Studies on Antibiotics and Related Substances. XV. Syntheses of Acetobromo Derivatives of 3-Amino-3-deoxyglucose and 6-Amino-6-deoxyglucose[1]

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Acetohalogeno derivatives of sugars are important intermediates used for the synthesis of glycosides, however, the corresponding derivatives of aminosugars represent a relatively unexplored territory. In the course of our studies on the synthesis of glycosides relating to carbohydrate-antibiotics, such as kanamycin and paromomycin, a program was instituted toward the synthesis of acetobromo derivatives of aminosugars. The synthesis of 2, 4, 6-tri-*O*-acetyl-3-amino-α-1-bromo-1, 3-dideoxy-D-glucopyranose (III), 2, 3, 4-tri-*O*-acetyl-6-amino-α-1-bromo-1, 6-dideoxy-D-glucopyranose (VII) and their derivatives is the subject of this paper.

The synthesis of III and their derivatives is outlined in the following Chart A:

Methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-glucopyranoside (I) was synthesized by a modification of the route described by Peat and Wiggins[2]. When this route was followed, the yield of α-anomer of methyl 2, 4, 6-tri-*O*-acetyl-3-*O*-(*p*-toluene-sulfonyl)-D-glucoside was found to be too low to make progress in further synthesis. The difficulty has been overcome by the transformation of β-anomer to α-anomer by a modification of the method described by Ohle and Wilcke[3]. It has been found that treatment with titanium tetrachloride in chloroform transformed the β- to α-anomer in 91% yield. It has also been found that isopropanol is an appropriate solvent for the crystallization of α-anomer resulting in a

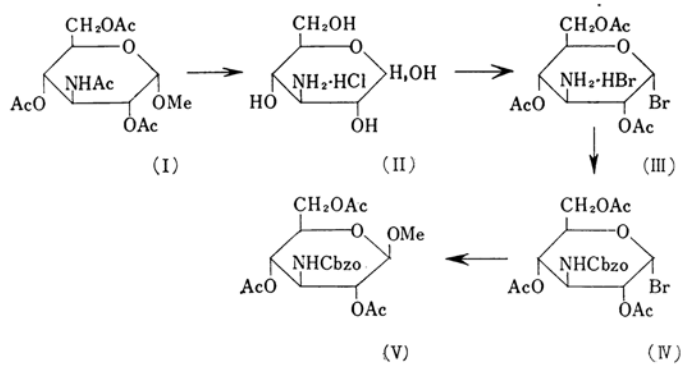

Chart A

1) Presented at the Division of Organic Chemistry of the 15th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1962.

2) S. Peat and L. F. Wiggins, *J. Chem. Soc.*, 1938, 1092, 1810.

3) H. Ohle and H. Wilcke, *Ber.*, 71, 2327 (1938).

relatively good yield (28.9%)[4]. Thus the total yield of α-anomer has been raised to 62.5%. The α-anomer has been subjected to ammonolysis by methanolic ammonia in an autoclave at 150°C, followed by acetylation, to give methyl 3-amino-3-deoxy-α-D-glucoside tetraacetate (I) by the method of Peat and Wiggins. Attempts have been made to effect ammonolysis of β-anomer by analogous procedure, followed by acetylation, but these have not been successful.

3-Amino-3-deoxy-D-glucose has been obtained by hydrolysis of the above tetraacetate. Acid hydrolysis studies revealed optimum conditions, namely, refluxing in 6 N hydrochloric acid for three hours, whereby 79.2% of the tetraacetate has been converted to 3-amino-3-deoxy-D-glucopyranose hydrochloride (II).

When treated with acetyl bromide at room temperature for three hours, 3-amino-3-deoxy-D-glucopyranose hydrochloride gave 2, 4, 6-tri-*O*-acetyl-3-amino-α-1-bromo-1, 3-dideoxy-D-glucopyranose hydrobromide (III) in a 96.2% yield.

Masking of the amino group of III with the carbobenzoxy group by treatment with carbobenzoxy chloride in potassium bicarbonate solution gave 2,4,6-tri-*O*-acetyl-α-1-bromo-3-carbobenzoxyamino-1, 3-dideoxy-D-glucopyranose (IV) in a 53.2% yield.

An attempt to prepare a glycoside from IV proved to be practical. When shaken with methanol in the presence of mercuric cyanide by Koenigs-Knorr reaction, methyl 2, 4, 6-tri-*O*-acetyl-3-carbobenzoxyamino-3-deoxy-β-D-glucopyranoside (V) has been obtained in a 77.4% yield.

Synthesis of 2, 3, 4-tri-*O*-acetyl-6-amino-α-1-bromo-1, 6-dideoxy-D-glucopyranose (VII) and their derivatives is outlined in the following Chart B:

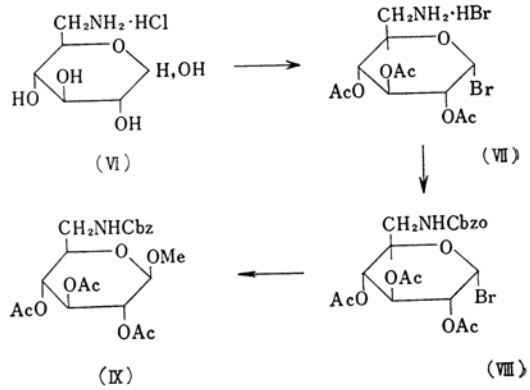

Chart B

6-Amino-6-deoxy-D-glucopyranose hydrochloride (VI) was synthesized from tetra-*O*-acetyl-α-D-glucopyranosyl bromide via benzylglucoside-derivatives by the route described by Cramer et al.[5] Reaction of VI with acetyl bromide at room temperature for seventy-four hours yielded 2,3,4-tri-*O*-acetyl-α-1-bromo-1,6-dideoxy-D-glucopyranose hydrobromide (VII), m. p. 162~164°C (decomp.), in a 96.3% yield. It should be noted that VII is almost insoluble in chloroform and other common organic solvents, while the corresponding derivative III is soluble in chloroform.

When a suspension of VII in chloroform was shaken with carbobenzoxy chloride in the presence of a saturated solution of potassium bicarbonate at 0°C for twenty minutes, the reaction product dissolved in chloroform-layer, from which 2, 3, 4-tri-*O*-acetyl-α-1-bromo-6-carbobenzoxyamino-1, 6-dideoxy-D-glucopyranose (VIII) was obtained in a 76% yield. When subjected to Koenigs-Knorr reaction, using

Table I

Compound	Specific rotation	IR absorption, cm^{-1}
III	$[\alpha]_D^{15}$ +127.5° (*c* 1.77, $CHCl_3$)	undetectable
VII	—	843 (weak)
IV	$[\alpha]_D^{15}$ +131.6° (*c* 1.77, $CHCl_3$)	847
VIII	$[\alpha]_D^{17}$ +156° (*c* 1.62, $CHCl_3$)	833
V	$[\alpha]_D^{12}$ −19.6° (*c* 1.77, $CHCl_3$)	885
IX	$[\alpha]_D^{15}$ +4.5° (*c* 2.00, $CHCl_3$)	900
2ABG*	$[\alpha]_D^{19}$ +148° (*c* 0.84, CH_3COCH_3)[6]	—
2ABCG**	$[\alpha]_D$ +146.5° (*c* 1.6, $CHCl_3$)[7]	845
2MACG***	$[\alpha]_D$ +17° (*c* 3.4, $CHCl_3$)[7]	—

* 3,4,6-Tri-*O*-acetyl-2-amino-α-1-bromo-2-deoxy-D-glucopyranose hydrobromide
** 3,4,6-Tri-*O*-acetyl-α-1-bromo-2-carbobenzoxyamino-1,2-dideoxy-D-glucopyranose
*** Methyl 3,4,6-tri-*O*-acetyl-2-carbobenzoxyamino-2-deoxy-β-D-glucoside

4) Yield reported by Peat and Wiggins, loc. cit., was 19.4%.
5) F. Cramer, O. Otterbach and H. Springman, *Chem. Ber.*, **92**, 384 (1959).
6) W. O. Cutler, W. N. Haworth and S. Peat, *J. Chem. Soc.*, 1937, 1979.
7) L. Zervas and S. Konstas, *Chem. Ber.*, **93**, 435 (1960).

mercuric cyanide as a catalyst, VIII gave methyl 2,3,4-tri-*O*-acetyl-6-carbobenzoxyamino-6-deoxy-α-D-glucopyranoside (IX) in a 61.2% yield. The same reaction using silver carbonate-calcium sulfate as a catalyst gave the same product IX in a 57% yield.

Infrared spectra of the acetobromo derivatives (IV, VII, VIII) showed absorptions near 840 cm^{-1} which is characteristic of α-configuration, while the methylglucosides (V, IX) prepared from IV and VIII showed absorptions near 890 cm^{-1}, indicating that the methylglycosides have a β-configuration, as anticipated from the usual results of the Koenigs-Knorr reaction. Moreover, values of specific rotation of the above-mentioned derivatives are consistent with the spectroscopic results, as shown in Table I, where these data are shown together with those of the corresponding derivatives of 2-amino-2-deoxy-D-glucose.

Experimental

Methyl 2,4,6-Tri-*O*-acetyl-3-*O*-(*p*-toluenesulfonyl)-α-D-glucoside. — A solution of 84 g. of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-toluenesulfonyl)-α-D-glucofuranose[8] in 650 g. of 2% methanolic hydrogen chloride was refluxed for 15 hr. on a steam bath. After being cooled, the reaction mixture was neutralized with basic lead carbonate, filtered and the filtrate was evaporated under reduced pressure to give a yellowish syrup. A mixture of the syrup, 67 g. of anhydrous sodium acetate and 335 ml. of acetic anhydride was heated at 110°C for 3 hr. The reaction mixture was cooled and then poured into 500 g. of ice-water, followed by stirring for 30 min. The resulting mixture was extracted with six 100 ml. portions of chloroform. The chloroform extracts were combined, washed with a saturated solution of sodium carbonate, and then with water thoroughly to give a neutral chloroform-solution, which was dried over sodium sulfate and filtered. Evaporation of the filtrate at 55°C under reduced pressure gave a reddish-brown syrup, which was crystallized from 100 ml. of ether to give 32.2 g. of methyl 2,4,6-tri-*O*-acetyl-3-*O*-(*p*-toluenesulfonyl)-β-D-glucopyranoside, m. p. 126.9~130°C., yield 33.6%.

The mother liquor separated from the above-mentioned β-anomer was evaporated to dryness to give a syrup. When dissolved in 35 ml. of hot isopropanol and allowed to stand, the syrup gave the corresponding α-anomer, the title compound, m. p. 94~95°C, yield 27.8 g. (28.9%). The crude product was used for amination. Peat and Wiggins[2] reported m. p. 97°C, $[\alpha]_D^{16}+87.1°$ ($CHCl_3$) and 19.4% yield.

Transformation of Methyl 2,4,6-Tri-*O*-acetyl-3-*O*-(*p*-toluenesulfonyl)-β-D-glucoside to its α-Anomer. —The transformation was effected by a modified method of Ohle and Wilcke[3] as follows: To a solution of 10 g. of methyl 2,4,6-tri-*O*-acetyl-3-*O*-(*p*-toluenesulfonyl)-β-D-glucoside in 120 g. of dry chloroform was added a solution of 5 g. of titanium tetrachloride in 80 g. of dry chloroform and the mixture was refluxed on a water bath for 75 min. After being cooled, the reaction mixture was poured into 200 g. of ice-water and shaken vigorously. The chloroform-layer was separated and the aqueous layer was extracted with three 10 ml. portions of chloroform. The chloroform extracts were combined, washed with water and dried over sodium sulfate. After being filtered, the chloroform solution was evaporated to dryness under reduced pressure. The resulting brown syrup was dissolved in 5 ml. of hot isopropanol and allowed to stand in the refrigerator to give a crystalline solid of methyl 2,4,6-tri-*O*-acetyl-3-*O*-(*p*-toluenesulfonyl)-α-D-glucopyranoside, m. p. 96.8~97.4°C, $[\alpha]_D^{20.7}+89°$ (*c* 2.0, $CHCl_3$), yield 9.1 g. (91%). Mixed melting point of the product with the above-described α-anomer showed no depression. The product was also used for amination.

3-Amino-3-deoxy-D-glucopyranose Hydrochloride (II).—A solution of 4.0 g. of methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-glucoside[9] in 80 ml. of 6 N hydrochloric acid was heated on a steam bath for 3.5 hr. The reaction mixture was evaporated to dryness at 50°C in vacuo. The residue was dissolved in 2 ml. of methanol and evaporated again to dryness. The evaporation to remove water was repeated seven times to give a pale-yellow spongy residue. The residue was dissolved in 60 ml. of warm methanol, neutralized with silver carbonate and shaken with 1 g. of decolorizing charcoal for 30 min., followed by filtration. The filtrate was evaporated to dryness in vacuo at about 50°C to give 2.4 g. of a spongy residue. The residue was dissolved in 15 ml. of warm methanol, added dropwise with isopropanol until the solution became somewhat turbid and the mixture was allowed to stand in a refrigerator to give a hygroscopic powder of 3-amino-3-deoxy-D-glucopyranose hydrochloride, yield 1.2 g. (79.2%).

Found: C, 33.37; H, 6.96; N, 6.76. Calcd. for $C_6H_{13}NO_5 \cdot HCl$ (215.6): C, 33.42; H, 6.54; N, 6.50%.

Paperchromatography of the product showed a single spot by ninhydrin coloration and gave the same R_f value with that of a natural specimen which was obtained from the hydrolyzate of kanamycin.

2,4,6-Tri-*O*-acetyl-3-amino-α-1-bromo-1,3-dideoxy-D-glucopyranose Hydrobromide (III).—A mixture of 2.27 g. of 3-amino-3-deoxy-D-glucopyranose hydrochloride (II) and 10 g. of freshly distilled acetyl bromide was allowed to stand for 3 hr. at room temperature with frequent shaking. The resulting solution was subjected to distillation in vacuo to remove unchanged acetyl bromide and the residue was dried in a brown vacuum-desiccator over sodium hydroxide overnight. The residue was dissolved in 25 ml. of hot chloroform, added with 1 g. of decolorizing charcoal and refluxed for 15 min. After the mixture was filtered, 100 ml. of absolute ether was added to the solution and the mixture was allowed to stand in a refrigerator overnight to

8) K. Freundenberg and O. Ivers, *Ber.*, 55, 929 (1922).

9) S. Peat and L. F. Wiggins, *J. Chem. Soc.*, 1938, 1810

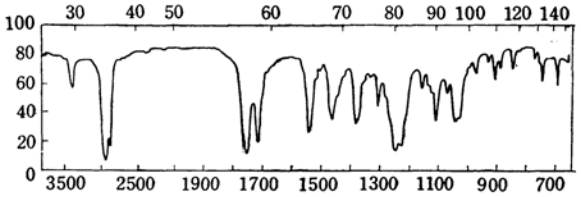

Fig. 1. Infrared spectrum of 2,4,6-tri-*O*-acetyl-α-1-bromo-3-carbobenzoxyamino-1,3-dideoxy-D-glucopyranose (IV) in Nujol.

to precipitate colorless powdery 2,4,6-tri-*O*-acetyl-3-amino-α-1-bromo-1,3-dideoxy-D-glucopyranose hydrobromide (III). The mother liquor was concentrated and added with absolute ether to obtain a second crop. The total yield was 4.56 g. (96.2%). The first crop showed m. p. 131~135°C, $[\alpha]_D^{15}$ +127.5° (*c* 1.77, $CHCl_3$).

Found: C, 31.30; H, 4.19; N, 3.38. Calcd. for $C_{12}H_{19}O_7NBr_2$ (449.1): C, 32.09; H, 4.26; N, 3.12%.

The infrared spectrum of the product in potassium bromide shows absorption bands at 3225 (νNH), 1759, (νC=O in OAc), 1593 (δNH_3^+), and 1219 (νC-O in OAc).

2, 4, 6-Tri-*O*-acetyl-α-1-bromo-3-carbobenzoxyamino-1, 3-dideoxy-D-glucopyranose (IV).—A mixture of the first and second crops of 2,4,6-tri-*O*-acetyl-3-amino-α-1-bromo-1,3-dideoxy-D-glucopyranose (III) was used for the following preparation: A mixture of 4.36 g. of III, 3 ml. of carbobenzoxy chloride (purity 58.5%), 77 ml. of chloroform and 41 ml. of saturated solution of potassium bicarbonate was stirred vigorously at −5°C for 20 min. The chloroform layer was separated and the aqueous layer was extracted with three 5 ml. portions of chloroform. The chloroform extracts were combined, washed three tmies with each 5 ml. of water and dried over 10 g. of sodium sulfate for 3 hr. The filtrate was concentrated under reduced pressure to yield a residue of colorless crystals of 2,4,6-tri-*O*-acetyl-α-1-bromo-3-carbobenzoxyamino-1,3-dideoxy-D-glucopyranose. To the residue was added 30 ml. of ether, allowed to stand overnight and then filtered; m. p. 146~148°C (decomp.), $[\alpha]_D^{10}$ +131.6° (*c* 1.77, $CHCl_3$), yield 2.59 g. (53.2%).

Found: C, 47.90; H, 4.64; N, 3.03; Br, 15.67. Calcd. for $C_{20}H_{24}O_9NBr$ (502.3): C, 47.82; H, 4.81; N, 2.79; Br, 15.91%.

The infrared spectrum of the product in Nujol shows absorption bands at 3383, (νNH), 1753 (νC=O in OAc), 1714 (νC=O in Cbzo), 1540 (δNH), 1244, 1225 (νC-O in OAc), 848 (type 2a of pyranose ring) and 776, 748, 698 (phenyl) (Fig. 1).

Methyl 2,4,6-Tri-*O*-acetyl-3-carbobenzoxyamino-3-deoxy-β-D-glucopyranoside (V).—A mixture of 0.2 g. of 2,4,6-tri-*O*-acetyl-α-1-bromo-3-carbobenzoxyamino-1,3-dioxy-D-glucopyranose (IV) and 0.05 g. of mercuric cyanide in 1.0 ml. of absolute methanol was shaken at 27°C for 1.0 hr. to obtain a yellowish solution. The solution was cooled in ice-water and added with water dropwise, whereupon the solution became turbid and then there were colorless crystals of methyl 2,4,6-tri-*O*-acetyl-3-carbobenzoxyamino-3-deoxy-β-D-glucopyranoside deposited, which were collected and washed with water until the washings became neutral; yield 0.14 g. (77.4%), m. p. 139°C, $[\alpha]_D^{13}$ −19.6° (*c* 1.77, $CHCl_3$).

Found: C, 55.50; H, 5.99; N, 3.12; OCH_3, 6.58. Calcd. for $C_{21}H_{27}O_{10}N$ (453.5): C, 55.62; H, 6.00; N, 3.09; OCH_3, 6.84%.

The infrared spectrum of the product in chloroform shows absorption bands at 3415 (νNH), 1753 (νC=O in OAc), 1735 (νC=O in Cbzo) 1520 (δNH), 1227, 1210 (νC-O in OAc) and 895 (type 2b of pyranose ring).

2, 3, 4-Tri-*O*-acetyl-6-amino-α-1-bromo-6-deoxy-D-gulcopyranose Hydrobromide (VII).—A mixture of 0.2 g. of 6-amino-6-deoxy-D-glucose hydrochloride[5] and 0.72 g. of freshly distilled acetyl bromide was placed in a brown flask and allowed to stand for 74 hr. with frequent shakings. The resulting mixture was subjected to vacuum-distillation to remove unchanged acetyl bromide and the residue was dried thoroughly in a vacuum-desiccator over sodium hydroxide overnight. The residue was triturated with 8 ml. of chloroform to give colorless crystals of 2,3,4-tri-*O*-acetyl-6-amino-α-1-bromo-6-deoxy-D-glucopyranose hydrobromide, which were washed three times with a portion of 2.0 ml. of chloroform each, yield 0.4 g. (96.3%), m. p. 142°C (decomp.). A specific rotation pattern of the product could not be ascertained because it is not soluble enough for the determination in ordinary organic solvents. A small quantity of the product was recrystallized from a large quantity of dioxane-tetrahydrofuran for the elementary analysis; m. p. was raised to 162~164°C (decomp.).

Found: C, 31.81; H, 4.61; N, 3.04. Calcd. for $C_{12}H_{19}O_7NBr_2$ (449.1): C, 32.09; H, 4.26; N, 3.12%.

The infrared spectrum of the product in potassium bromide shows 3218 (νNH) 1765 (νC=O in OAc), 1594 (δNH_3^+), 1249, 1224 (νC-O in OAc) 843 (type 2a of pyranose ring).

2, 3, 4-Tri-*O*-acetyl-α-1-bromo-6-carbobenzoxyamino-1, 6-dideoxy-D-glucopyranose (VIII).—A mixture of 0.2 g. of 2,3,4-tri-*O*-acetyl-6-amino-α-1-bromo-6-deoxy-D-glucopyranose hydrobromide (VII), 0.12 g. of carbobenzoxy chloride, 3.5 ml. of chloroform and 1.5 ml. of a saturated solution of sodium bicarbonate was shaken at about 0°C for 20 min. Thereby the suspension of VII which is almost insoluble in both chloroform and water disappeared, resulting in two layers of clear chloroform and aqueous solutions. The chloroform layer was separated, washed with water and dried over sodium sulfate. The filtrate was evaporated under reduced

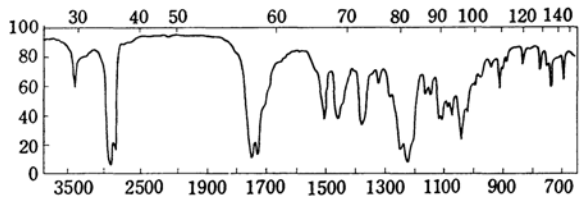

Fig. 2. Infrared spectrum of 2,3,4-tri-*O*-acetyl-α-1-bromo-6-carbobenzoxyamino-1,6-dideoxy-D-glucopyranose (VIII) in Nujol.

pressure and the resulting residue was recrystallized twice from ether-petroleum ether to give colorless tiny crystals of 2,3,4-tri-*O*-acetyl-α-1-bromo-6-carbobenzoxyamino-1,6-dideoxy-D-glucopyranose; yield 0.17 g. (76%), m. p. 89°C, $[\alpha]_D^{17}$ +156° (*c* 1.67, $CHCl_3$).

Found: C, 48.29; H, 4.72; N, 2.91; Br, 15.43. Calcd. for $C_{20}H_{24}O_9NBr$ (502.3): C, 48.72; H, 4.81; N, 2.79; Br, 15.92%.

The infrared spectrum of the product in Nujol shows absorption bands at 3390 (νNH), 1751 (νC=O in OAc), 1731 (νC=O in Cbzo), 1507 (δNH), 1249, 1222 (νC-O in OAc), 833 (type 2a of pyranose ring) and 776, 732, 739, 697 cm^{-1} (phenyl) (Fig. 2).

Methyl 2, 3, 4-Tri-*O*-acetyl-6-carbobenzoxyamino-6-deoxy-β-D-glucopyranoside (IX). — *By Mercuric Cyanide as a Condensing Reagent.*—A mixture of 0.2 g. of 2, 3, 4-tri-*O*-acetyl-α-1-bromo-6-carbobenzoxyamino-1,6-dideoxy-α-D-glucopyranose (VIII), 0.05 g. of mercuric cyanide in 1.0 ml. of absolute methanol was placed in a brown flask and shaken at 29°C for 1 hr. and then poured into 8 ml. of ice-water. The resulting viscous precipitate was taken in chloroform and washed with water. After drying over sodium sulfate, the chloroform solution was evaporated to dryness and the residue was triturated with isopropanol to start crystallization, yield 0.11 g. (61.2%), m. p. 95~100°C. Recrystallization from isopropanol raised the m. p. to 103~104°C; $[\alpha]_D^{15}$ +4.5° (*c* 2.00, $CHCl_3$).

Found: C, 55.77; H, 5.76; N, 3.11; OCH_3, 6.44. Calcd. for $C_{21}H_{27}O_{10}N$ (453.5): C, 55.62; H, 6.00; N, 3.09, OCH_3, 6.84%.

The infrared spectrum of the product in chloroform shows absorption bands at 3465 (νNH), 1764 (νC=O in OAc), 1734 (νC=O in Cbzo), 1519 (δNH), 1245, 1215 (νC-O in OAc), 903 (type 2b of pyranose ring).

By Silver Carbonate as a Condensing Reagent.—A mixture of 0.2 g. of 2,3,4-tri-*O*-acetyl-α-1-bromo-6-carbobenzoxyamino-1, 6-dideoxy-D-glucopyranose, 9.1 ml. of methanol, 1.2 g. of silver carbonate, 0.61 g. of calcium sulfate and 9.1 ml. of chloroform was sealed in a test tube to keep completely free from moisture and shaken at 29°C for 4.5 hr. The reaction mixture was filtered through active charcoal placed on a filter paper and the active charcoal was washed ten times with a portion of 2 ml of methanol. The filtrate and washings were combined and evaporated to dryness under reduced pressure. The residue was recrystallized from isopropanol to give colorless crystals of m. p. 99~101°C, yield 0.1 g. (57%). Mixed melting point of the product and the sample obtained by the above method showed no depression and the respective infrared spectra were completely superimposable.

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