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THE SYNTHESIS OF 2-AMINO-2-DEOXYSUGARS FROM ACETYLATED GLYCALS

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The widespread natural occurrence (1,2,3) of 2-amino -2-deoxysugars in important biological and pharmaceutical compounds has led to much interest in the synthetic availability of these compounds. The purpose of this communication is to report convenient syntheses of D-glucosamine, D-mannosamine, D-galactosamine and D-talosamine by way of simple procedures proceeding from the corresponding acetylated glycals (acetylated 1,2-dideoxy-glyc-1-ene-pyranoses) in 65-70% overall yields.

Although D-glucosamine is readily available from chitin, its synthesis (4) and preparations of isotopically labelled (5) and other derivatives are of considerable interest. Of the several methods (6-10) published for the synthesis of D-mannosamine, the modification (10) of the procedure by Sowden and Oftedahl (9) appears most attractive although the yield was only 17.5% from D-arabinose. Only multi-step syntheses with low overall yields are reported for D-galactosamine (11,12) and D-talosamine (11,13).

Reaction of acetylated glycals with nitrosyl chloride results in cis-addition to give the acetylated 2-deoxy-2-nitrosoglycopyranosyl chloride as the dimers with the chlorine in axial orientation (14,15). These nitrosoglycosyl chlorides undergo facile dehydrochlorination to acetylated 2-nitrosoglycals which are highly susceptible to nucleophilic attack to give derivatives of 2-oximinosugars. As will be seen below, 2-amino-2-deoxysugars are readily obtained by reduction of these oximes and the configuration assumed by the 2-position can be effectively controlled by the choice of the method for the reduction.

A 2.5% solution of 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso--α-D-glucopyranosyl chloride dimer (I) (15) in 20% aqueous acetic acid was reduced by stirring for two days at room temperature with three times the weight of I of a 2:1 by weight mixture of zinc dust and hydrated copper sulfate. The solids were removed by filtration and washed with acetic acid. The combined filtrates were made about 2% in acetic anhydride and the solution was stirred for one hour. The product was isolated in the usual manner. A 60% yield of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-D-glucose (16) was readily obtained by crystallization of the syrup. De-O-acetylation of this compound gave N-acetyl-D-glucosamine (17) m.p. 188-190°, $[\alpha]_D^{23}$ + 40° (c, 1 in water). On the other hand, treatment of the syrupy product from the reduction with 4N hydrochloric acid at 100° for one hour

followed by decolorization with charcoal and evaporation *in vacuo* in the presence of ethanol left a crystalline residue which was recrystallized from ethanol-acetone. The yield was 80% from I of D-glucosamine hydrochloride, $[\alpha]_D^{23}$ + 72° (*c*, 1 in water) identified by direct comparison (chromatographic behaviour and infrared spectra) with an authentic sample.

Application of the above procedure to the *galacto* isomer (II) (15) of I provided 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-D-galactose (18) in 60% yield. Acid hydrolysis of the crude reduction product gave D-galactosamine hydrochloride, in 84% yield from II and identified by direct comparison with an authentic sample.

Hydrogenation at 60 p.s.i. and room temperature of the previously described (15) penta-O-acetyl-2-oximino-D-*arabino*-hexopyranose (III), 2.5 g. in 45 ml of 30% aqueous acetic acid and in the presence of 0.75 g. of palladium on charcoal for 48 hours gave a colorless syrup which was hydrolyzed by treatment with 4N hydrochloric acid for 40 minutes at 100°. The product was recovered as indicated above for similar mixtures and crystallized from moist ethanol-acetone. The yield was 1.1 g. (84%) of D-mannosamine hydrochloride (9), m.p. 178-180°, $[\alpha]_D^{23}$ - 3.0° (*c*, 2 in water). The compound was identical (X-ray and infrared) to a specimen prepared by acid hydrolysis of N-acetyl-D-mannosamine which was obtained as described by Satoh and Kiyomoto (10). Furthermore, the

crystalline N-acetyl derivative had the expected physical constants (10) and ninhydrin oxidation (19) of the aminosugar gave D-arabinose.

Reaction of II with acetic anhydride and sodium acetate at 60° for 20 minutes gave a syrupy product, $[\alpha]_D^{23}$ + 18.1° (c, 2.8 in chloroform) which had a proton magnetic resonance spectrum compatible (15) with that to be expected for penta-O-acetyl-2-oximino-D-xylo-hexopyranose. Hydrogenation followed by acid hydrolysis as described above for the arabino-isomer gave D-talosamine hydrochloride, m.p. 152-153°, $[\alpha]_D^{23}$ - 5.8° at equil. (c, 1 in water) in 80% yield from II. These physical constants agree with those published (12) for this compound. Furthermore, ninhydrin oxidation (19) gave D-lyxose and the substance was clearly different (infrared and n.m.r. spectra) to D-galactosamine.

The reaction of I with alcohols is highly stereospecific to provide alkyl 3,4,6-tri-O-acetyl-2-oximino-α-D-arabino-hexopyranoside which proved much more resistant to hydrogenation than did compound III (20). Deacetylation followed by hydrogenation in hydrochloric acid using palladium-on-charcoal catalyst gave alkyl α-D-glucopyranosaminide hydrochloride in high yield. It is interesting to compare the stereochemical route of this hydrogenation with those described above.

It can be expected that the above methods for the synthesis of aminosugars can be extended to glycals in general. Attempts are underway in this laboratory to utilize the procedure for the synthesis of a number of diaminosugars.

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