13. *The Preparation of 3-Methyl Glucosamine.*

By Albert Neuberger.

The preparation of 3-methyl glucosamine and 3-methyl glucosamic acid is described and the structure proved by the behaviour of these compounds towards periodic acid.

Many biologically important carbohydrate derivatives contain amino-sugars and it may be expected that methylation will be, as in non-nitrogenous polysaccharides, a very fruitful method for the elucidation of their structures. It was thought desirable, therefore, to prepare reference compounds, *i.e.*, partially methylated glucosamine and chondrosamine derivatives. As a first step in this work the preparation of 3-*methyl glucosamine hydrochloride* is here described.

N-Acetyl α-methylglucosaminide (I) (Moggridge and Neuberger, J., 1938, 745) was condensed with benzaldehyde to give N-*acetyl* 4 : 6-*benzylidene* α-*methylglucosaminide* (II), the structure of which follows from the reactions of the compounds derived from it. (II) was very sparingly soluble in most solvents and refractory to methylation under the conditions usually applied. N-*Acetyl* 4 : 6-*benzylidene* 3-*methyl* α-*methylglucosaminide* (III) could, however, be obtained from (II) by using dioxan as a solvent. (III) on hydrolysis with 60% acetic acid gave N-*acetyl* 3-*methyl* α-*methylglucosaminide* (IV), which on further hydrolysis by 2·5N-hydrochloric acid yielded 3-*methyl glucosamine hydrochloride* (V). This compound was oxidised with yellow mercuric oxide to 3-methyl glucosamic acid (VI).

The position of the methyl group proposed for these compounds is proved by the following considerations. Since (I) is a pyranoside (Neuberger, J., 1939, 29), it can be assumed that condensation with benzaldehyde leads, as in other pyranosides, to a 4 : 6-benzylidene compound; the methyl group therefore must enter in position 3. More definite evidence, however, is obtained from the behaviour of (IV) and (VI) towards periodic acid (preceding paper). Periodic acid splits oxidatively carbon–carbon bonds, where either two hydroxyl (Malaprade, *Bull. Soc. chim.*, **1934**, **1**, 833) or one hydroxyl and one amino-group (Nicolet and Shinn, *J. Amer. Chem. Soc.*, **1939**, **61**, 1615) are attached to two adjacent carbon atoms. In the latter case ammonia is liberated. One atom of oxygen is taken up for each bond split and formic acid is formed if more than two adjacent hydroxyls are present. Now, (IV) is not attacked by periodic acid, indicating that no adjacent hydroxyls are available; this limits the

position of the methyl group to 3 or 4. The behaviour of (VI) to periodic acid, however, excludes the possibility of the methyl group being in position 4. (VI) in the presence of periodic acid takes up two atoms of oxygen, one mol. of formaldehyde and one mol. of formic acid being formed, and no ammonia is liberated. This shows that, first, no free hydroxyl is adjacent to the amino-group and, secondly, all three hydroxyls present in the molecule are adjacent, *i.e.*, positions 4, 5, and 6 must be free.

Experimental.

N-Acetyl 4 : 6-*Benzylidene* α-*Methylglucosaminide.*—A mixture of finely ground *N*-acetyl α-methylglucosaminide (7 g.), anhydrous zinc chloride (7 g.), and benzaldehyde (18 ml.) was shaken for 8 hours. The syrup was then poured into water, washed with ligroin, and filtered. The crystalline dried material was recrystallised from methyl alcohol (yield, 85%); m. p. 255°, $[\alpha]_D$ + 19° in chloroform (c = 0·5, l = 2·0) (Found : C, 58·6; H, 6·3; N, 4·3. $C_{16}H_{21}O_6N$ requires C, 59·1; H, 6·5; N, 4·3%).

N-Acetyl 4 : 6-*Benzylidene* 3-*Methyl* α-*Methylglucosaminide.*—*N*-Acetyl 4 : 6-benzylidene α-methylglucosaminide (7 g.), dissolved in dioxan (350 ml.), was treated with ten portions of methyl sulphate (30 ml.) and 30% sodium hydroxide solution (66 ml.) at 10-minute intervals at 55°. The mixture was poured into a large volume of water and the crystalline precipitate was filtered off (yield, 90%) and recrystallised from methyl alcohol; m. p. 277—279°, $[\alpha]_D$ + 39° in chloroform (c = 0·52) (Found : C, 60·2; H, 7·0; N, 4·2; OMe, 18·3. $C_{17}H_{23}O_6N$ requires C, 60·5; H, 6·8; N, 4·2; OMe, 18·4%).

N-Acetyl 3-*Methyl* α-*Methylglucosaminide.*—*N*-Acetyl 4 : 6-benzylidene 3-methyl α-methylglucosaminide (0·75 g.) was suspended in 60% acetic acid (15 ml.) and heated on a water-bath; the mixture became clear after 5 mins. and heating was continued for 30 mins. The solution was then evaporated to dryness, and the residue taken up in water, filtered, and evaporated in a vacuum. The crystalline residue was recrystallised from alcohol (yield, 65%); m. p. 211°, $[\alpha]_D$ + 116° in water (Found : C, 47·9; H, 7·5; N, 5·4; OMe, 25·2. $C_{10}H_{19}O_6N$ requires C, 48·2; H, 7·5; N, 5·6; OMe, 24·9%).

3-*Methyl Glucosamine Hydrochloride.*—*N*-Acetyl 3-methyl α-methylglucosaminide (7·5 g.) was refluxed with 2·5N-hydrochloric acid (100 ml.) for 4 hours. The solution was then treated with charcoal and evaporated to dryness. The solid was dissolved in a small volume of hot methyl alcohol and crystallised by addition of acetone (yield, 75%); m. p. 215° (decomp.). The following changes in specific rotation (in water) were noted : +123° (initial, by extrapolation); +119·5° (3 mins.); +115° (10 mins.); +100° (75 mins.); +91·3° (18 hours) (Found : C, 36·8; H, 6·9; N, 5·9; OMe, 13·4. $C_{17}H_{15}O_5N$,HCl requires C, 36·6; H, 7·0; N, 6·1; OMe, 13·5%).

3-*Methyl Glucosamic Acid.*—A mixture containing 3-methyl glucosamine hydrochloride (1 g.), dissolved in water (30 ml.), and yellow mercuric oxide (5·5 g.) was heated on a water-bath for 25 mins. and then over a free flame for a further 5 mins. The insoluble material was filtered off, mercury removed by hydrogen sulphide, and the solution evaporated to low bulk. The substance was crystallised by addition of alcohol and recrystallised in the same manner (yield, 70%); m. p. 230° (decomp.), $[\alpha]_D$ − 12° in 5% hydrochloric acid (Found : C, 40·2 ; H, 7·1; N, 6·7; OMe, 14·0. Calc. for $C_7H_{15}O_6N$: C, 40·2; H, 7·0; N, 6·7; OMe, 13·8%).

Biochemical Laboratory, Cambridge. [*Received, November 11th*, 1940.]