Studies on Catalytic Hydrogenation of the Exocyclic Double Bond in Reducing Disaccharides

Hajime Goto, Masami Mori, and Setsuzo Tejima

Faculty of Pharmaceutical Sciences, Nagoya City University

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Effects of solvents and catalysts in catalytic hydrogenation of the exocyclic double bond in disaccharide-5-ene heptaacetate, synthesized from maltose, lactose, and cellulbiose, were investigated. A stereospecific hydrogenation proceeded in such a way that the corresponding 6-deoxy-1-ido isomer was predominant over the 6-deoxy-6-glucosyl-1-ido isomer. Preparations of 6-deoxy-maltose, 6-deoxy-α-cellulbiose, 4-O-α-D-glucopyranosyl-6-deoxy-1-idopyranose, and 4-O-β-D-glucopyranosyl-6-deoxy-1-idopyranose were also described.

Keywords—catalytic hydrogenation; maltose-5-ene heptaacetate; lactose-5-ene heptaacetate; cellulbiose-5-ene heptaacetate; 6-deoxy-maltose; 6-deoxy-α-cellulbiose; disaccharides having 6-deoxy-1-idopyranose

We reported previously that the exocyclic double bond in lactose-5-ene heptaacetate (8) was reduced as formation of the 6-deoxy-1-ido isomer (11) was predominant over the 6-deoxy-6-glucosyl isomer (5). Khan and Jenner showed subsequently that catalytic hydrogenation of sucrose-5-ene heptaacetate gave the 1-ido and the 6-glucosyl isomers in the yields of 45 and 10%, respectively. Except for the two papers, no paper has been reported on catalytic hydrogenation of the exocyclic double bond in disaccharides. Therefore, to clarify the mode of hydrogenation in disaccharide-5-ene heptaacetate, we reduced this compound under different conditions. In this paper, we report the results in full detail.

Authentic heptaacetyl-6-deoxy-β-maltose (4) or -lactose (5) was synthesized from the corresponding 6-deoxy-6-ido compound (1 or 2), respectively. Heptaacetyl-6-deoxy-β-cellulbiose (6) was prepared from heptaacetyl-6-deoxy-6-ido-β-cellulbiose (3). Disaccharide-5-ene heptaacetate (7, 8, or 9) was synthesized by stirring 1, 2, or 3 in dry pyridine with dry silver fluoride, respectively. In the preparation of 8, silver fluoride was added in twice and time of stirring was reduced to almost 1/3, which improved the yield.

1) Location: Tanabe-dori, Misuho-ku, Nagoya, 467, Japan.
Hydrogenation of 7, 8, or 9 afforded two products. They were separated from each other by column chromatography on silica gel. Elution of the mixture from the column with a definite solvent gave the α-gluco isomer (4, 5, or 6), and the structure was identified by comparison with an authentic sample. After elution of the α-gluco isomer was completed, the second crystal (10, 11, or 12) was eluted from the column with the same solvent. The product had the same elemental composition as the α-gluco isomer and, in the nuclear magnetic resonance (NMR) spectrum, the methyl protons at C-5 appeared at 1.40, 1.27, or 1.24 ppm as a doublet having J_{5,α} = 6.7, or 5 Hz, respectively. Therefore, 10, 11, or 12 was assigned to the corresponding l-ido isomer. In Table I the ratios of the l-ido isomer to the α-gluco isomer under different conditions were summarized.

**Table I. Ratio of 6-Deoxy-l-ido Isomer to 6-Deoxy-d-gluco Isomer**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>PtO₂₄</td>
<td>AcOEt</td>
<td>7.1</td>
<td>10.4</td>
<td>5.4</td>
</tr>
<tr>
<td>PtO₂₃</td>
<td>MeOH</td>
<td>9.2</td>
<td>5.4</td>
<td>10.7</td>
</tr>
<tr>
<td>PtO₂₃</td>
<td>Toluene</td>
<td>4.2</td>
<td>1.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Pd</td>
<td>AcOEt</td>
<td>1.7</td>
<td>11.0</td>
<td>7.2</td>
</tr>
<tr>
<td>Pd</td>
<td>MeOH</td>
<td>0.6</td>
<td>4.4</td>
<td>100.0</td>
</tr>
<tr>
<td>Pd</td>
<td>Toluene</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Raney Ni</td>
<td>AcOEt</td>
<td>3.1</td>
<td>9.8</td>
<td>9.5</td>
</tr>
<tr>
<td>Raney Ni</td>
<td>MeOH</td>
<td>4.2</td>
<td>4.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Raney Ni</td>
<td>Toluene</td>
<td>1.1</td>
<td>2.9</td>
<td>12.0</td>
</tr>
</tbody>
</table>

a) Maltose-5-ene heptaacetate.  
b) Lactose-5-ene heptaacetate.  
c) Cellobiose-5-ene heptaacetate.  
d) Hydrogenation proceeded very slowly and almost all of the starting material was recovered.

The results are briefly summarized as follows. 1) The l-ido isomers are always predominant under all conditions used besides one example: when maltose-5-ene heptaacetate (7) is hydrogenated in methanol over palladium, the α-gluco isomer (4) is predominant over the l-ido isomer (10), and the reason is not yet explicable. 2) Hydrogenation proceeds more stereospecifically in disaccharides having β-d-glycosidic linkage than α-d-glycosidic linkage.

Deacetylation of 4, 6, 10, and 12 afforded 6-deoxy-maltose (13), 6-deoxy-α-cellobiose (14), 4-O-α-d-glucopyranosyl-6-deoxy-l-idopyranose (15), and 4-O-β-d-glucopyranosyl-6-deoxy-l-idopyranose (16), respectively, in which only 14 crystallized. The other products were chromatographically homogeneous, amorphous powders.

![Chart 1](image-url)
Experimental

Melting points were uncorrected. Optical rotations were measured with a Yanagimoto OR-10 automatic polarimeter. Infrared (IR) spectra were recorded with a Jasco Model IR-S spectrometer. NMR spectra were recorded at 100 MHz with a Jeol Model JNM-MH-100 spectrometer for solution in CDCl₃ (internal Me₄Si). Chemical shifts were given on the ppm scale. Thin-layer chromatography (TLC) with the multiple (twice) ascending method on pre-coated Silica Gel 60 (E. Merck, Darmstadt, Germany) was performed with solvent combination (v:v): (A), ether–benzene (1:2), (B), hexane–AcOEt (2:3), (C), benzene–ether (1:2). Detection was effected with H₂SO₄. Paper partition chromatography (PPC) was performed by the ascending method with solvent combination (v:v): (D), BuOH–pyridine–H₂O (6:4:3), (E), AcOEt–AcOH–H₂O (3:3:1), (F), BuOH–EtOH–H₂O (40:11:19), and detection was effected with alkaline silver nitrate.⁶

**Heptaacetyl-6-deoxy-β-cellobiose (6)**—Compound 3⁹ (150 mg) was dissolved in AcOEt (10 ml) containing pyridine (10 drops), and the suspension was shaken with H₂ in the presence of freshly prepared Raney Ni catalyst at room temperature under atmospheric pressure: the catalyst was prepared⁷ from 2 g of alloy. After removal of the catalyst by filtration, the filtrate was concentrated to dryness. The residue was dissolved in CH₂Cl₂ (20 ml), washed with 10% Na₂S₂O₃ and H₂O (dried, CaCl₂), and the solution was evaporated to give a sirup which crystallized from EtOH. Recrystallization from EtOH gave pure 6 (100 mg, 80%), mp 209—212⁰, [α]D²⁵ = 25.3⁰ (c = 1, CHCl₃). TLC: RF 0.89 (solvent B), NMR δ: 1.33 (3H, d, J₅,₆ = 5 Hz, C–CH₃), 2.01, 2.08 (21H, each s, 7 × OAc). Anal. Calcd. for C₅₈H₃₉O₁₇: C, 50.32; H, 5.85. Found: C, 50.35; H, 5.82.

1,2,3-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-a-D-glucopyranosyl)-β-D-xyl-o-hex-5-eno-pyranose (Maltose 5-ene Heptaacetate) (7)—Dry silver fluoride (0.2 g) (completely dried over H₂SO₄ beforehand) was added to a solution of 1 (1 g) in dry pyridine (10 ml) and the suspension was stirred, with exclusion of light, at room temperature. After 6 hr another portion of silver fluoride (0.2 g) was added, and the stirring was continued for further 2 hr. The mixture was diluted with CH₂Cl₂ (50 ml), poured into ice–H₂O (100 ml), filtered, and the filtrate was successively washed with 10% H₂SO₄, satd. NaHCO₃, and H₂O. After desiccation (CaCl₂), the solvant was removed to afford a sirup which crystallized from EtOH. Recrystallization from EtOH gave pure 7 (613 mg, 74%), mp 129—131.5⁰, [α]D³⁵ = +64.4⁰ (c = 0.5, CHCl₃). TLC: RF 0.24 (solvent A). IR νmax: 1664 cm⁻¹ (C=C). Anal. Calcd. for C₅₉H₄₇O₁₇: C, 50.49; H, 5.34. Found: C, 50.50; H, 5.39.

1,2,3-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-a-D-galactopyranosyl)-β-D-xyl-o-hex-5-eno-pyranose (Lactose 5-ene Heptaacetate) (8)—Treatment of 2⁸ (800 mg) as for 7 afforded 8 (504 mg, 76%), mp 166—168⁰, [α]D²⁵ = 59.1⁰ (c = 0.99, CHCl₃) (lit.¹⁰ mp 168—169⁰, [α]D²⁵ = 57.7⁰ (c = 1.04, CHCl₃)).

1,2,3-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-a-D-glucopyranosyl)-β-D-xyl-o-hex-5-eno-pyranose (Cellobiose 5-ene Heptaacetate) (9)—Treatment of 3⁹ (1 g) as for 7 afforded 9 (640 mg, 82%), mp 113—116⁰, [α]D²⁵ = 70⁰ (c = 0.08, CHCl₃). TLC: RF 0.90 (solvent B). IR νmax: 1663 cm⁻¹ (C=C). Anal. Calcd. for C₅₇H₄₅O₁₆: C, 50.49; H, 5.54. Found: C₅₇H₄₅O₁₆: C, 50.32; H, 5.36.

**Catalytic Hydrogenation of Disaccharide 5-ene Heptaacetate**—To a solution of compound (100 mg of 7, 8, or 9) in solvent (10 ml) was added catalyst: commercial Adams' catalyst having 1—3 mol of H₂ (100 mg), freshly prepared Pd catalyst by reduction⁴ of PdCl₂ (150 mg) in the same solvent, or Raney Ni catalyst® from alloy (2 g) was used. The mixture was hydrogenated at room temperature under atmospheric pressure. The catalyst was removed by filtration and the solvent was evaporated to dryness. The residue was chromatographed on a column of silica gel, in which solvent combination (v:v), ether–benzene (1:2), benzene–ether (1:2), or hexane–AcOEt (2:3), was used as eluent of 7, 8, or 9, respectively. The lido isomer (10, 11, or 12) was eluted with the same solvent after elution of the n-glucos isomer (4, 5, or 6) was completed. The corresponding cluate was evaporated to dryness which crystallized on adding EtOH.

1,2,3-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-a-D-glucopyranosyl)-6-deoxy-a-D-idopyranose (10)—mp 158—159.5⁰. [α]D²⁵ = +28.6⁰ (c = 0.64, CHCl₃). TLC: RF 0.18 (solvent A). NMR δ: 1.40 (3H, d, J₅,₆ = 6 Hz, C–CH₃), 2.00, 2.04, 2.08, 2.10, 2.12 (21H, each s, 7 × OAc). Anal. Calcd. for C₅₈H₃₉O₁₃: C, 50.32; H, 5.85. Found: C, 50.26; H, 5.75.

1,2,3-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-a-D-glucopyranosyl)-6-deoxy-a-D-idopyranose (12)—mp 142—144⁰. [α]D²⁵ = −60.3⁰ (c = 0.82, CHCl₃). TLC: RF 0.77 (solvent B). NMR δ: 1.24 (3H, d, J₅,₆ = 5 Hz, C–CH₃), 1.98, 2.00, 2.06, 2.08, 2.10 (21H, each s, 7 × OAc). Anal. Calcd. for C₅₈H₃₉O₁₃: C, 50.32; H, 5.85. Found: C, 50.16; H, 5.76.

6-Deoxy-maltose (13)—To a solution of 4 (165 mg) in dry MeOH (3 ml) was added 0.1 N methanolic sodium methoxide (0.14 ml). The mixture was stirred for 3 hr; complete deacetylation was monitored by

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TLC. Dry Amberlite IR-120 (H+ *) resin was added and the suspension was stirred for 30 min, filtered, and the filtrate was concentrated to dryness to give an amorphous powder (60 mg, 60%). [x]D +126.3° (c = 0.66, H2O). PPC: Rf 0.43 (solvent D), 0.25 (solvent E), 0.29 (solvent F). Anal. Calcd. for C18H21O10·2H2O: C, 39.77; H, 7.23. Found: C, 39.64; H, 7.03.

6-Deoxy-α-cellobiose (14)—Decacylation of 6 (630 mg) as for 13 afforded 14 (300 mg, 91%). After recrystallization from MeOH, 15 showed mp 242–245° (dec.) and [x]D +30° → +25.5° (5 hr) (c = 1, H2O). PPC: Rf 0.38 (solvent D), 0.27 (solvent E), 0.23 (solvent F). Anal. Calcd. for C18H21O10: C, 44.17; H, 6.80. Found: C, 43.74; H, 6.96.

4-O-α-D-Glucopyranosyl-6-deoxy-l-idopyranose (15)—Decacylation of 10 (330 mg) as for 13 afforded 15 (121 mg, 70%), amorphous powder, [x]D +91.2° (c = 0.62, H2O). PPC: Rf 0.42 (solvent D), 0.28 (solvent E), 0.32 (solvent F). Anal. Calcd. for C12H14O10·2H2O: C, 39.77; H, 7.23. Found: C, 39.48; H, 7.18.

4-O-β-D-Glucopyranosyl-6-deoxy-l-idopyranose (16)—Decacylation of 12 (128 mg) afforded 16 (67 mg, 99%), amorphous powder, [x]D +28.7° (c = 0.65, H2O). PPC: Rf 0.39 (solvent D), 0.24 (solvent E), 0.30 (solvent F). Anal. Calcd. for C12H14O10·2H2O: C, 39.77; H, 7.23. Found: C, 39.85; H, 7.13.

Purines. XX.1) Synthesis of 1-Substituted 5-Aminimidazole-4-carboxamides and Related Compounds2)

TOZO FUJII, TAISUKE ITAYA, TOHRU SAITO, and MITSURU KAWANISHI

Faculty of Pharmaceutical Sciences, Kanazawa University3)

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Several 1-substituted 5-aminimidazole-4-carboxamides (5g−j) have been prepared from the corresponding N'-alkoxyamidines (4a−f) by catalytic hydrogenolysis. In the hydrogenolysis of 4a−f using Raney Ni catalyst, addition of one molar equivalent of hydrochloric acid accelerated the reaction to give 5g−j in acceptable yields. The structures of 5g−j have been confirmed by cyclization to 2-substituted adenines (6g−j) and by alkaline hydrogenolysis to 1-substituted derivatives (7g−j) of 5-aminimidazole-4-carboxamide (AICA).

Keywords—imidazoles; adenines; alkoxyamidine; amidoxime; catalytic hydrogenolysis; Raney nickel catalyst; palladium-on-carbon; cyclization; hydrogenolysis

In previous papers4) from this laboratory, we have already shown that the pyrimidine ring of 1-alkoxyadenines (type 1) is easily opened under mild hydrolytic conditions to produce imidazole derivatives (types 2 and 4), and that the formamido derivatives (type 2) cyclize readily to N8-alkoxyadenines (type 3). The synthetic utility of this ring opening reaction

3) Location: 13-1 Takara-machi, Kanazawa 920, Japan.