The synthesis of 2-amino-2-deoxyhexoses: D-glucosamine, D-mannosamine, D-galactosamine, and D-talosamine[1]

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Methods for the preparation of the hydrochlorides of 2-amino-2-deoxy-D-glucose (D-glucosamine) and 2-amino-2-deoxy-D-mannose (D-mannosamine) from tri-*O*-acetyl-D-glucal and of 2-amino-2-deoxy-D-galactose (D-galactosamine) and 2-amino-2-deoxy-D-talose (D-talosamine) from tri-*O*-acetyl-D-galactal are described. The reactions involve addition of nitrosyl chloride to the acetylated glycal followed by conversion of the adduct to acetylated derivative of the 2-oximinohexose and reduction of the oxime to amine.

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Although 2-amino-2-deoxy-D-glucose (D-glucosamine) is readily available from natural sources (1), other naturally occurring 2-amino-2-deoxyhexoses such as D-galactosamine (2), D-mannosamine (3–5), and D-talosamine (6, 7) can only be obtained through multi-step chemical syntheses in low overall yield. Thus, D-galactosamine hydrochloride was prepared from D-lyxose by way of 2-amino-2-deoxy-D-galactononitrile in 33–38% overall yield (8). Another method proceeds from 1,6:2,3-dianhydro-β-D-talopyranose (9). Several methods for the preparation of D-mannosamine have been reported (10–14). Of these, the modified synthesis (12) of Sowden and Oftedahl (11) seems most practical. The general epimerization procedure (13) has been applied to the preparation of D-talosamine from D-galactosamine (15). Jeanloz and co-workers (16) have reported a multi-step synthesis of D-talosamine from D-galactose.

The purpose of this publication is to report in further detail the procedures outlined in a preliminary communication (17) for the synthesis of either D-glucosamine or D-mannosamine from tri-*O*-acetyl-D-glucal and of either D-galactosamine or D-talosamine from tri-*O*-acetyl-D-galactal. In the first step, nitrosyl chloride is added to the acetylated glycal to yield the dimeric tri-*O*-acetyl-2-deoxy-2-nitroso-α-D-hexopyranosyl chloride—a reaction which yields well defined crystalline products in near quantitative yield (18–20). Acetolysis of this glycosyl halide yields the tetra-*O*-acetyl-2-oximinosugar (**1***a* or **1***b*) and reduction of the oxime with zinc – copper couple in glacial acetic acid followed by acetylation provides, as expected, the acetylated derivative of the 2-amino-2-deoxyhexose with the amino group in equatorial orientation, e.g., either D-glucosamine or D-galactosamine, which after deacetylation provides the crystalline hydrochloride (**2***a* or **2***b*). On the other hand, treatment of the glycosyl chloride with acetic anhydride and a base (for example, sodium acetate or triethylamine) provides the penta-*O*-acetyl derivative of the 2-oximinohexose (**3***a* or **3***b*) (20) and catalytic hydrogenation of this compound using palladium on carbon affords, after deacetylation of the product, the 2-amino-2-deoxyhexose as the hydrochloride (**4***a* or **4***b*) with the amino group in axial orientation, e.g., either D-mannosamine or D-talosamine. The yields are in the range 70–80% from the acetylated glycal and the method should prove of general application for the synthesis of 2-amino-2-deoxysugars from glycals. Serfontein, Jordaan, and White (18) have identified D-glucosamine by paper and thin-layer chromatography as a product from the zinc – copper couple in glacial acetic acid reduction of tri-*O*-acetyl-2-deoxy-2-nitroso-α-D-glucopyranosyl chloride followed by deacetylation.

Experimental

D-Glucosamine Hydrochloride

Zinc–copper couple (0.7 g, Ventron Corporation, Congress Street, Beverly, Massachusetts) was added to a stirred solution of dimeric tri-*O*-acetyl-2-deoxy-2-nitroso-α-D-glucopyranosyl chloride (20) (0.38 g) in glacial acetic acid (3.5 ml) and acetic anhydride (0.5 ml). The mixture was stirred efficiently for two days at room temperature, after which time the same amounts of zinc–copper couple,

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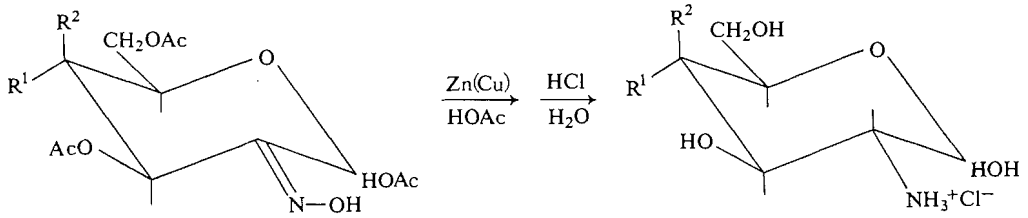
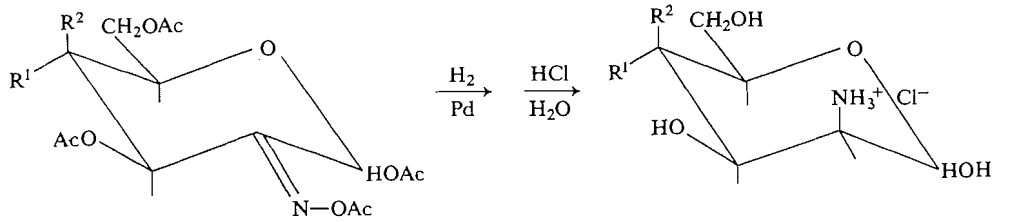


1*a*, R^1 = OAc, R^2 = H
1*b*, R^1 = H, R^2 = OAc

2*a*, R^1 = OH, R^2 = H
2*b*, R^1 = H, R^2 = OH



3*a*, R^1 = OAc, R^2 = H
3*b*, R^1 = H, R^2 = OAc

4*a*, R^1 = OH, R^2 = H
4*b*, R^1 = H, R^2 = OH

acetic acid, and acetic anhydride were introduced and the stirring continued for an additional two days. The solids were collected by filtration and washed with chloroform. The combined filtrates were diluted with chloroform (20 ml) and the chloroform solution was washed successively with water, saturated aqueous sodium bicarbonate solution, and again water. The resulting chloroform solution was dried over sodium sulfate and taken to dryness. The syrupy residue was heated with stirring on a steam bath for 70 min with 1.5 ml of 4 *N* hydrochloric acid. The light-brown solution was decolorized with active charcoal, filtered through Celite, and taken to dryness *in vacuo*. The residual syrup was dehydrated by adding 2-propanol and its removal *in vacuo*. The white solid material was dried and crystallized from ethanol–acetone. A 0.171 g yield (80%) of a crystalline precipitate was deposited which gave infrared and nuclear magnetic resonance (n.m.r.) spectra identical to those of a commercial sample of D-glucosamine hydrochloride and which possessed the expected specific rotation (1). Furthermore, when examined by high voltage paper electrophoresis, under conditions which separated D-glucosamine (mobility, 17.5 cm) and D-mannosamine (mobility, 20.4 cm) (3 kV, 35 min; pyridine, acetic acid, water buffer of pH 6.5) the compound showed a single spot (mobility, 17.5 cm) after development with the cadmium acetate – ninhydrin reagent (21).

In a separate experiment, the residue (1.15 g) from the chloroform extraction was dissolved in 15 ml of 70% aqueous methanol and 4 ml of triethylamine was added. After standing overnight at room temperature, the solution was taken to dryness *in vacuo*, the residue dissolved in water, and the aqueous extract decolorized. The solution was then neutralized with a small amount of Amberlite IR-120 ion-exchange resin in the proton form. Removal of the water left a syrup which crystallized from a mixture of ethanol and ether. The yield was 0.51 g (70%) of a compound, m.p. 186–190°, $[\alpha]_D^{23}$ +40° (*c*, 1 in water), with the same n.m.r. and infrared spectra as those for an authentic sample of *N*-acetyl-D-glucosamine (22), m.p. 186–189°, $[\alpha]_D^{23}$ +42° (*c*, 1 in water), prepared by *N*-acetylation of D-glucosamine hydrochloride following the procedure of Roseman and Ludowieg (23).

Reduction of 1,3,4,6-Tetra-O-acetyl-2-oximino-α-D-arabino-hexopyranose (24)

A solution of the 1,3,4,6-tetra-*O*-acetyl-2-oximino-α-D-*arabino*-hexopyranose (0.722 g, 2 mmoles) in glacial acetic acid (7 ml) and acetic anhydride (1 ml) was reduced with zinc – copper couple (1.4 g) as described above and worked-up in the usual manner afforded a syrupy product which was chromatographed on a silicic acid column (1 × 30 cm) using ethyl acetate as the solvent. Evaporation of the solvent left a white solid residue which was crystallized from ethanol. The yield of the compound, m.p. 136–138°, $[\alpha]_D^{24}$ +90° (*c*, 2 in chloroform), was 0.4 g (52%) (reported in the literature (25) for α-D-glucosamine pentaacetate, m.p. 139°, $[\alpha]_D$ +92°).

D-Galactosamine Hydrochloride

Dimeric tri-*O*-acetyl-2-deoxy-2-nitroso-α-D-galactopyranosyl chloride (20) (0.34 g) was reduced with the zinc – copper couple described above and the product isolated and deacetylated as described above for the preparation of D-glucosamine hydrochloride. The yield, after one recrystallization from ethanol–ether was 0.175 g (82%), m.p. 180° (decomp.), $[\alpha]_D^{23}$ +91.4° (*c*, 2 in water, final). D-Galactosamine hydrochloride is reported (26) to melt at 178° with $[\alpha]_D$ +93° (*c*, 0.75 in water). The n.m.r. and infrared spectra of the compound were identical to those of an authentic commercial sample of D-galactosamine hydrochloride. The high voltage paper electrophoresis of the synthetic compound (see section under D-Glucosamine Hydrochloride) showed a single spot (mobility, 18.2 cm).

D-*Mannosamine Hydrochloride*

A solution of syrupy penta-*O*-acetyl-2-oximino-D-*arabino*-hexopyranose (20) (2.5 g) in glacial acetic acid (25 ml) and acetic anhydride (10 ml) was hydrogenated in the presence of 5% palladium on carbon (0.75 g) at room temperature and an initial pressure of 60 p.s.i. for 48 h. The catalyst was removed by filtration through Celite. The filter cake was washed with glacial acetic acid and the combined filtrates were evaporated to a syrup at diminished pressure. The syrupy product was heated with 4 *N* hydrochloric acid (30 ml) on a steam bath, within initial swirling in order to obtain a homogenous solution, for 50 min. The light-brown colored solution was treated with charcoal and the solids were removed by filtration. The filter cake was washed with water and the combined filtrates evaporated to a syrup at reduced pressure. The syrup was dehydrated by the addition of isopropyl alcohol followed by its removal by evaporation *in vacuo*. The residual white crystals, gathered by filtration with the aid of ice-cold isopropyl alcohol, were washed with ether and dried. Recrystallization of the crude product from ethanol–acetone mixture gave 1.04 g (80%) of a compound, m.p. 178–180°, $[\alpha]_D^{23}$ −3.0° (*c*, 2 in water, no mutarotation), literature (11) m.p. not given, $[\alpha]_D^{25}$ −3.2°, (*c*, 10 in water, no mutarotation). Ninhydrin degradation (27) of the compound afforded D-arabinose which was identified by paper chromatography.

Anal. Calcd. for $C_6H_{14}NO_5Cl$: C, 33.40; H, 6.49; N, 6.49. Found: C, 33.38; H, 6.51; N, 6.49.

Although the *x*-ray powder diagram was identical to that of an authentic sample of D-mannosamine hydrochloride prepared following the procedure of Satoh and Kiyomoto (12), a high-voltage paper electrophoresis examination showed the presence of a trace of D-glucosamine.

The compound was *N*-acetylated following the procedure of Roseman and Ludowieg (23) to yield a product which crystallized from 70% aqueous ethanol on the addition of ether to the point of turbidity. A 76% yield of substance, m.p. 107–108°, $[\alpha]_D^{23}$ +10° (*c*, 2.5 in water, final) was obtained with physical constants in close agreement with those reported for *N*-acetyl-D-mannosamine (12).

D-*Talosamine Hydrochloride*

Penta-*O*-acetyl-2-oximino-D-*lyxo*-hexopyranose (20) (2.5 g) was reduced in a mixture of glacial acetic acid (25 ml) and acetic anhydride (10 ml) using the procedure described above for the reduction of the *arabino* isomer. The syrupy product was hydrolyzed with 4 *N* hydrochloric acid (30 ml) for 80 min at 100° and the residue, on solvent removal, was recrystallized from a mixture of hot ethanol and acetone. The yield was 1.03 g (80%) of a compound, m.p. 152–153° with decomposition, $[\alpha]_D^{23}$ −5.8° (*c*, 1 in water). D-Talosamine hydrochloride is reported (16) to melt at 150–151° with $[\alpha]_D^{23}$ +3° (3 min) to −6° (final) (*c*, 0.9 in water). Ninhydrin oxidation gave D-lyxose as identified by paper chromatography (27).

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