138. 3-*Nitro-* and 3-*Amino*-4-*hydroxybenzenesulphonamide.*

By William O. Kermack, Walter T. Spragg, and Walter Tebrich.

Nitration of 4-hydroxybenzenesulphonamide yields a mononitro-derivative, from which the corresponding amino-derivative is obtained on reduction. That these substituents are in the 3-position is shown by the formation of the same *nitrohydroxybenzenesulphonamide* from 3-*nitro*-4-*aminobenzenesulphonamide* by treatment of the latter with boiling sodium hydroxide solution, which readily brings about the replacement of the amino-group by hydroxyl.

In order that their chemotherapeutic activities might be investigated (cf. McLeod, *Biochem. J.*, 1938, **32**, 1770), it became necessary to synthesise 3-*nitro-* and 3-*amino*-4-*hydroxybenzenesulphonamide.* By suitable application of the diazo-reaction, 4-aminobenzenesulphonamide was converted in good yield into 4-hydroxybenzenesulphonamide, which on nitration gave a mononitro-derivative. The structure of the nitro-compound was proved by synthesis. *p*-Acetamidobenzenesulphonyl chloride was nitrated to yield

the 3-*nitro*-derivative, which readily reacted with aqueous ammonia to form 3-*nitro*-4-*acetamidobenzenesulphonamide*. Hydrolysis of this with hydrochloric acid gave 3-nitro-4-aminobenzenesulphonamide, m. p. 207°, already synthesised by Fischer (*Ber.*, 1891, **24**, 3785). This observation confirms that the nitration of *p*-acetamidobenzenesulphonamide does effect substitution in the 3-position, and also that the melting point, 207°, given by Fischer for 3-nitro-4-aminobenzenesulphonamide is the correct one and not the much lower one of 155° recorded by Goslich (*Annalen*, 1876, **180**, 104). Replacement of the amino-group in this compound by hydroxyl could not be effected by diazotisation and heating, but was achieved by boiling sodium hydroxide solution; on acidification, 3-nitro-4-hydroxybenzenesulphonamide separated, identical with the nitro-compound prepared as described above.

Experimental.

p-*Hydroxybenzenesulphonamide.*—A solution of *p*-aminobenzenesulphonamide (34·5 g.) in a warm mixture of concentrated sulphuric acid (36 c.c.) and water (600 c.c.) was stirred and cooled to — 5°, and diazotised (sodium nitrite, 14 g., in water, 30 c.c.). The orange solution was warmed at 70—80° for 1—2 hours, filtered, heated to boiling, and exactly neutralised with a hot solution of barium hydroxide (about 200 g.) in water (500 c.c.). After cooling, the barium sulphate was removed, and the filtrate evaporated to about 50 c.c.; 22 g. of a mixture of *p*-hydroxybenzenesulphonamide and its sodium salt slowly crystallised. Recrystallised from dilute acetic acid, *p*-hydroxybenzenesulphonamide separated in almost colourless, rhombic plates, m. p. 178°, soluble in water and alcohol, slightly soluble in benzene, and insoluble in ligroin. The *sodium* salt crystallised from alcohol–water in clusters of colourless needles, m. p. 276° (Found: N, 5·9. $C_6H_6O_3NSNa,2H_2O$ requires N, 6·0%).

3-*Nitro*-4-*hydroxybenzenesulphonamide.*—To a stirred solution of *p*-hydroxybenzenesulphonamide (10·4 g.) in concentrated sulphuric acid (65 c.c.) at — 5°, a mixture of nitric acid (4·2 c.c., *d* 1·42) and sulphuric acid (4·5 c.c.) was added so that the temperature did not rise above 0°. After standing at room temperature for 1 hour, the solution was poured on ice. The precipitate was washed with water, dried on the water-bath (yield, 12·0 g.) and recrystallised from much hot alcohol, 3-*nitro*-4-*hydroxybenzenesulphonamide* separating in long, yellow, rectangular plates, m. p. 210° (Found: N, 12·6. $C_6H_6O_5N_2S$ requires N, 12·8%), which gave a red-brown colour with alcoholic ferric chloride.

The sodium salt formed orange rectangular plates, exploding at 330°, insoluble in alcohol and moderately soluble in water. The sparingly soluble lead salt crystallised from water in orange needles.

3-*Amino*-4-*hydroxybenzenesulphonamide.*—To a solution of 3-nitro-4-hydroxybenzenesulphonamide (2·2 g.) in N-sodium hydroxide (30 c.c.), sodium hyposulphite was added slowly in about 0·2 g. lots, with addition of sodium hydroxide from time to time. When reduction was complete, the reaction was adjusted to about neutral, and the mixture kept. Small plates crystallised; recrystallised from alcohol, white plates, m. p. 202°, of 3-*amino*-4-*hydroxybenzenesulphonamide* were obtained (Found: N, 14·7. $C_6H_8O_3N_2S$ requires N, 14·9%). These were insoluble in water, soluble in alcohol, and gradually darkened in the air.

3-*Nitro*-4-*acetamidobenzenesulphonyl Chloride.*—*p*-Acetamidobenzenesulphonyl chloride (23·3 g.), dissolved in sulphuric acid (120 c.c.), was nitrated with a mixture of nitric acid (9 c.c., *d* 1·42) and sulphuric acid (10 c.c.) at 4—6°. After 1 hour the mixture was poured on ice. The yellow plastic product solidified overnight in contact with water. After being washed and dried, it was dissolved in boiling benzene. On cooling, *p*-acetamidobenzenesulphonyl chloride separated. From the mother-liquor, after concentration, 3-*nitro*-4-*acetamidobenzenesulphonyl chloride* was obtained; it formed very pale yellow needles, m. p. 104°, from ligroin (Found: N, 10·4. $C_8H_7O_5N_2ClS$ requires N, 10·1%). It was soluble in alcohol, ether, acetone and benzene and dissolved in dilute sodium hydroxide solution with an orange colour.

3-*Nitro*-4-*acetamidobenzenesulphonamide.*—3-Nitro-4-acetamidobenzenesulphonyl chloride (1 g.) was stirred with aqueous ammonia (10 c.c., *d* 0·94), the mixture being warmed by the heat of the hand until reaction set in. The product was filtered off, washed with water, and dried on the water-bath. Yield 0·8 g., m. p. 186° (Found: N, 16·0. $C_8H_9O_5N_3S$ requires N, 16·2%). 3-*Nitro*-4-*acetamidobenzenesulphonamide* crystallised from 70% alcohol in fine yellow needles, insoluble in ether and benzene, soluble in alcohol, acetone, and dilute sodium hydroxide solution.

3-*Nitro*-4-*aminobenzenesulphonamide.*—The acetyl compound (0·8 g.) was warmed with hydrochloric acid (1 c.c., *d* 1·08) on the water-bath. Solution gradually took place, and rect-

angular yellow crystals began to separate from the hot solution; yield, 0·6 g., m. p. 207° (Found : N, 19·1. Calc. for $C_6H_7O_4N_3S$: N, 19·35%).

Conversion of 3-*Nitro*-4-*aminobenzenesulphonamide into* 3-*Nitro*-4-*hydroxybenzenesulphonamide.*—The amino-compound (0·5 g.) was added in small portions to a boiling 10% solution of sodium hydroxide (5 c.c.). There was an immediate copious evolution of ammonia. After 20 minutes the dark red solution was cooled and neutralised with 10% hydrochloric acid. A golden-yellow precipitate was obtained, which crystallised from hot alcohol in rectangular plates, m. p. 210°, not depressed by 3-nitro-4-hydroxybenzenesulphonamide prepared from *p*-hydroxybenzenesulphonamide, but lowered by 10° by 3-nitro-4-aminobenzenesulphonamide (m. p. 206°).

The authors thank the Trustees of the Carnegie Trust for the Universities of Scotland for the award of a Research Fellowship to one of them (W. T.).

RESEARCH LABORATORY, ROYAL COLLEGE OF PHYSICIANS,
EDINBURGH.

[*Received, February 8th,* 1939.]