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Syntheses of 2-Amino-2,3-dideoxy-L- and -D-Ribohexose by Utilizing an O→N Acetyl Migration

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2-Amino-2,3-dideoxy-L- and -D-ribohexose ($\mathbf{1_L}$ and $\mathbf{1_D}$) were synthesized from 2-amino-2-deoxy-L- and -D-glucose, respectively, through a reaction sequence which involves 3-O→2-N acetyl migration of methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-*β*-L- and -D-glucopyranoside ($\mathbf{3_L}$ and $\mathbf{3_D}$). A preparative method of methyl 4,6-di-*O*-acetyl-2-amino-2-deoxy-*β*-D-glucopyranoside ($\mathbf{11_D}$) is given.

In a program directed towards the synthesis of deoxy variants of streptomycin, Sano *et al.*[1] reported a novel method for the preparation of 2-amino-2,3-dideoxy-L-ribohexose ($\mathbf{1_L}$) from 2-amino-2-deoxy-L-glucose achieved without protection of the anomeric hydroxyl group throughout the reaction sequence. In the present paper we wish to report an alternative method for the preparation of $\mathbf{1_L}$ from 2-amino-2-deoxy-L-glucose by utilizing O→N acetyl migration. The same synthesis for the D-sugar ($\mathbf{1_D}$) is also described.

Results and Discussion

2-Amino-2-deoxy-L-glucose ($\mathbf{2_L}$) was prepared from L-arabinose by the method of Kuhn and Kirschenlohr.[2] Treatment of the hydrochloride of $\mathbf{2_L}$ with acetyl bromide followed by treatment with methanol according to the method for the corresponding D-sugar described by Irvine *et al.*[3] and Wolfrom and Shen Han[4] gave methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-*β*-L-glucopyranoside ($\mathbf{3_L}$) hydrobromide. Treatment of the hydrobromide with 5% aqueous sodium carbonate gave the free base ($\mathbf{3_L}$) in 93% yield, O→N acetyl migration being successfully avoided. Fodor and Oetvoes[5] obtained the corresponding D-sugar base from its hydrobromide by treatment with sodium methoxide in chloroform in 97% yield.

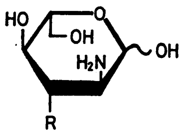
The regiospecific removal of the acetyl group at C-3 of $\mathbf{3_L}$ by utilizing O→N acetyl migration was studied in detail. Fodor *et al.*[5,6] reported that the behavior of ethyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-*β*-D-glucoside in organic solvents (methanol, ethanol, and acetone) is complicated and that O→N acetyl migration or deacetylation occurs as the main reaction, depending on the reaction conditions (solvents, their dryness, and temperature). We further attempted the O→N acetyl migration of $\mathbf{3_L}$ in pyridine,[7] toluene, and diglyme, but without success. However, we found that, with *N*,*N*-dimethylformamide (DMF) at reflux temperature, $\mathbf{3_L}$ was converted into the migration product, methyl 2-acetamido-4,6-di-*O*-acetyl-2-deoxy-*β*-L-glucopyranoside ($\mathbf{4_L}$) in a high yield (72%).

It should be noted that, in ethanol at room temperature, deacetylation at C-3 of methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-*β*-D-glucopyranoside ($\mathbf{3_D}$) takes place almost completely to afford methyl 4,6-di-*O*-acetyl-2-amino-2-deoxy-*β*-D-glucopyranoside ($\mathbf{11_D}$) in a 93% yield, in accord with the result reported by Fodor and Oetvoes.[5]

Tosylation or mesylation of $\mathbf{4_L}$ was readily achieved by the conventional method to give the 3-*O*-tosylate ($\mathbf{5_L}$) or 3-*O*-mesylate ($\mathbf{6_L}$). Iodination with sodium iodide in DMF gave the 3-iodo derivative ($\mathbf{7_L}$), which was then hydrogenolyzed with Raney nickel to afford methyl 2-acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-*β*-L-ribohexopyranoside ($\mathbf{8_L}$). To confirm the structure, $\mathbf{8_L}$ was de-*O*-acetylated and the *N*-acetyl derivative ($\mathbf{9_L}$) was acetonated with 2,2-dimethoxypropane to give $\mathbf{10_L}$. The position of the isopropylidene group in the derivative was determined by PMR studies; the large coupling constants of H-3$_{\rm ax}$ ($J=\approx 11$ Hz) indicated the 3-deoxy-4,6-*O*-isopropylidene, not 4-deoxy-3,6-*O*-isopropylidene, structure.

Finally acid hydrolysis of $\mathbf{8_L}$ was carried out in 1 M hydrochloric acid at 110 °C to afford 2-amino-2,3-dideoxy-L-ribohexose ($\mathbf{1_L}$), which shows a specific rotation numerically compatible with that of D-isomer[8] but opposite in direction.

2-Amino-2,3-dideoxy-D-ribohexose ($\mathbf{1_D}$) and the intermediates of D-series were prepared in a similar manner to that described in the preparation of the corresponding L-series.



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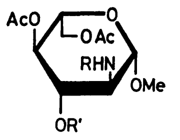
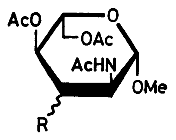
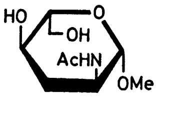
2L R = OH



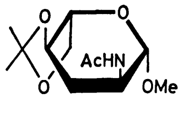
3L R = H, R' = Ac
4L R = Ac, R' = H
5L R = Ac, R' = Ts
6L R = Ac, R' = Ms



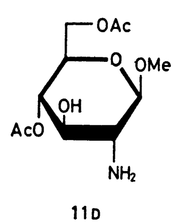
7L R = I
8L R = H



9L



10L



11D

Experimental

General. Melting points were determined on a Kofler block and are uncorrected. Infrared spectra were recorded for potassium bromide pellets with a Hitachi Model 285 grating infrared spectrophotometer. PMR spectra were recorded a 60 and 100 MHz with Hitachi R-24A and Varian XL-100 spectrometers. Thin layer chromatography was performed on Wakogel B-5 with sulfuric acid spray for detection. For column chromatography, silica gel (Wakogel C-200) was used.

Methyl 3,4,6-Tri-O-acetyl-2-amino-2-deoxy-β-L- and D-glucopyranoside ($\mathbf{3}_\mathrm{L}$ and $\mathbf{3}_\mathrm{D}$). Acetyl bromide (15.4 ml) was added to a well dried (dried *in vacuo* at 60 °C for 2 h in the presence of P_2O_5) 2-amino-2-deoxy-L-glucose ($\mathbf{2}_\mathrm{L}$) hydrochloride (4.8 g), and the mixture in a sealed tube was allowed to stand at room temperature for 3 days. Deposition of deep-brown needles was observed. The reaction mixture was concentrated *in vacuo*. To the resulting solid were added methanol (200 ml) and pyridine (20 ml) and the solution was allowed to stand for 30 min at room temperature. After concentration of the solution, the residue hydrobromide was suspended in chloroform (250 ml) and the mixture was washed with 5% aqueous sodium carbonate and water. The chloroform layer was dried over sodium sulfate, and concentrated to give crystals (6.3 g, 93%). Recrystallization from hexane–chloroform gave needles of $\mathbf{3}_\mathrm{L}$; mp 152.5—153 °C, $[\alpha]_\mathrm{D}^{24}$ −17.5° (*c* 1, methanol). IR: 1750 (OAc), 1605 (NH_2) cm^{-1}. PMR ($CDCl_3$): δ 1.40 (2H s, disappeared on deuteration), 2.05 (3H s, Ac), 2.10 (6H s, Ac), 2.95 (1H q, *J*=8 and 10.5 Hz, H-2), 3.61 (3H s, OCH_3), 4.0—4.55 (2H double q, *J*=3, 4.5, and 12 Hz, H-6,6′), 4.21 (1H d, *J*=8 Hz, H-1), 4.99—5.17 (2H m, H-3, 4). Irradiation at δ 5.1 caused the quartet at 2.95 to collapse to a doublet. Irradiation at δ 2.95 caused the doublet at δ 4.21 to collapse to a singlet.

Found: C, 48.84; H, 6.56; N, 4.29%. Calcd for $C_{13}H_{21}NO_8$: C, 48.90; H, 6.63; N, 4.39%.

$\mathbf{3}_\mathrm{D}$: mp 151—152 °C (lit,[5] 152 °C), $[\alpha]_\mathrm{D}^{27}$ +15° (*c* 1, methanol) (lit,[5] +10° (methanol)).

Found: C, 49.20; H, 6.58; N, 4.14%.

Methyl 2-Acetamido-4,6-di-O-acetyl-2-deoxy-β-L- and D-glucopyranoside ($\mathbf{4}_\mathrm{L}$ and $\mathbf{4}_\mathrm{D}$). A solution of $\mathbf{3}_\mathrm{L}$ (4.30 g) in dry DMF (86 ml) was refluxed for 4 h. On being subjected to TLC with chloroform–acetone (1: 1), $\mathbf{3}_\mathrm{L}$ (R_f 0.5) almost disappeared and $\mathbf{4}_\mathrm{L}$ (R_f 0.25) appeared. Concentration of the solution under reduced pressure gave a residue, which was dissolved in methanol (200 ml). The solution was decolorized with charcoal and concentrated to give a solid, which was recrystallized from hexane–chloroform to give needles (2.36g). Concentration of the mother liquor gave a syrup, which was chromatographed on a silica gel column with chloroform–acetone (2: 1) as a developer to give $\mathbf{4}_\mathrm{L}$ (720 mg) and $\mathbf{3}_\mathrm{L}$ (111 mg). Total yield of $\mathbf{4}_\mathrm{L}$ was 72%. Mp 172.5—173 °C, $[\alpha]_\mathrm{D}^{24}$ +35° (*c* 1, methanol). IR: 3430 (OH), 1740 (OCO); 1620, 1560 (NHCO) cm^{-1}. PMR ($(CD_3)_2SO$): δ 1.81 (3H s, Ac), 2.02 and 2.03 (each 3H s, Ac), 3.33 (3H s, OCH_3), 3.35—3.75 (3H m, H-2,3,5), 3.85—4.25 (2H double q, *J*=3, 5, and 12 Hz, H-6,6), 4.35 (1H d, *J*=8 Hz, H-1), 4.63 (1H q, *J*=8 and 10 Hz, H-4), 5.28 (1H d, *J*=5 Hz, disappeared on deuteration), 7.75 (1H d, *J*=8 Hz, disappeared on deuteration). Irradiation at δ 3.5 caused the doublets at δ 4.35, 5.28, and 7.75 collapsed to singlets, respectively.

Found: C, 48.93; H, 6.58; N, 4.25%. Calcd for $C_{13}H_{21}NO_8$: C, 48.89; H, 6.64; N, 4.39%.

$\mathbf{4}_\mathrm{D}$: mp 173—173.5 °C, $[\alpha]_\mathrm{D}^{27}$ −38° (*c* 1, methanol).

Found: C, 48.98; H, 6.50; N, 4.33%.

Methyl 2-Acetamido-4,6-di-O-acetyl-2-deoxy-3-O-tosyl-β-L- and D-glucopyranoside ($\mathbf{5}_\mathrm{L}$ and $\mathbf{5}_\mathrm{D}$). *p*-Toluenesulfonyl chloride (840 mg) was added to a cold solution of well dried $\mathbf{4}_\mathrm{L}$ (700 mg) in dry pyridine (14 ml), and the solution was allowed to stand at −10 °C overnight. The solution showed a single spot at R_f 0.57 on being subjected to TLC with chloroform–acetone (2: 1). After addition of water (0.2 ml), the mixture was concertrated and coevaporated with toluene. The residue was extracted with ethyl acetate. The solution was washed successively with 0.4 M potassium hydrogensulfate, aqueous sodium hydrogencarbonate, and water, dried over sodium sulfate and concentrated. The residue was recrystallized from hexane–ethyl acetate to give needles, 638 mg (61%); mp 137—138.5 °C (dec), $[\alpha]_\mathrm{D}^{24}$ +18° (*c* 1, methanol). PMR ($CDCl_3$): δ 1.91 (6H s, Ac), 2.06 (3H s, Ac), 2.46 (3H s, $C_6H_4C\mathit{H}_3$), 3.54 (3H s, OCH_3), 4.90 (1H d, *J*=8.5 Hz, H-1). 5—5.5 (2H m, H-3,4).

Found: C, 50.57; H, 5.73; N, 2.71; S, 6.91%. Calcd for $C_{20}H_{27}NO_{10}S$: C, 50.73; H, 5.75; N, 2.96; S, 6.77%.

$\mathbf{5}_\mathrm{D}$: mp 138—139 °C (dec), $[\alpha]_\mathrm{D}^{27}$ −22° (*c* 1, methanol).

Found: C, 50.87; H, 5.79; N, 2.74; S, 6.61%.

Methyl 2-Acetamido-4,6-di-O-acetyl-2-deoxy-3-O-mesyl-β-L- and D-glucopyranoside ($\mathbf{6}_\mathrm{L}$ and $\mathbf{6}_\mathrm{D}$). Compounds $\mathbf{4}_\mathrm{L}$ and $\mathbf{4}_\mathrm{D}$ were treated as described above for $\mathbf{5}_\mathrm{L}$ using methanesulfonyl chlororide instead of *p*-toluenesulfonyl chloride to give $\mathbf{6}_\mathrm{L}$ and $\mathbf{6}_\mathrm{D}$ (∼80%), respectively.

$\mathbf{6}_\mathrm{L}$: mp 157—158 °C (dec), $[\alpha]_\mathrm{D}^{23}$ +20° (*c* 1, methanol).

Found: C, 42.47; H, 5.65; N, 3.23; S, 8.17%. Calcd for $C_{14}H_{23}NO_{10}S$: C, 42.31; H, 5.83; N, 3.52; S, 8.07%.

$\mathbf{6}_\mathrm{D}$: mp 158—159.5°C (dec), $[\alpha]_\mathrm{D}^{27}$ −20° (*c* 1, methanol).

Found: C, 42.25; H, 5.65; N, 3.35; S, 8.24%.

Methyl 2-Acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-iodo-β-L- and D-gluco and/or allopyranoside ($\mathbf{7}_\mathrm{L}$ and $\mathbf{7}_\mathrm{D}$). To a solution of $\mathbf{5}_\mathrm{L}$ (1.01 g) in dry DMF (20 ml) was added dry sodium iodide (10 g) and after displacement of the air in the reaction vessel with nitrogen, the mixture was heated in a tightly stoppered vessel at 100 °C for 2 h. Chloroform (200 ml) was added and the mixture was filtered. The organic layer was washed successively with water, aqueous 20% sodium thiosulfate, and water, and dried over sodium sulfate. The solution showed, on being subjected to TLC with chloform–ether (1: 1), a single spot at R_f 0.15 (*cf.* $\mathbf{5}_\mathrm{L}$: R_f 0.1). Concentration of the solution gave a solid of $\mathbf{7}_\mathrm{L}$, 677 mg (74%); mp 186—188 °C (dec), $[\alpha]_\mathrm{D}^{24}$ +5° (*c* 1, methanol).

Found: C, 36.35; H, 4.63; N, 3.20; I, 29.20%. Calcd for $C_{13}H_{20}INO_7$: C, 36.38; H, 4.70; N, 3.26; I, 29.51%.

$\mathbf{7}_\mathrm{D}$: mp 184—186 °C (dec), $[\alpha]_\mathrm{D}^{26}$ −7.5° (*c* 1, methanol).

Found: C, 36.75; H, 4.80; N, 2.95; I, 29.24%.

Methyl 2-Acetamido-4,6-di-O-acetyl-2,3-dideoxy-β-L- and D-ribohexopyranoside ($\mathbf{8}_\mathrm{L}$ and $\mathbf{8}_\mathrm{D}$). To a solution of $\mathbf{7}_\mathrm{L}$ (582 mg) in aqueous dioxane (1: 9, 10 ml) was added sodium hydrogencarbonate (40 mg) and the mixture was hydrogenated over Raney nickel under pressure (50 lb/in^2) at room temperature for 3 h. Filtration followed by evaporation gave a syrup, which was chromatographed on a silica gel column with ethyl acetate to give a solid of $\mathbf{8}_\mathrm{L}$, 298 mg (72%), mp 150—150.5 °C, $[\alpha]_\mathrm{D}^{24}$ +43° (*c* 1, methanol). PMR (DMF-d_7): δ 1.60 (1H q, *J*=≈11.5 Hz, H-3_ax), 1.88 (3H s, Ac), 2.07 (6H s, AcO), 2.37 (1H double t, *J*=5 and 12 Hz, H-3_eq), 3.43 (3H s, OCH_3), octet centered at 4.22 (q in higher field, *J*=3 and 12 Hz; q in lower field, *J*=5 and 12 Hz, H-6,6′), 4.49 (1H d, *J*=8 Hz, H-1), 4.72 (1H octet, *J*=5, 10, and 11 Hz, H-4), 7.97 (1H broad d, *J*=≈8 Hz, NH). Irradiation of H-4 caused the signal of H-3_ax and H-3_eq to collapse to a triplet (*J*=≈11 Hz) and a quartet (*J*=5 and 12 Hz), respectively.

Found: C, 51.65; H, 6.92; N, 4.53%. Calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62%.

$\mathbf{8}_\mathrm{D}$: mp 149—149.5 °C, $[\alpha]_\mathrm{D}^{27}$ −44° (*c* 1, methanol).

Found: C, 51.41; H, 6.91; N, 4.53%.

Methyl 2-Acetamido-2,3-dideoxy-β-L-ribohexopyranoside ($\mathbf{9}_\mathrm{L}$). To a solution of $\mathbf{8}_\mathrm{L}$ (64 mg) in dry methanol (2 ml) was added a piece of sodium metal. After 5 min, the solution was neutralized with Amberlite CG 50 (H form, pretreated with methanol) and concentrated. The residue was recrystallized from ethanol–ether to give needles of **9**$_\mathrm{L}$, 39 mg (85%); mp 152—153 °C, $[\alpha]^{23}_\mathrm{D}$ +58° (*c* 1, methanol). IR: 1560, 1650 cm^{-1}. PMR (CDCl$_3$): δ 1.92 (3H s, Ac), 4.28 (1H d, *J*=8 Hz, H-1).

Found: C, 49.09; H, 7.73; N, 6.16%. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39%.

*Methyl 2-Acetamino-2,3-dideoxy-4,6-O-isopropylidene-β-*L*-ribo-hexopyranoside (**10**$_\mathrm{L}$).* To a solution of **9**$_\mathrm{L}$ (27 mg) in DMF (1 ml) were added 2,2-dimethoxypropane (0.1 ml), molecular sieves 5A, and a trace amount of *p*-toluenesulfonic acid and the solution was allowed to stand at 25 °C for 3 h. The solution showed, on being subjected to TLC with chloroform–methanol (5: 1), a single spot at R_f 0.42 (*cf.* **7**$_\mathrm{L}$: R_f 0.1). After addition of triethylamine (0.1 ml), the mixture was filtered and concentrated. The residue was purified by passing through a short column of silica gel with chloroform–methanol (15: 1) to give a syrup, which, on standing, crystallized into prisms, 30 mg (95%); mp 148—149 °C, $[\alpha]^{23}_\mathrm{D}$ +81° (*c* 1, methanol). PMR (CDCl$_3$): δ 1.41 and 1.50 (each 3H s, $C(CH_3)_2$), 1.54 (1H q, *J*=12 Hz, H-3$_\mathrm{ax}$), 1.99 (3H s, Ac), 2.36 (1H double t, *J*=≈4.5×2 and 12 Hz, H-3$_\mathrm{eq}$), 3.48 (3H s, OCH$_3$), 4.34 (1H d, *J*=8 Hz, H-1).

Found: C, 55.31; H, 7.97; N, 5.30%. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40%.

*2-Amino-2,3-dideoxy-*L*- and *D*-ribohexose (**1**$_\mathrm{L}$ and **1**$_\mathrm{D}$) Hydrochloride.* A solution of **8**$_\mathrm{L}$ (100 mg) in 1 M hydrochloric acid (2 ml) was heated at 110 °C for 2 h in the atmosphere of nitrogen in a sealed tube. Water (20 ml×2) was added to the reaction mixture which was then concentrated. To the concentrate (∼0.5 ml) were added methanol and acetone to give a syrup, which was dissolved in methanol and decolorized with charcoal. The solution was concentrated to give a residue which was recrystallized from methanol–acetone to give needles of **1**$_\mathrm{L}$ hydrochloride, 31 mg. Another crop (15 mg) was obtained from the mother liquor. Total yield was 72%, mp 150—160 °C (gradually decomposes), $[\alpha]^{23}_\mathrm{D}$ −49° (*c* 1, water, final value). R_f 0.30 (TLC with ethyl acetate–pyridine–acetic acid-water 5: 5: 1: 3) (*cf.* 2-amino-2-deoxy-L-glucose hydrochloride: R_f 0.27).

Found: C, 36.32; H, 6.94; N, 6.89; Cl, 17.81%. Calcd for $C_6H_{13}NO_4 \cdot HCl$: C, 36.10; H, 7.07; N, 7.02; Cl, 17.76%.

1$_\mathrm{D}$: $[\alpha]^{23}_\mathrm{D}$ +43° (*c* 0.3, water, final value) (lit,[8] +43.9° (water)).

*Methyl 4,6-Di-O-acetyl-2-amino-2-deoxy-β-*D*-glucopyranoside (**11**$_\mathrm{D}$).* A solution of **3**$_\mathrm{D}$ (1.83 g) in ethanol (200 ml) was kept at room temperature for 2 days. Concentration of the solution gave a residue, which was recrystallized from hexane–chloroform to give plates, 1.71 g (93%), mp 138—139 °C, $[\alpha]^{23}_\mathrm{D}$ −37° (*c* 1, methanol). PMR (CDCl$_3$): δ 2.08 and 2.13 (each 3H s, Ac), 2.35 (3H s, disappeared on deuteration, NH$_2$ and OH), 2.75 (1H q, *J*=8 and 10 Hz, H-2), 3.48 (1H t, *J*=10 Hz, H-3), 3.55 (3H s, OCH$_3$), 3.65 (1H m, H-5), 4.12 (1H d, *J*=8 Hz, H-1), 4—4.55 (2H double q, *J*=3, 4.5 and 12 Hz, H-6,6′), 4.87 (1H t, *J*=10 Hz, H-4). Irradiation of H-2 caused the signals of H-1 (δ 4.12) and H-3 (δ 3.48) to collapse to a singlet and a doublet, respectively, but the signals of H-4 (δ 4.87) remained unchanged.

Found: C, 47.35; H, 6.62; N, 4.76%. Calcd for $C_{11}H_{19}NO_7$: C, 47.65; H, 6.91; N, 5.05%.

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