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Hydrazinolysis of Sugar Sulfonates*[1]

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Hydrazinolysis of methyl 4,6-di-*O*-acetyl-2,3-di-*O*-tosyl-α-D-glucopyranoside (I) or methyl 2,6-di-*O*-benzoyl-3,4-di-*O*-mesyl-α-D-glucopyranoside (VI), followed by catalytic hydrogenation and acetylation, afforded methyl 2,4-diacetamido-3,6-di-*O*-acetyl-2,4-dideoxy-α-D-idopyranoside (II). Also methyl 2,3-di-*O*-acetyl-4,6-di-*O*-mesyl-α-D-glucopyranoside (VII) was treated analogously as described above to give methyl 4,6-diacetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-galactopyranoside (IX). The structures were studied by means of proton magnetic resonance spectra. And a reaction mechanism was also discussed.

In the previous papers,[1–5] it has been described that hydrazinolysis of inositol sulfonate, followed by catalytic hydrogenation, affords diamino-dideoxyinositol of practical importance. Prior to these reports, Wolfrom and his coworkers described a displacement of sulfonyloxy group in a sugar derivative with hydrazine.[6–9]

Since a diamino-sugar has been found in several antibiotics, such as neomycin B, C,[10] kanamycin

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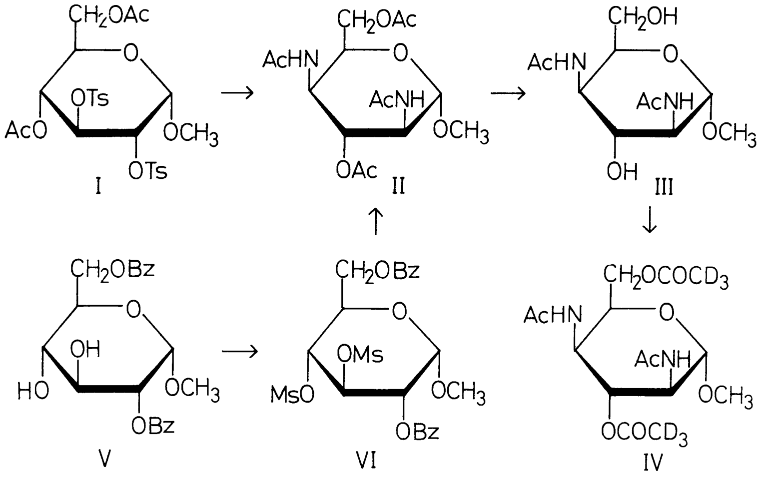

Scheme 1

B[11] and paromomycin,[12] it would be desirable to explore a new process for the synthesis of diaminosugars. For this aim, the above hydrazinolysis of sugar disulfonates seems to be an attractive method.

In the present article, it will be described that methyl 4,6-di-*O*-acetyl-2,3-di-*O*-tosyl-α-D-glucopyranoside (I), methyl 2,6-di-*O*-benzoyl-3,4-di-*O*-mesyl-α-D-glucopyranoside (VI) and methyl 2,3-di-*O*-acetyl-4,6-di-*O*-mesyl-α-D-glucopyranoside (VII) are treated with hydrazine and the reaction products are readily converted to methyl diamino-dideoxyhexosides by the catalytic hydrogenation.

The compound I was prepared by acetylation of methyl 2,3-di-*O*-tosyl-α-D-glucopyranoside which had been prepared by the method of Littmann and Hess.[13] When I was heated with anhydrous hydrazine in 2-methoxyethanol under reflux for 26 hr and the reaction product was hydrogenated in the presence of Raney nickel catalyst, an oily product was obtained. Acetylation of the product afforded methyl diacetamido-di-*O*-acetyl-dideoxyhexoside (II) as crystals of mp 245—247°C in a yield of 43%. A selective de-*O*-acetylation of II yielded methyl diacetamido-dideoxyhexoside (III) of mp 242—244°C in 74% yield.

To establish the structure of II, a proton magnetic resonance (PMR) spectrum was measured with 100 MHz spectrometer. The spectrum of II in deuteriochloroform showed three sharp signals at δ 1.99, 2.00 and 2.09 with a relative intensity of 3 : 3 : 6, which were attributed to four acetyl groups. To find the signal due to the acetamido groups, methyl di-*O*-trideuterioacetyl-diacetamido-dideoxyhexoside (IV) was prepared by trideuterioacetylation of III. The PMR spectrum of IV revealed the signal at δ 2.00 with an intensity of six protons, which was attributed to the two acetamido groups. Hence the signal at δ 2.09(6H) in the spectrum of II was ascribed to the two acetoxy groups. The two acetamido groups were considered to be in axial positions, because their signals appeared in a relatively low field.[14] One of the two acetoxy groups was on C-6, since an acetoxy group on C-6 of methyl α-D-glucopyranoside tetraacetate showed its signal at the same position (δ 2.09).[15] Another acetoxy group seemed to be axial but this was not definitive, because the signal was on an overlapped position of an axial and an equatorial acetoxy group.[14]

A more information on the conformation of II was obtained from the signal pattern of ring protons in a low field (Fig. 1). There were two doublets at δ 7.11 and 7.29 with a same coupling constant of 9.0 Hz, and these signals were removed by adding deuterium oxide to the sample (Fig. 1). Consequently, these signals were ascribed to the two N$\underline{\text{H}}$ protons of acetamido groups.

An anomeric proton should appear as a doublet, since there was only one proton on C-2 to couple with it. This doublet was found at δ 4.76 with a $J_{1,2}$ coupling of 3.5 Hz and the signal was slightly broadened by a long range coupling of less than 1 Hz. The small value of the coupling constant between H-1 and H-2 indicated that H-2 was not anti-parallel to H-1, and accordingly the C1 conformation was supported.

A triplet was observed at δ 4.97 with a coupling

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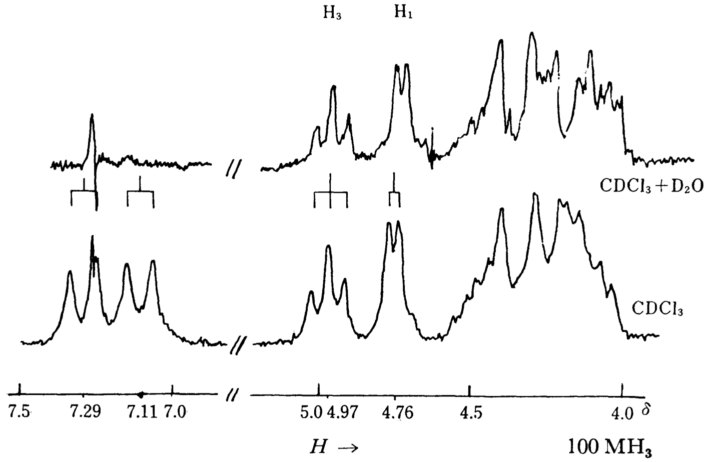
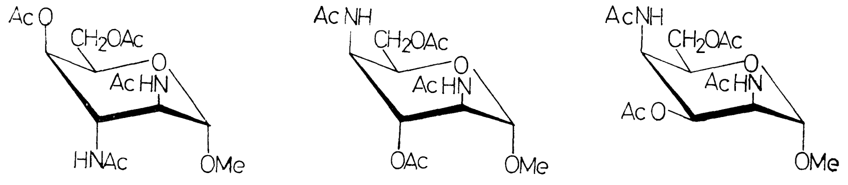
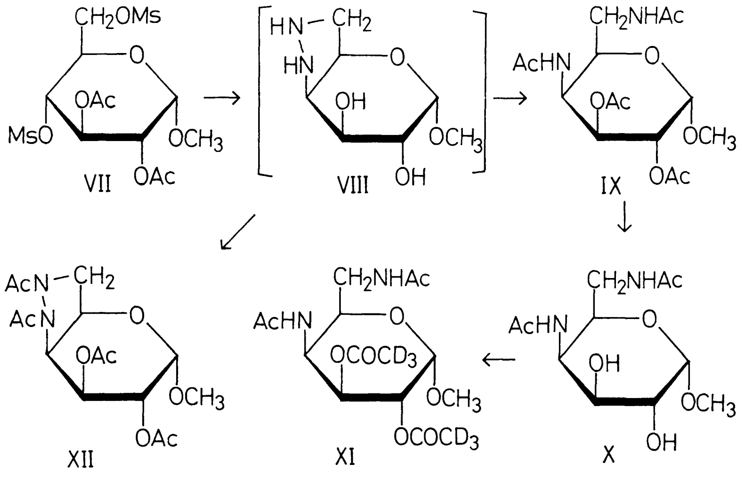


Fig. 1



(a) (b) (c)

Scheme 2



Scheme 3

constant of 5.7 Hz. The fact that a magnitude of the coupling constant was not the same as $J_{1,2}$ showed that the signal was not due to H-2. Also, the triplet was not affected by the addition of D_2O, indicating that the proton was bonded to a carbon atom which held an acetoxy group. If the proton were on C-4, the configuration of II would be (a), and if it were on C-3, the configuration would be (b) or (c).

To establish the configuration, another synthetic study was carried out. When methyl 2,6-di-*O*-benzoyl-3,4-di-*O*-mesyl-α-D-glucopyranoside (VI) was treated with hydrazine and subsequently hydrogenated and acetylated, the compound II was obtained in 26% yield.

In the configuration (a), H-4 should appear as a quartet and therefore, this configuration could be omitted. If it were (c), the intermediary cyclic carbonium ions which were formed in the both reactions (I→II and VI→II) should be opened in the *cis*-configuration. The *cis*-opening of the cyclic carbonium ion has not been observed in these reaction condition.[16] In the configuration (b), there was no such a contradiction and this configuration was consistent with all respects.

In 1968, Hill and his coworkers[17] described that 4,6-diamino-4,6-dideoxy-D-galactose derivative was prepared by a reaction between methyl 2,3-di-*O*-acetyl-4,6-di-*O*-mesyl-α-D-glucopyranoside (VII) and sodium azide. Very recently, it has been described by Paulsen and Stoye[18] that methyl 2,3-di-*O*-benzyl-4,6-di-*O*-mesyl-α-D-glucopyranoside was treated with hydrazine and subsequently hydrogenated to give the diamino-sugar.

Independently, the present authors have attempted to prepare a diamino-sugar by hydrazinolysis of VII, since hydrazine might induce a different reaction from that of sodium azide. In the present study, hydrazinolysis of VII, followed by catalytic hydrogenation and acetylation, afforded methyl diamino-dideoxyhexoside tetraacetate of mp 220—221°C which was identical with methyl 4,6-diacetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-galactopyranoside (IX) described by Hill *et al.*[17] A selective de-*O*-acetylation of IX yielded methyl 4,6-diacetamido-4,6-dideoxy-α-D-galactopyranoside (X).[18]

The conformation of the product was studied by PMR spectra. The spectrum of IX revealed three sharp signals at δ 2.00, 2.01 and 2.10 with a relative intensity of 3 : 3 : 6, which were ascribed to four acetyl groups. To find out a signal arisen from the acetamido groups, the spectrum of the trideuterioacetyl derivative of X was measured. In the spectrum, two sharp signals at δ 1.99 (3H) and 2.10 (3H) were observed as the two acetamido signals. The latter signal was in a lower field as compared with an acetamido signal given by the group on a pyranose ring, and this signal was thus ascribed to the one on C-6. The former signal was ascribed to an axial acetamido group.[14] Hence, the two signals at δ 2.01 (3H) and 2.10 (3H) were attributed to two equatorial acetoxy groups.

In the lowest field of the spectrum, a signal pattern of two protons appeared as a modified quartet centered at δ 6.5, which were ascribed to two NH protons. These signals were removed step by step by adding deuterium oxide to the $CDCl_3$ solution of the sample. In five minutes after the addition of D_2O, a signal pattern of one proton disappeared to leave a doublet with a coupling constant of 9.8 Hz. This doublet was further removed by warming the sample solution at 40—50°C for 10 min. These facts were not contradictory with the above mentioned structure.

The reaction mechanism was established by isolating the intermediary bicyclic compound (VIII) as the crystalline acetyl derivative (XII). That is, the attack of hydrazine occurred at C-6 of VII and then the hydrazino group on C-6 attacked C-4 to give VIII. The N-N linkage was cleaved by the catalytic hydrogenation to yield the product with the galacto-configuration.

Experimental

The melting points reported were determined on a Mitamura Riken micro hot stage. The melting point marked with an asterisk was measured in a liquid bath and was uncorrected. The PMR spectra of the samples were determined at 60 or 100 MHz in deuteriochloroform with tetramethylsilane as an internal standard. The peak positions are given in δ-values.

Methyl 4,6-Di-*O*-acetyl-2,3-di-*O*-tosyl-α-D-glucopyranoside (I). A 0.85 g portion of methyl 2,3-di-*O*-tosyl-α-D-glucopyranoside which had been prepared by the method of Littmann and Hess[13] was acetylated with acetic anhydride in pyridine at room temperature overnight. The mixture was evaporated under reduced pressure and the residue was crystallized in ethanol. Recrystallization of the crude product from ethanol-ether gave 0.89 g (90%) of I, mp 126—128°C; $[\alpha]^{22}_{D}+31°$ (*c* 1, $CHCl_3$).

Found: C, 51.16; H, 5.49; S, 10.77%. Calcd for $C_{25}H_{30}O_{12}S_2$ (586.6): C, 51.19; H, 5.12; S, 10.92%.

Methyl 2,6-Di-*O*-benzyl-α-D-glucopyranoside (V). The product was prepared by the method of Lieser and Schweizer[19] in a yield of 31% from methyl D-glucopyranoside, mp 142°C; $[\alpha]^{22}_{D}+81.9°$ (*c* 2, $CHCl_3$). Lit,[19] mp 144°C; $[\alpha]^{23}+80.4°$ (*c* 4, $CHCl_3$).

Methyl 2,6-Di-*O*-benzoyl-3,4-di-*O*-mesyl-α-D-glucopyranoside (VI). To a solution of 1.78 g of V in 20 m*l* of pyridine, 4.5 m*l* of methanesulfonyl chloride was added under ice cooling. The mixture was settled at room temperature for 48 hr and was poured into a large amount of ice-water. The precipitate was collected by filtration and washed with water. The product was dissolved in ethanol and decolorized with charcoal. The solution was evaporated to give 1.51 g (61%) of amorphous powder: mp 59—64°C. The crude product was recrystallized from isopropanol to give crystals of mp 74—77°C: $[\alpha]^{22}_{D}+138.0°$ (*c* 1, $CHCl_3$).

Found: C, 49.38; H, 4.84; S, 11.33%. Calcd for $C_{23}H_{26}O_{12}S_2$ (558.6): C, 49.45; H, 4.69; S, 11.48%.

Methyl 2,4-Diacetamido-3,6-di-*O*-acetyl-2,4-dideoxy-α-D-idopyranoside (II). (a) A mixture of 2.08 g of I and 4.4 m*l* of anhydrous hydrazine in 28 m*l* of 2-methoxyethanol was heated under reflux for 26 hr. The mixture was evaporated *in vacuo* and the residue was dissolved in water. The aqueous solution was treated with Amberlite IRA-400 to remove an acidic substance and then evaporated. The residue was hydrogenated in ethanol under the presence of Raney nickel catalyst in 3.4 kg/cm² of hydrogen atmosphere for 23 hr.

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[16] E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, Inc., New York (1962), pp. 565—566.

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After the catalyst was removed by filtration, the filtrate was evaporated to give 1.02 g of an oily residue. Acetylation of the residue with acetic anhydride in pyridine afforded a crystalline product. Recrystallization of the product from ethanol afforded 0.55 g (43%) of crystals: mp* 245—247°C; $[\alpha]_D^{22}$ + 80° (*c* 1, water).

Found: C, 50.10; H, 6.78; N, 7.81%. Calcd for $C_{15}H_{24}N_2O_8$ (360.4): C, 49.99; H, 6.71; N, 7.77%.

(b) A mixture of 7.3 g of methyl 2,3-di-*O*-tosyl-α-D-glucopyranoside[13] and 15 m*l* of anhydrous hydrazine in 80 m*l* of 2-methoxyethanol was heated under reflux for 48 hr and subsequently treated as described in (a) to give 0.84 g (16%) of the product: mp 242—246°C. The product was identified with II by a mixed melting point determination and IR spectra.

(c) A 3.97 g portion of VI was heated with 20 m*l* of anhydrous hydrazine in 50 m*l* of 2-methoxyethanol for 22 hr under reflux. The reaction mixture was treated analogously as described in (a), giving 662 mg (26%) of II: mp 243—245°C.

Methyl 2,4-Diacetamido-2,4-dideoxy-α-D-idopyranoside (III). A 123 mg portion of II was selectively de-*O*-acetylated in 30 m*l* of methanol previously saturated with ammonia. The solution was evaporated under reduced pressure and the residue was washed with ethanol to give 70 mg (73%) of the product: mp 242—244°C. Recrystallization from ethanol afforded an analytically pure sample: mp 242—244°C; $[\alpha]_D^{22}$+61° (*c* 0.2, water).

Found: C, 47.97; H, 7.32; N, 10.29%. Calcd for $C_{11}H_{20}N_2O_6$ (276.3): C, 47.82; H, 7.30; N, 10.14%.

Methyl 2,4-Diacetamido-3,6-di-*O*-trideuterioacetyl-2,4-dideoxy-α-D-idopyranoside (IV). A 55 mg portion of III was acetylated with 0.2 m*l* of acetic anhydride-d_6 in 0.6 m*l* of pyridine overnight. The mixture was evaporated *in vacuo* and the residue was crystallized in ethanol-ether to give 55 mg (76%) of the product: mp 240—244°C.

Methyl 2,3-Di-*O*-acetyl-4,6-di-*O*-mesyl-α-D-glucopyranoside (VII). The compound was prepared by the method of Hill *et al.*[17]

Methyl 4,6-Diacetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-galactopyranoside (IX). A 2.0 g portion of VII was heated under reflux in a mixture of 6 m*l* of anhydrous hydrazine and 30 m*l* of 2-methoxyethanol for 24 hr. After the mixture was evaporated under reduced pressure, the residue was hydrogenated in ethanol with Raney nickel catalyst at 3.4 kg/cm² of hydrogen stream at 40—50°C for 24 hr. The catalyst was removed by filtration and the filtrate was evaporated. The residue was acetylated with acetic anhydride in pyridine. An excess amount of the reagent was removed by evaporation, and the residue was crystallized from ethanol to give 0.45 g (28%) of the product: mp 220—221°C; $[\alpha]_D^{22}$ +121° (*c* 1, water). Lit,[17] mp 218—219°C; $[\alpha]_D$ +123° (*c* 1, water). Found: C, 50.15; H, 6.86; N, 7.86%.

Methyl 4,6-Diacetamido-4,6-dideoxy-α-D-galactopyranoside (X). A 32 mg portion of IX was selectively de-*O*-acetylated with methanolic ammonia, giving 16 mg (64%) of the product: mp 213.5—214°C; $[\alpha]_D^{24}$ +161° (*c* 1.1, MeOH). Lit,[17] mp 212—213°C; $[\alpha]_D$ +151° (*c* 1.0, water). Lit,[18] mp 215—216°C; $[\alpha]_D^{20}$ +153° (*c* 0.5, MeOH).

Methyl 4,6-Diacetamido-2,3-di-*O*-trideuterioacetyl-4,6-dideoxy-α-D-galactopyranoside (XI). An 89 mg portion of X was acetylated with 0.3 m*l* of acetic anhydride-d_6 in 0.7 m*l* of pyridine overnight. The mixture was evaporated under reduced pressure and the residue was crystallized in ethanol-ether to give 82 mg (70%) of the product: mp 218—219°C.

7,8-Di-*N*-acetyl-4,5-di-*O*-acetyl-3-*O*-methyl-7,8-diaza-2-oxabicyclo[4.3.0]nonane-3,4,5-triol (XII). A 1.3g portion of VII was heated with anhydrous hydrazine (4 m*l*) in 2-methoxyethanol (20 m*l*), and then the mixture was evaporated *in vacuo*. The residue was dissolved in ethanol and an insoluble material was removed by filtration. The filtrate was evaporated and the residue was acetylated with acetic anhydride in pyridine. After an excess reagent was evaporated *in vacuo*, the residue was crystallized in ethanol to give 184 mg (17%) of the product: mp 199—200°C. Recrystallization from ethanol did not raise its melting point. $[\alpha]_D^{22}$ +106° (*c* 0.5, $CHCl_3$); ν_{max}^{KBr} 1740 and 1687 cm^{-1}.

Found: C, 50.40; H, 6.30; N, 7.74%. Calcd for $C_{15}H_{22}N_2O_8$ (358.2): C, 50.27; H, 6.19; N, 7.82%.

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