163. *A Synthesis of Glucosamine.*

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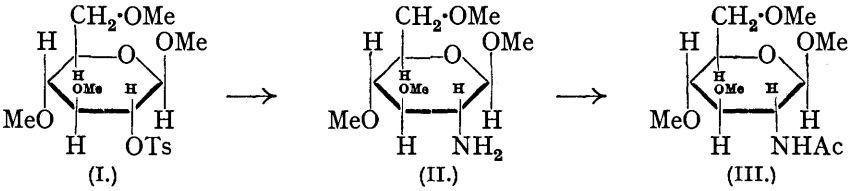
The configuration of glucosamine has been confirmed by the direct replacement by an amino-group of the *p*-toluenesulphonyl residue in 2-*p*-toluenesulphonyl 3 : 4 : 6-trimethyl β-methylglucopyranoside. This replacement is not accompanied by Walden inversion.

Confirmation of the structure assigned to glucosamine on the basis of synthetical experiments by Haworth, Lake, and Peat (this vol., p. 271) is now furnished as a consequence of the synthesis of *N*-acetyl trimethyl β-methylglucosaminide by an alternative route. This method concerns the direct replacement of a *p*-toluenesulphonyl residue by an amino-group.

It is well established that the removal of the ester residue from a sugar *p*-toluensulphon-

ate is accompanied by Walden inversion only when the possibility exists within the sugar molecule of anhydro-ring formation involving two asymmetric carbon atoms. When the hydroxyl groups other than that bearing the *p*-toluenesulphonyl residue are suitably protected, as, for instance, by ether formation, it is found that alkaline reagents either do not bring about hydrolysis or cause separation of the *p*-toluenesulphonyl group without Walden inversion (cf. Freudenberg and Ivers, *Ber.*, 1922, **55**, 929; Haworth, Hirst, and Pannizon, J., 1934, 154; Oldham and Robertson, J., 1935, 685; Peat and Wiggins, J., 1938, 1088). It was clear, therefore, that if the *p*-toluenesulphonyl group in 2-*p*-toluenesulphonyl 3 : 4 : 6-trimethyl β-methylglucopyranoside (I) were replaceable by the amino-group, the product would be a derivative of *d*-glucose (II).



The exchange of groups was accomplished by heating the compound (I) with methyl-alcoholic ammonia in an autoclave at 175° for 72 hours. Subsidiary reactions involving decomposition of the sugar greatly diminished the yield of the amino-sugar (II), which also was accompanied by a large proportion of unchanged material. It was found possible, however, to isolate the amino-sugar in the form of its *N*-acetyl derivative (III). This product (2-acetamido trimethyl β-methylglucopyranoside) was identical with the corresponding compound prepared from natural glucosamine by Cutler, Haworth, and Peat (J., 1937, 1979). It follows that the configuration on C_2 is the same in glucosamine as in *d*-glucose.

Experimental.

The Action of Methyl-alcoholic Ammonia on 2-p-*Toluenesulphonyl* 3 : 4 : 6-*Trimethyl* β-*Methylglucoside.*—The glucoside (2·7 g.) (Haworth, Hirst, and Pannizon, *loc. cit.*) was heated at 175° for 72 hours in an autoclave with dry methyl alcohol (500 c.c.) saturated with anhydrous ammonia. The solution was then cooled and concentrated under diminished pressure. The residue, after being freed from ammonia by heating it at 60° in a vacuum for several hours, was extracted with chloroform, the solution filtered, and the solvent evaporated. The residual syrup (1·5 g.) was subjected to fractional distillation in a high vacuum. Fraction I (0·5 g.) distilled at bath temp. 115—120°/0·015—0·020 mm. Little further distillation occurred when the bath temperature was raised and the dark residue (0·85 g.) in the flask consisted largely of unchanged 2-*p*-toluenesulphonyl 3 : 4 : 6-trimethyl β-methylglucoside. Fraction I showed n_D 1·4415 and $[\alpha]_D^{20°}$ + 11·1° in dry methyl aclohol (*c*, 1·264). It reduced Fehling's solution only after boiling with dilute sulphuric acid. The Molisch test was positive (Found : N, 1·3; OMe, 54·0%). A van Slyke estimation showed the presence of a small amount of amino-nitrogen.

Acetylation of Fraction I.—The distillate (0·3 g.), dissolved in dry methyl alcohol (5 c.c.), was mixed with acetic anhydride (0·5 c.c.) and kept at room temperature for 12 hours. Thereafter the solution was poured into iced water, neutralised with sodium bicarbonate, and extracted with chloroform, and the extract dried over anhydrous magnesium sulphate. On filtration and removal of the chloroform, a syrup (0·25 g.) remained, which was subjected to fractional distillation in a high vacuum. A nitrogen-free fraction distilled at 95—100°/0·004 mm. The residue in the flask crystallised on cooling; after two recrystallisations from ethyl acetate, it had m. p. 195° and $[\alpha]_D^{17°}$ — 29·4° in water (*c*, 0·408). It was *N*-acetyl 3 : 4 : 6-trimethyl β-methylglucosaminide. There was no depression of m. p. in admixture with a specimen of *N*-acetyl 3 : 4 : 6-trimethyl β-methylglucosaminide prepared from glucosamine. Cutler, Haworth, and Peat (*loc. cit.*) record for *N*-acetyl 3 : 4 : 6-trimethyl β-methyl-glucosaminide : $[\alpha]_D^{16°}$ — 29·0° in water (*c*, 0·280), m. p. 195°.

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