## 149. *5-Amino-2-hydroxybenzenesulphonamide and Some Related Compounds.*

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The synthesis of *5-amino-2-hydroxybenzenesulphonamide* from *p*-aminophenol is described. Its preparation was necessary because it could be an oxidation product of metanilamide in the animal body. *5-Amino-2-hydroxybenzenesulphonanilide*, *3-amino-4-hydroxybenzenesulphonanilide*, and *4-amino-2-hydroxybenzenesulphonanilide* have also been prepared.

A comparative study of the metabolism of the therapeutically inactive isomerides of sulphanilamide, *i.e.*, orthanilamide and metanilamide, has necessitated the synthesis of certain aminohydroxybenzenesulphonamides. During the biological oxidation of metanilamide, the formation of three such amides is possible, namely, 2-hydroxy-, 4-hydroxy-, and 6-hydroxy-5-aminobenzenesulphonamide. Experimental evidence (unpublished) indicates that the oxidation product in rabbits is either the 4-hydroxy- or the 6-hydroxy- but not the 2-hydroxy-derivative.

The present paper deals with the synthesis of 2-hydroxy- and 4-hydroxy-5-aminobenzenesulphonamides, both of which were required for comparison with biological material. The synthesis of the 2-hydroxy-derivative (*p*-aminophenol-*o*-sulphonamide) was straightforward and is similar to that of 4-amino-2-hydroxybenzenesulphonamide (Thorpe and Williams, *Biochem. J.*, 1941, **35**, 61). · 5-Amino-2-hydroxybenzenesulphonic acid was acetylated, and the *acetyl* derivative converted into *5-acetamido-2-acetoxybenzenesulphonyl chloride*. *5-Amino-2-hydroxybenzenesulphon-amide* and *-anilide*, m. p. 159°, were then obtained by the usual methods. Post (*Annalen*, 1880, **205**, 62) prepared a crystalline solid, m. p. 98°, claimed to be 5-amino-2-hydroxybenzenesulphonanilide by the action of aniline on a crude chloride obtained by the direct action of phosphorus pentachloride at 100° on 5-amino-2-hydroxybenzenesulphonic acid. It differs considerably in m. p. from the anilide prepared here, but since the latter was prepared by a direct synthesis there is little doubt as to its structure.

3-Amino-4-hydroxybenzenesulphonamide has been synthesised by Kermack, Spragg, and Tebrich (J., 1939, 608) by reduction of the corresponding nitro-compound with sodium hydrosulphite, but much improved yields can be obtained by the use of tin and hydrochloric acid. Attempts to prepare it by the method used for the 5-amino-2-hydroxy-derivative were unsuccessful, although the corresponding *anilide* was obtained as expected. Acetylation of 3-amino-4-hydroxybenzenesulphonic acid, followed by treatment with phosphorus pentachloride, gave *3-acetamido-4-acetoxybenzenesulphonyl chloride*. Treatment of this chloride with aqueous ammonia, followed by evaporation, then hydrolysis of the residue with 2N-hydrochloric acid, gave a solution

which, on neutralisation and evaporation to dryness, gave a syrupy residue which did not crystallise. This non-crystalline residue gave a red coloration when diazotised and coupled with alcoholic dimethyl-α-naphthylamine (Marshall's diazo-reaction; Marshall, Emerson, and Cutting, *J. Amer. Med. Assoc.*, **1937**, **108**, 935). Authentic crystalline 3-amino-4-hydroxybenzenesulphonamide, prepared from the corresponding nitro-compound after diazotisation, does not give a red colour with this reagent.

A sample of 4-acetamido-2-acetoxybenzenesulphonyl chloride (Thorpe and Williams, *loc. cit.*) being available, *4-amino-2-hydroxybenzenesulphonanilide* was prepared and is described.

## Experimetal.

*5-Acetamido-2-acetoxybenzenesulphonyl Chloride.*—A solution of 5-amino-2-hydroxybenzenesulphonic acid (Bauer, *Ber.*, 1909, **42**, 2107) (7 g.) in pyridine (12 c.c.) was treated with acetic anhydride (10 c.c.) with cooling. The mixture was kept at room temperature and *pyridine 5-acetamido-2-acetoxybenzenesulphonate* soon separated in thick rhombic plates, m. p. 143—144°, which were not quite pure after repeated crystallisation from absolute alcohol (Found: C, 52·0; H, 4·5. $C_{15}H_{16}O_6N_2S$ requires C, 51·1; H, 4·6%). The dried pyridine salt was triturated with phosphorus pentachloride (9 g.), and the product poured into ice-water. The solid was crushed under water; after 12 hours it was collected and dried (yield, 6·9 g.). *5-Acetamido-2-acetoxybenzenesulphonyl chloride* crystallised from toluene in thick plates, m. p. 148—149° (Found: C, 41·4; H, 3·6; Cl, 12·1; $CH_3$·CO, 28·7. $C_{10}H_{10}O_5NClS$ requires C, 41·2; H, 3·45; Cl, 12·15; $CH_3$·CO, 29·5%).

*5-Amino-2-hydroxybenzenesulphonamide.*—The foregoing chloride (4 g.) was added to 50% ammonia solution (5 c.c.). Next day the filtered solution was evaporated on the water-bath, and the residue dissolved in 2N-hydrochloric acid (10 c.c.). *5-Acetamido-2-hydroxybenzenesulphonamide* (0·75 g.) was slowly deposited (long flat rods from water, m. p. 215°). It was very sparingly soluble in cold water and gave a stable purplish-blue colour with ferric chloride (Found: N, 11·3; $CH_3$·CO, 17·45. $C_8H_{10}O_4N_2S,H_2O$ requires N, 11·3; $CH_3$·CO, 17·3%).

The filtrate from the acetyl compound was concentrated to 10 c.c., made 3N with respect to hydrochloric acid, and refluxed for an hour. The solution was cooled, neutralised with solid sodium carbonate, and extracted with ether for 24 hours. *5-Amino-2-hydroxybenzenesulphonamide* (1·2 g.), obtained on evaporation of the ether, darkened considerably during recrystallisation from water and was obtained in clear brown prismatic rods, m. p. 202° (decomp.) (Found: C, 38·35; H, 4·25; S, 17·45. $C_6H_8O_3N_2S$ requires C, 38·3; H, 4·3; S, 17·0%). It was sparingly soluble in cold water and gave, with ferric chloride, a purplish-blue colour which quickly turned to purple, purple-red, and finally orange-red. It reduced ammoniacal silver nitrate and gave an orange-red coloration with nitrous acid, followed by alcoholic dimethyl-α-naphthylamine.

*5-Amino-2-hydroxybenzenesulphonanilide.*—Treatment of the above chloride (1 mol.) with aniline (2 mols.) in ethyl acetate gave *5-acetamido-2-acetoxybenzenesulphonanilide*, which formed rectangular plates, m. p. 150° (decomp.), from aqueous alcohol (yield, quantitative) (Found: N, 7·9; $CH_3$·CO, 23·1. $C_{16}H_{16}O_5N_2S$ requires N, 8·0; $CH_3$·CO, 24·7%). The acetyl compound was boiled with 2N-hydrochloric acid for 15 mins.; from the resulting solution, after neutralisation, ether extracted the *anilide* (yield, 50%), which crystallised from hot water in balls of needles, m. p. 159° (Found: C, 54·9; H, 4·6; S, 11·5. $C_{12}H_{12}O_3N_2S$ requires C, 54·55; H, 4·5; S, 12·1%). It gave in aqueous alcohol a brown colour with ferric chloride; it quickly reduced ammoniacal silver nitrate, and in Marshall's diazo-test it gave a purple colour (similar to that given by *p*-aminophenol) which quickly faded to yellow.

*3-Acetamido-4-acetoxybenzenesulphonyl Chloride.*—3-Amino-4-hydroxybenzenesulphonic acid (B.D.H.) (10 g.) was dissolved in pyridine (50 c.c.) with cooling, acetic anhydride (20 c.c.) gradually added, and the mixture kept at room temperature. After 2 hrs. the whole crystallised on scratching. The *pyridine 3-acetamido-4-acetoxybenzenesulphonate* * (13 g.), recrystallised from alcohol, had m. p. 162° (Found: C, 50·0; H, 4·8; N, 7·4. $2C_{15}H_{16}O_6N_2S,H_2O$ requires C, 49·9; H, 4·7; N, 7·8%). It was very soluble in water. The pyridine salt (10 g.) was stirred with phosphorus pentachloride (10 g.), the product poured into ice-water, and the *chloride* recrystallised from toluene; m. p. 143° (yield, 6·9 g.). (Found: C, 41·45; H, 3·3; Cl, 12·05. $C_{10}H_{10}O_5NClS$ requires C, 41·2; H, 3·45; Cl, 12·15%).

*3-Amino-4-hydroxybenzenesulphonanilide.*—The foregoing chloride (3 g.) was dissolved in ethyl acetate (100 c.c.), and aniline (1·8 c.c.) added. After an hour, the separated aniline hydrochloride was removed and washed with a little ethyl acetate. The filtrates after 2 hours deposited *3-acetamido-4-acetoxybenzenesulphonanilide* (2 g.). This was washed with water and recrystallised from aqueous acetone. A further amount was obtained on evaporation of the ethyl acetate mother-liquor. It formed stellate crystals, m. p. 205° (Found: N, 8·4; $CH_3$·CO, 24·8. $C_{16}H_{16}O_5N_2S$ requires N, 8·0; $CH_3$·CO, 24·7%). The acetyl compound was boiled with 3N-hydrochloric acid until it dissolved (*ca.* 1 hr.). The solution was filtered, diluted with water, and neutralised with sodium carbonate; *3-amino-4-hydroxybenzenesulphonanilide*, which separated in poor yield, was purified by precipitation (needles, m. p. 172°) from alcoholic or ethyl acetate solution with light petroleum (Found: C, 54·4; H, 4·65; S, 11·6. $C_{12}H_{12}O_3N_2S$ requires C, 54·55; H, 4·5; S, 12·1%). It reduced ammoniacal silver nitrate and gave with ferric chloride a purple-red coloration which quickly turned red and finally gave a brown precipitate. It gave a bright yellow colour on diazotisation, but did not couple to form a red dye with 1% alcoholic dimethyl-α-naphthylamine. This lack of coupling is typical of *o*-aminophenols, *e.g.*, *o*-aminophenol, 4-amino-3-hydroxy- and 3-amino-4-hydroxy-benzenesulphonamide (cf. Thorpe, Williams, and Shelswell, *Biochem. J.*, 1941, **35**, 52).

*4-Amino-2-hydroxybenzenesulphonanilide.*—4-Acetamido-2-acetoxybenzenesulphonyl chloride (1·3 g.) (Thorpe and Williams, *loc. cit.*) was converted into *4-acetamido-2-acetoxybenzenesulphonanilide* in the usual manner (yield, 1·4 g.). This was recrystallised from aqueous alcohol and formed prisms, m. p. 213—214° (Found: N, 8·0; $CH_3$·CO, 24·9. $C_{16}H_{16}O_5N_2S$ requires N, 8·0; $CH_3$·CO, 24·7%). On boiling with 50% hydrochloric acid it gradually dissolved; the solution, on cooling, deposited needles, presumably of the hydrochloride of the anilide. The solution was diluted with water, and the crystals dissolved; on neutralisation with sodium carbonate, *4-amino-2-hydroxybenzenesulphonanilide* crystallised. It was purified by solution in ethyl acetate and precipitation with light petroleum. It formed needles m. p. 184°, and gave in aqueous alcohol a faint brownish-red colour with ferric chloride. It gave a red Marshall diazo-test, but did not reduce ammoniacal silver nitrate (Found: C, 54·4; H, 4·6; S, 12·0. $C_{12}H_{12}O_3N_2S$ requires C, 54·55; H, 4·5; S, 12·1%).

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* This salt was prepared by Miss Jean Shelswell (Thesis, University of Birmingham, Dec., 1940).