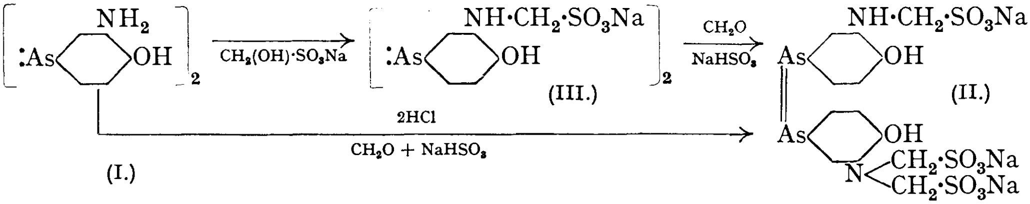
410. *Sulpharsphenamine. A New Method of Preparation.*

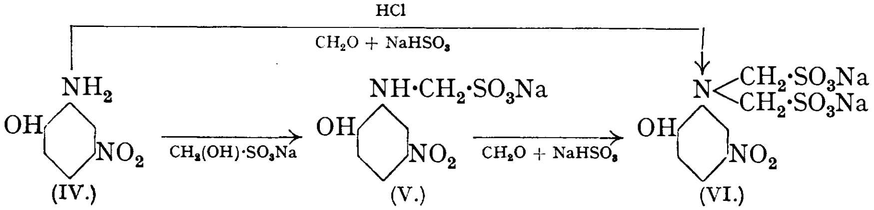
By W. J. C. Dyke and Harold King.

When 3 : 3'-diamino-4 : 4'-dihydroxyarsenobenzene (I) as dihydrochloride is treated with formaldehyde, followed after an interval by sodium hydrogen sulphite, sulpharsphenamine is formed (Voegtlin, Johnson, and Dyer, *U.S. Pub. Health Rep.*, 1922, **37**, 2783; Christiansen, *J. Amer. Chem. Soc.*, 1923, **45**, 2184), the constitution of commercial preparations of which has been shown (Dyke and King, this vol., p. 805) to be that of an *NNN'*-trimethylenesulphite of 3 : 3'-diamino-4 : 4'-dihydroxyarsenobenzene (II). If, however, the base (I) is condensed at 60° with 4 molecular proportions of preformed sodium formaldehyde-bisulphite, only an *NN'*-dimethylenesulphite (III) is formed. Such a product can, however, be converted into a typical sulpharsphenamine (II) by the action of formaldehyde and sodium hydrogen sulphite in succession. The contrast in properties between (II) and (III) is striking, for whereas (III) in 33% aqueous solutions gives an immediate precipitate (see J., 1933, 1007) with 10% hydrochloric acid, no change is observed with (II).



Furthermore, the whole of the sulphur found as sulphate by oxidation of (III) with alkaline iodine (Elvove's method) is the same as that found by distillation with acid, but in the case of (II) only a fraction of the sulphur found by the distillation method can be estimated by Elvove's method. The results are in fact an interesting amplification of our views on the constitution of sulpharsphenamine.

A similar series of reactions can be carried through with crystalline substances. It has already been shown that when 4-nitro-2-aminophenol (IV) is condensed with sodium formaldehydebisulphite, the mono-*N*-methylenesulphite (V) is formed (Dyke and King, *loc. cit.*). If this product is treated with formaldehyde, followed after an interval by sodium hydrogen sulphite, disodium 5-nitro-2-hydroxyanilino-*NN*-dimethylenesulphite (VI) is produced and is readily isolated as its highly characteristic trisodium salt containing methyl alcohol of crystallisation. This dimethylenesulphite (VI) is identical with the product obtained by the action of formaldehyde and sodium hydrogen sulphite in succession on 4-nitro-2-aminophenol in hydrochloric acid solution.



EXPERIMENTAL.

Disodium 3 : 3′-*Diamino*-4 : 4′-*dihydroxyarsenobenzene*-NN′-*dimethylenesulphite* (III).—Salvarsan base (3·66 g. : As, 38·0; Elvove S, 0·3; H_2O, 4·6%), suspended in water (20 c.c.) containing sodium formaldehydebisulphite (5·63 g.; 4 mols.) and stirred at 60° in an atmosphere of carbon dioxide, was completely in solution after 8 minutes. The solution was kept at 60° for 35 minutes, cooled, and poured in a thin stream into absolute ethyl alcohol (450 c.c.). The yellow precipitate was quickly collected, washed with alcohol, and dried in a high vacuum; yield, 6·64 g. (Found: As, 18·5; volatile S, 10·2; Elvove S, 9·7; CH_2O, 8·9%, whence As : vol. S : Elv. S : CH_2O = 1 : 1·3 : 1·2 : 1·2).

Sulpharsphenamine (II).—A portion of the above product (2·5 g.), dissolved in water (25 c.c.) and stirred rapidly in an atmosphere of carbon dioxide, was treated with formalin (0·7 c.c., 40%; 3 mols.) for 2 minutes and then with a concentrated sodium hydrogen sulphite solution freshly made by saturating an aqueous suspension of sodium hydrogen carbonate (0·8 g.; 3 mols.) in water (5 c.c.) with sulphur dioxide. The yellow solution became intensely orange on addition of the sulphite and then gradually recovered its yellow colour. After 10 minutes the solution was poured in a thin stream into absolute ethyl alcohol (200 c.c.); yield, 2·6 g. (Found: As, 16·9; vol. S, 14·8; Elv. S, 3·8; CH_2O, 12·2%, whence As : vol. S : Elv. S : CH_2O = 1 : 2·0 : 0·5 : 1·8). The significant feature is the fall of Elvove S from 1·2 atoms in the initial material to 0·5 atom in the final product, although the volatile sulphur has increased from 1·3 atoms to 2·0 atoms. This product gives the striking colour reactions previously described for sulpharsphenamine (Dyke and King, *loc. cit.*). Another preparation under somewhat similar conditions gave the following results (Found: As, 19·8; vol. S, 12·2; Elv. S, 4·8; CH_2O, 11·1%, whence As : vol. S : Elv. S : CH_2O = 1 : 1·4 : 0·5 : 1·4); to determine the minimum degree of substitution the preparation (2 g. in 6 c.c. of water) was precipitated by addition to glacial acetic acid (40 c.c.). This process removes uncombined salts (Found: As, 19·2; vol. S, 10·7; Elv. S, 3·6; CH_2O, 10·2%, whence As : vol. S : Elv. S : CH_2O = 1 : 1·3 : 0·45 : 1·3).

In the preparation of sulpharsphenamine by this new process it is not essential to isolate the intermediate *NN′*-dimethylenesulphite (III), for when salvarsan base (3·66 g.) was condensed with sodium formaldehydebisulphite (2 mols.) in 15 c.c. of water at 60° for 20 minutes, and the mixture cooled to room temperature, diluted with water (45 c.c.), and treated with formalin (2·25 c.c., 40%; 3 mols.) for 1 minute and then with sodium hydrogen sulphite solution (8·44 c.c., 37%; 3 mols.), a typical sulpharsphenamine was produced; yield 7 g., p_H6 (Found: As, 19·2; vol. S, 12·6; Elv. S, 4·6; CH_2O, 11·2%, whence As : vol. S : Elv. S : CH_2O = 1 : 1·55 : 0·5 : 1·5).

5-*Nitro*-2-*hydroxyanilino*-NN-*dimethylenesulphite* (VI).—The mono-*N*-methylenesulphite of 4-nitro-2-aminophenol (1·5 g.) in water (5 c.c.) was treated at room temperature with formalin (0·8 c.c., 40%; 2 mols.) for 2 minutes and then with sodium hydrogen sulphite solution (3 c.c., 37%; 2 mols.). Free sulphur dioxide was pumped off and the solution after neutralisation to litmus was treated with sodium hydroxide solution (0·4 c.c., 50%; 1 mol.). Slightly more than an equal volume of methyl alcohol was then added, causing the separation of a crude salt containing some sulphate. After solution in warm water and addition of warm methyl alcohol a fine crystalline precipitate was obtained of the characteristic salt, trisodium 5-nitro-2-hydroxyanilino-*NN*-dimethylenesulphite, free from inorganic impurities (Found: vol. S, 13·2; CH_2O, 11·5; Na, 14·2. Calc.: vol. S, 13·0; CH_2O, 12·2; Na, 14·0%).

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