38. *Pyridine and Piperazine Derivatives of Sulphanilamide.*

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2-(3′-*Nitro*-4′-*hydroxybenzenesulphonamido*)*pyridine* has been prepared by the condensation of 3-nitro-4-acetamidobenzenesulphonyl chloride with 2-aminopyridine, followed by hydrolysis and replacement of the amino- by the hydroxy-group. By

reduction 2-(3′-*amino*-4′-*hydroxybenzenesulphonamido*)*pyridine* has been obtained. A number of di- and mono-substituted piperazine derivatives have also been prepared. These compounds have been synthesised in order that their possible chemotherapeutic value may be ascertained.

In order to synthesise 2-(3′-*nitro*- and 3′-*amino*-4′-*hydroxybenzenesulphonamido*)*pyridine* an attempt was first made to convert 2-(4′-aminobenzenesulphonamido)pyridine into the 4-hydroxy-derivative by the ordinary diazo-method. In spite, however, of the fact that the diazotisation and decomposition proceed smoothly in the case of the simple 4-aminobenzenesulphonamide (cf. Kermack, Spragg, and Tebrich, J., 1939, 608) it was found that with the pyridine derivative the evolution of nitrogen took place much more slowly and a tarry product was obtained from which none of the desired compounds could be isolated. The method was therefore abandoned in favour of the following. 3-Nitro-4-acetamidobenzenesulphonyl chloride was condensed with 2-aminopyridine, and the product, 2-(3′-*nitro*-4′-*acetamidobenzenesulphonamido*)*pyridine*, hydrolysed to give 2-(3′-*nitro*-4′-*aminobenzenesulphonamido*)*pyridine*. On treatment with hot alkali this compound slowly liberated ammonia to yield the required 2-(3′-nitro-4′-hydroxybenzenesulphonamido)pyridine. Reduction of the latter with sodium hyposulphite yielded 2-(3′-amino-4′-hydroxybenzenesulphonamido)pyridine.

In order to prepare derivatives of *p*-aminobenzenesulphonic acid containing piperazine, 4-acetamidobenzenesulphonyl chloride was treated with piperazine. The only product obtained, even in presence of a large excess of piperazine, was 1 : 4-*di*-(p-*acetamidobenzenesulphonyl*)*piperazine*. Hydrolysis of this compound with hot alcoholic hydrochloric acid yielded 1 : 4-*di*-(p-*aminobenzenesulphonyl*)*piperazine*. As the monopiperazine could not be obtained directly, use was made of the process developed by Moore, Boyle, and Thorne (J., 1929, 39). *p*-Acetamidobenzenesulphonyl chloride was condensed with ethyl piperazinecarboxylate and the *ethyl* 4-(p-*acetamidobenzenesulphonyl*)*piperazine*-1-*carboxylate* so formed was hydrolysed either with alcoholic hydrochloric acid or with dilute alcoholic potassium hydroxide solution to give *ethyl* 4-(p-*aminobenzenesulphonyl*)*piperazine*-1-*carboxylate*. Further hydrolysis of this product with alcoholic potassium hydroxide yielded 1-p-*aminobenzenesulphonylpiperazine*.

Ethyl 4-(*p*-acetamidobenzenesulphonyl)piperazine-1-carboxylate was condensed with a further molecule of *p*-acetamidobenzenesulphonyl chloride, the product being *ethyl* 4-(p-*acetamidobenzenesulphonamidobenzenesulphonyl*)*piperazine*-1-*carboxylate*. In spite of many efforts this very sparingly soluble compound could not be hydrolysed with removal of acetyl or carbethoxy-groups.

Experimental.

2-(3′-*Nitro*-4′-*acetamidobenzenesulphonamido*)*pyridine*.—To a solution of *o*-aminopyridine (0·5 g.) in dry pyridine (2 c.c.), 3-nitro-4-acetamidobenzenesulphonyl chloride (1·4 g.) (Kermack, Spragg, and Tebrich, J., 1939, 608), dissolved in dry pyridine (5 c.c.), was added. After a few hours, on dilution with much water, a brown precipitate was obtained, which was washed and dried (yield, 1·2 g.). The *compound* crystallised from *cyclo*hexanone in yellow needles, m. p. 270° (Found : N, 16·9. $C_{13}H_{12}O_5N_4S$ requires N, 16·7%), insoluble in water, most organic solvents and sodium carbonate, but easily soluble in dilute alkali solution.

2-(3′-*Nitro*-4′-*aminobenzenesulphonamido*)*pyridine*.—The acetyl compound (5 g.) was heated with 5N-hydrochloric acid (25 c.c.) on the water-bath. The precipitate which gradually separated was filtered off after ½ hour, washed (yield, 4 g.), and crystallised from nitrobenzene, giving yellow needles of 2-(3′-*nitro*-4′-*aminobenzenesulphonamido*)*pyridine*, m. p. 232° (Found : N, 19·4. $C_{11}H_{10}O_4N_4S$ requires N, 19·1%), insoluble in water, alcohol, acetone, and ether and soluble in concentrated hydrochloric acid, alkali, and hot nitrobenzene. The acid aqueous solution gave a strong diazo-reaction.

2-(3′-*Nitro*-4′-*hydroxybenzenesulphonamido*)*pyridine*.—2-(3′-Nitro-4′-aminobenzenesulphonamido)pyridine (4 g.) was refluxed with 25% sodium hydroxide solution (40 c.c.) for several hours until the evolution of ammonia ceased. The dark brown solution was then slightly acidified with 10% hydrochloric acid, and the buff-coloured precipitate filtered off and washed with water (yield, 3·8 g.). The compound crystallised from alcohol in pale yellow needles,

m. p. 234°; usually some charcoal was required to remove associated brown pigment (Found: N, 14·5. $C_{11}H_9O_5N_3S$ requires N, 14·2%). 2-(3′-*Nitro*-4′-*hydroxybenzenesulphonamido*)*pyridine*, though having the same m. p., was readily differentiated from 2-(3′-nitro-4′-aminobenzenesulphonamido)pyridine, as it lowered the m. p. of the latter and gave no diazo-test. It was insoluble in water and acids, ether and acetone, sparingly soluble in aclohol, and easily soluble in caustic soda, sodium carbonate, and bicarbonate solutions.

2-(3′-*Amino*-4′-*hydroxybenzenesulphonamido*)*pyridine*.—To a solution of 2-(3′-nitro-4′-hydroxybenzenesulphonamido)pyridine (1 g.) in N-sodium hydroxide (12 c.c.), sodium hyposulphite (2 g.) was added in small portions, the solution being kept slightly alkaline by the addition of sodium hydroxide. If necessary the solution was adjusted to approximate neutrality to complete the precipitation of the compound, which was filtered off and washed (yield, 0·4 g.). The *product* crystallised from water containing sodium hyposulphite in colourless hexagonal plates, m. p. 211° (Found: N, 15·6. $C_{11}H_{11}O_3N_3S$ requires N, 15·8%), insoluble in ether and acetone, soluble in dilute acid, alkali, and sodium carbonate solutions, and moderately easily soluble in hot water. Its acid solution gave a strong diazo-test. The compound, especially in aqueous solution, was readily oxidised in the air with the formation of brown products.

1 : 4-*Di*-(p-*acetamidobenzenesulphonyl*)*piperazine*.—A solution of *p*-acetamidobenzenesulphonyl chloride (2·3 g.) in wet ether (the compound is relatively sparingly soluble in dry ether) was vigorously shaken with a solution of piperazine hexahydrate (1 g.) in 0·1N-sodium hydroxide (100 c.c.). After some hours a microcrystalline white precipitate formed in the aqueous layer, which was separated from the ether and filtered (yield, 1·75 g.). The *compound* crystallised from *cyclo*hexanone in fine colourless needles, m. p. 324° (Found: N, 11·2. $C_{20}H_{24}O_6N_4S_2$ requires N, 11·5%), insoluble in water and most organic solvents except pyridine, in which it easily dissolved in the cold.

1 : 4-*Di*-(p-*aminobenzenesulphonyl*)*piperazine*.—The above acetyl compound (2·4 g.) was refluxed with 10% alcoholic potassium hydroxide (25 c.c.) for 2 hours. Although no apparent change took place, the solid suspension, when filtered off, washed, and dried, melted at 330° and gave a positive diazo-test (yield, 1·9 g.). The *product* crystallised from nitrobenzene in colourless needles, m. p. 331—332° (Found: N, 14·0. $C_{16}H_{20}O_4N_4S_2$ requires N, 14·0%), insoluble in water and most organic solvents, and moderately easily soluble in hot nitrobenzene.

Ethyl 4-(p-*Acetamidobenzenesulphonyl*)*piperazine*-1-*carboxylate*.—A solution of ethyl piperazine-1-carboxylate (9·6 g.) (Moore, Boyle, and Thorne, *loc. cit.*) in 0·1N-sodium hydroxide (500 c.c.) was shaken with a solution of *p*-acetamidobenzenesulphonyl chloride (13·8 g.) in methylated ether (500 c.c.). The white crystalline precipitate was filtered off, washed, and dried in a vacuum desiccator (yield, 18·5 g.). The product crystallised from alcohol in colourless needles, m. p. 132°. For analysis it was dried in a vacuum at 50° (Found: N, 11·1. $C_{15}H_{21}O_5N_3S$ requires N, 11·4%). *Ethyl* 4-(p-*acetamidobenzenesulphonyl*)*piperazine*-1-*carboxylate* was insoluble in water and ether, moderately easily soluble in alcohol, and sparingly soluble in benzene.

Ethyl 4-(p-*Aminobenzenesulphonyl*)*piperazine*-1-*carboxylate*.—The acetyl compound (2 g.) was refluxed with 5% alcoholic potassium hydroxide for 1 hour, and the solution filtered hot from a little insoluble residue. The white crystalline precipitate which separated on cooling was washed with water (yield, 1·1 g.) and recrystallised from alcohol. *Ethyl* 4-(p-*aminobenzenesulphonyl*)*piperazine*-1-*carboxylate*, m. p. 170° (Found: N, 13·8. $C_{13}H_{19}O_4N_3S$ requires N, 13·5%), was insoluble in water and ether, moderately easily soluble in hot alcohol, from which it crystallised in long hexagonal prisms, and easily soluble in acetone and dilute acid; the latter solution gave a positive diazo-test. The hydrochloride had m. p. 198°.

1-p-*Aminobenzenesulphonylpiperazine*.—The preceding ester (2 g.) was refluxed with 10% alcoholic potassium hydroxide (20 c.c.) for 4 hours, and the solution filtered hot from a little potassium carbonate. The white crystalline material which separated almost immediately from the filtrate was collected, washed with water, and dried (yield, 0·8 g.). The *product*, which gave a strong diazo-test and crystallised from alcohol in colourless leaflets, m. p. 204° (Found: N, 17·7. $C_{10}H_{15}O_2N_3S$ requires N, 17·4%), was insoluble in water, ether, and benzene, moderately easily soluble in alcohol, and easily soluble in dilute acids.

Ethyl 4-(p-*Acetamidobenzenesulphonamidobenzenesulphonyl*)*piperazine*-1-*carboxylate*.—A solution of *p*-acetamidobenzenesulphonyl chloride (1·2 g.) in dry pyridine (4 c.c.) was slowly added with water-cooling, to a solution of ethyl 4-(*p*-aminobenzenesulphonyl)piperazine-1-carboxylate (1·6 g.) in dry pyridine. After 12 hours the mixture was diluted with water and slightly acidified with hydrochloric acid. The pinkish material obtained after prolonged scratching was filtered off and washed (yield, 1·2 g.). The *product* crystallised from alcohol in colourless rhombic

plates, m. p. 194° (Found : N, 11·0. $C_{21}H_{26}O_7N_4S_2$ requires N, 11·1%), insoluble in water, ether, benzene, and dilute acid, moderately easily soluble in alcohol, and soluble in acetone and dilute alkali.

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