[Contribution from Biochemical Laboratory, College of Agriculture, Kyoto University]

Debenzyloxycarbonylation of 1,3,4,6-Tetra-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-D-hexopyranoses in the Conversion of α,β-Acetoxy to Glycosyl Bromide

KONOSHIN ONODERA AND TOHRU KOMANO

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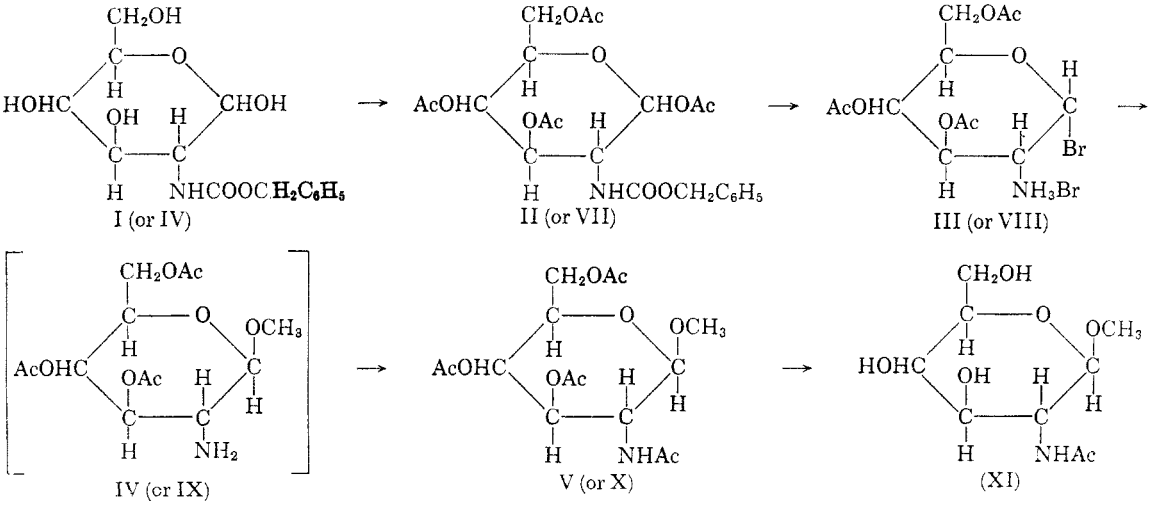
Substitution of bromide for acetoxy at the C-1 position of α,β-1,3,4,6-tetra-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-D-glucose or -D-galactose takes place with acetic anhydride and hydrogen bromide to yield the respective 1-α-bromo-3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-D-hexose hydrobromides. Concurrent debenzyloxycarbonylation accounts for the removal of the acyl radical bonded to nitrogen. When the 1-α-bromo products were treated with methanol and silver oxide, in a chloroform solution, and then with acetic anhydride, the corresponding methyl 3,4,6-tri-*O*-acetyl-2-acetylamino-2-deoxy-β-D-hexopyranosides were formed.

The Königs-Knorr reaction[1] is widely used for the synthesis of β-glycosides including those of 2-acetylamino-2-deoxy-D-hexoses.[2,3] In the latter case, however, an acetyl migration[3,4] was observed to occur under wet conditions with 1-α-halogeno-3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-D-glucose, which undergoes no acetyl migration under anhydrous conditions.

Methyl 2-benzyloxycarbonylamino-2-deoxy-β-D-glucoside has been synthesized by refluxing 2-benzyloxycarbonylamino-2-deoxy-D-glucose (I) in 0.7% methanolic hydrogen chloride which gave a very low yield of the substance[5,6] because of contamination with the α-form.



The methyl β-glycoside was supposed to be synthesized by the Königs-Knorr reaction. However, Weidmann and Zimmerman[7] reported that 1 - α - bromo - 3,4,6 - tri - *O* - benzoyl - 2 - amino-2-deoxy-D-glucose hydrobromide was obtained from α,β - 1,3,4,6 - tetra - *O* - benzoyl - 2 - benzyloxycarbonylamino-2-deoxy-D-glucose by the reaction with acetic acid and hydrogen bromide.

In our experiments α,β-1,3,4,6-tetra-*O*-acetyl-2-benzyloxycarbonylamino - 2 - deoxy - D - glucose (II) or -D-galactose (VII) was treated with acetic acid and hydrogen bromide for one hour, and a vigorous evolution of carbon dioxide was observed. The reaction mixture was shaken occasionally and then a large amount of ether was added to precipitate fine needles. The analysis of the compound revealed that it was the corresponding 1 - α - bromo - 3,4,6 - tri - *O* - acetyl - 2 - amino - 2-deoxy-D-hexose hydrobromide (III or VIII).

In order to confirm this reaction, the resulting compound (III or VIII) was treated in a chloroform solution with methanol and silver oxide. The reaction mixture gave methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside (IV) (or -D-galactopyranoside (IX)), which was then treated

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with acetic anhydride at 100° for fifteen minutes to produce methyl 3,4,6-tri-*O*-acetyl-2-acetylamino-2-deoxy-β-D-glucopyranoside (V) (or -D-galactopyranoside (X)). V was identical with an authentic sample and X showed the same constants as those reported in the literature.[8] Deacetylation of X with sodium methoxide gave methyl 2-acetylamino-2-deoxy-β-D-galactopyranoside (XI).

The above reactions indicate that α,β-1,3,4,6-tetra - *O* - acetyl - 2 - benzyloxycarbonylamino-2-deoxy-D-hexoses were converted by the treatment with acetic acid and hydrogen bromide into 1-α-bromo-3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-D-hexose hydrobromides with concurrent evolution of carbon dioxide and formation of benzylbromide.

EXPERIMENTAL[9]

2-Benzyloxycarbonylamino-2-deoxy-D-glucose (I). 2-Amino-2-deoxy-D-glucose hydrochloride (107.6 g.) dissolved in water (500 ml.) was treated in the usual procedure with sodium hydroxide (50 g.) and benzyl chloroformate[10] (124 g.). Two recrystallizations from methanol-water afforded white crystals (I), melting at 214°; yield, 164 g. (95%).

Anal. Calcd. for $C_{14}H_{19}O_7N$: C, 53.67; H, 6.11, N, 4.47. Found: C, 53.44; H, 6.30; N, 4.28.

α,β - 1,3,4,6 - Tetra - O - acetyl - 2 - benzyloxycarbonylamino - 2 - deoxy - D - glucose[11] (II). I (10 g.) was dissolved in pyridine (50 ml.) and to this was added dropwise with cooling acetic anhydride (50 ml.). The reaction mixture was kept at room temperature for 20 hr. and then was added to 1 l. of ice water.

The precipitated sirupy substance was washed thoroughly with water and extracted with chloroform, which was washed with a saturated aqueous sodium bicarbonate solution, and then with 1*N* hydrochloric acid. The dried chloroform solution upon evaporation gave a sirup which was dried over phosphorus pentoxide; yield, 12.2 g. (80%). This substance was considered to be the mixture of α- and β-form, and could be obtained in a low yield in crystalline form by repeated recrystallizations from ethanol, m.p. 148°.

1 - α - Bromo - 3,4,6 - tri - O - acetyl - 2 - amino - 2 - deoxy-D-glucose hydrobromide[12] (III). II (5 g.) was dissolved in 100 ml. of acetic acid saturated with dry hydrogen bromide. The reaction mixture was kept at room temperature for 24 hr. with exclusion of moisture and was often shaken vigorously.

When the reaction was over, the reaction mixture became yellowish red, and fine needles separated. After standing for 20 hr., a large amount of ether was added and the mixture was cooled with ice. The crystals were collected on a glass filter, washed with ether until the washings became negative for bromide ion, and were dissolved in hot ethanol. The solution was decolorized and placed in a refrigerator. Fine needles were obtained, yield, 3.6 g. (66%), m.p. 150° dec., $[\alpha]_D^{20}$ +151° (*c*, 1 ethyl acetate).

Anal. Calcd. for $C_{12}H_{19}O_7NBr_2$; C, 32.09; H, 4.26; N, 3.12. Found: C, 31.75; H, 4.69; N, 3.11.

Reported m.p., 149–150° dec., $[\alpha]_D$ +152.8° (*c*, 1.096 ethyl acetate).

Methyl 3,4,6-tri-O-acetyl-2-amino-2-deoxy-β-D-glucopyranoside (IV). III (1.5 g.) was dissolved in chloroform, and to this were added methanol (1 ml.), silver oxide (2 g.), and a small amount of anhydrous sodium sulfate. After stirring for 6 hr., the reaction mixture was filtered and the filtrate was decolorized. Silver oxide remained in the solution which was removed with hydrogen sulfide. The resulting methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside (IV) was a sirupy substance.

Methyl 3,4,6-tri-O-acetyl-2-acetylamino-2-deoxy-β-D-glucopyranoside (V). IV was dissolved in chloroform and 1.5 moles of acetic anhydride was added, and the solution was refluxed for 30 min. The solution was washed twice with a saturated aqueous sodium bicarbonate solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure to dryness. The residue was dissolved in a small amount of methanol and the solution was decolorized, and to this was added a large amount of ether which precipitated crystalline substance. Recrystallization was effected from methanol-ether, m.p. 160°, $[\alpha]_D^{20}$ −24° (*c*, 1 chloroform). Yield, 0.72 g. (60% based on III).

Anal. Calcd. for $C_{15}H_{23}O_9N$: C, 49.86; H, 6.42; N, 3.88. Found: C, 50.15; H, 6.42; N, 4.06.

Admixture with the compound prepared from 1-α-bromo-3,4,6-tri-*O*-acetyl-2-acetylamino-2-deoxy-D-glucose showed no depression of the melting point.

2 - Benzyloxycarbonylamino - 2 - deoxy - D - galactose (VI). VI was prepared from 2-amino-2-deoxy-D-galactose hydrochloride (5 g.) by a similar procedure as described for I. Recrystallization from methanol-water gave fine needles, yield, 5.9 g. (80%), m.p. 183°.

Anal. Calcd. for $C_{14}H_{19}O_7N$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.46; H, 6.16; N, 4.75.

α,β - 1,3,4,6 - Tetra - O - acetyl - 2 - benzyloxycarbonylamino-2-deoxy-D-galactose (VII). Acetylation of VI (2 g.) was carried out with acetic anhydride and pyridine. Repeated recrystallizations from ethanol gave crystals, melting at 115°; yield, 1.6 g. (51%).

Anal. Calcd. for $C_{22}H_{29}O_{10}N$: C, 56.53; H, 6.21; N, 3.00. Found: C, 56.38; H, 6.27; N, 3.20.

1 - α - Bromo - 3,4,6 - tri - O - acetyl - 2 - amino - 2 - deoxy-D-galactose hydrobromide (VIII). VIII was prepared from VII (500 mg.) by a similar procedure as described for III. VIII was unstable in moist air and turned fairly fast to a reddish-colored sirup. The crude substance which melted at 161° dec. was dried *in vacuo* over phosphorus pentoxide.

Methyl 3,4,6-tri-O-acetyl-2-amino-2-deoxy-β-D-galactopyranoside (IX). This compound was prepared from the above dried substance (VIII) by a similar procedure as described for IV. The product was hygroscopic, dried over phosphorus pentoxide, and used as such in the next reaction.

Methyl 3,4,6-tri-O-acetyl-2-acetylamino-2-deoxy-β-D-galactopyranoside (X). X was prepared from IX by a similar procedure as described for V. Yield, 85 mg. (19.7% based on VII), m.p. 215°.

Anal. Calcd. for $C_{15}H_{23}O_9N$: N, 3.88. Found: N, 3.94. The reported melting point is 216–217°.[8]

Methyl 2-acetylamino-2-deoxy-β-D-galactopyranoside (XI). Deacetylation of X (50 mg.) was performed with 0.5*N* sodium methoxide at room temperature for 20 hr. The reaction mixture was concentrated under reduced pressure and to this was added a large amount of ether. Upon standing in a refrigerator crystals separated. Yield, 22 mg. (70%), m.p. 191°, $[\alpha]_D^{31}$ −13.5° (*c*, 0.7 methanol).

Anal. Calcd. for $C_9H_{17}O_6N$: N, 5.96. Found: N, 6.04.

Reported m.p., 191–192° and $[\alpha]_D^{23}$ −12° (*c*, 1.05 methanol).[8]

KYOTO, JAPAN

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(9) All melting points are uncorrected.

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