 : 5-*Dihydroxybenzoic Acid* (*Gentisic Acid*).—A solution of freshly prepared 4-amino-2 : 5-dihydroxybenzoic acid hydrochloride (3·1 g.) in water (50 ml.) and hydrochloric acid (10 ml.) was diazotised with sodium nitrite solution (11 ml.; 10%). The cold diazo-solution was added to hypophosphorous acid (50 ml.; 30%) and kept for 12 hours at room temperature. After filtration the solution was saturated with ammonium sulphate and the product isolated by extraction with ether. It was purified by sublimation at 150°/2 mm. to give gentisic acid, m. p. and mixed m. p. 201°.

2 : 3-*Dihydroxybenzoic Acid*.—A solution of freshly prepared 4-amino-2 : 3-dihydroxybenzoic acid hydrochloride (2·1 g.) was diazotised as in the above case, and the diazo-compound was similarly reduced with hypophosphorous acid. 2 : 3-Dihydroxybenzoic acid (0·55 g.) was isolated; it sublimed at 150—180°/1 mm. The acid (0·3 g.) was heated in a sealed tube at 230° for 3 hours, and the catechol, m. p. 105°, which was produced by decarboxylation, gave no depression in m. p. with an authentic specimen.

4-*Amino*-2 : 5-*diacetoxybenzoic Acid*.—A solution of 4-nitro-2 : 5-diacetoxybenzoic acid (2 g.) in methanol (150 ml.) was shaken with hydrogen in the presence of Adams's catalyst (70 mg.). After gas absorption was complete (15 minutes) the solution was filtered and concentrated in the absence of air at 35°. The concentrated solution was kept at 5° overnight and give 4-*amino*-2 : 5-*diacetoxybenzoic acid* (1·1 g.) as needles, m. p. 220° (Found: C, 52·05; H, 4·3; N, 5·5. $C_{11}H_{11}O_6N$ requires C, 52·2; H, 4·4; N, 5·55%).

4-*Acetamido*-2 : 5-*diacetoxybenzoic Acid*.—A solution of 4-amino-2 : 5-diacetoxybenzoic acid (1 g.) in acetic anhydride (4 ml.) was heated for 3 hours at 100°. The clear solution after cooling was diluted with water (15 ml.) and stirred; the solid which separated was collected, washed with water, and crystallised from dilute alcohol to yield 4-*acetamido*-2 : 5-*diacetoxybenzoic acid* (0·8 g.), m. p. 196° (Found: C, 52·7; H, 4·5; N, 4·5. $C_{13}H_{13}O_7N$ requires C, 52·9; H, 4·45; N, 4·7%).

4-*Acetamido*-2 : 3-*diacetoxybenzoic Acid*.—Freshly prepared 4-amino-2 : 3-dihydroxybenzoic acid (0·7 g.) was heated with acetic anhydride (3 ml.) at 100° for 3 hours. The acetic anhydride was removed *in vacuo*, and the residue was crystallised from dilute alcohol (charcoal) giving 4-*acetamido*-2 : 3-*diacetoxybenzoic acid* as needles (0·4 g.), m. p. 186° (decomp.) (Found: C, 52·4; H, 4·4; N, 4·65%).

The authors thank Professor F. S. Spring for his advice and criticism, and the Directors of Herts Pharmaceuticals Limited for permission to publish these results.

THE RESEARCH LABORATORIES, HERTS PHARMACEUTICALS LIMITED,
WELWYN GARDEN CITY, HERTS. [*Received, January 27th*, 1950.]