Studies on Antibiotics and Related Substances. XVI. Syntheses of β-Acetochloro Derivatives of 3-Amino-3-deoxyglucose and 6-Amino-6-deoxyglucose

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Acetohalogeno derivatives of sugars are important intermediates for the synthesis of glycosides. However, the corresponding derivatives of aminosugars represent a relatively unexplored territory. In the preceding paper in this series, the syntheses of α-acetobromo derivatives of 3-carbobenzoxyamino-3-deoxy- and 6-carbobenzoxyamino-6-deoxy-glucose have been developed. This paper reports the synthesis of 2, 4, 6-tri-*O*-acetyl-3-carbobenzoxyamino-β-1-chloro-1,3-dideoxy-D-glucopyranose (III) and 2,3,4-tri-*O*-acetyl-6-carbobenzoxyamino-β-1-chloro-1, 6-dideoxy-D-glucopyranose (VII). These β-acetochloro derivatives are significant for preparing α-glycoside of aminosugars, as shown here in the prepartion of methyl 2, 4, 6-tri-*O*-acetyl-3-carbobenzoxyamino-3-deoxy-α-D-glucopyranoside (IV) and methyl 2, 3, 4-tri-*O*-acetyl-6-carbobenzoxyamino-6-deoxy-α-D-glucopyranoside (VIII).

The synthesis of III and IV are outlined in the following Chart A:

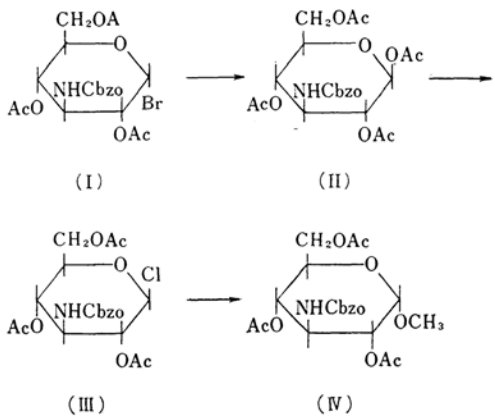

Chart A

2, 4, 6-Tri-*O*-acetyl-1-α-bromo-3-carbobenzoxyamino-1, 3-dideoxy-D-glucopyranose (I) prepared by our method[1] was acetylated by refluxing with silver acetate in dried benzene to give 1, 2, 4, 6-tetra-*O*-acetyl-3-carbobenzoxyamino-3-deoxy-β-D-glucopyranose (II) in 77% yield.

1) Y. Ito, S. Koto and S. Umezawa, This Bulletin, 35, 1618 (1962).

TABLE I

Compound	Specific rotation: Observed in $CHCl_3$	Specific rotation: Calcd.	IR-Absorption, cm^{-1}
II	$[\alpha]_D^{7.5}$ +17.5° (*c* 0.87)	+ 14.8°	898 (Nujol)
III	$[\alpha]_D^{15}$ − 3.5° (*c* 0.85)*	+ 6.3°	890 (KBr)
IV	$[\alpha]_D^{15}$ +75.6° (*c* 0.91)	+116°	847 ($CHCl_3$)
VI	$[\alpha]_D^{12}$ +10.2° (*c* 1.6)	+ 14.8°	892 (Nujol)
VII	$[\alpha]_D^{15}$ + 0.17° (*c* 1.7)**	+ 6.3°	901 (KBr)
VIII	$[\alpha]_D^{15}$ +81° (*c* 0.91)	+116°	847 ($CHCl_3$)

* A rotation change from −3.5 to +55° (192 hr.) was observed.
** A rotation change from +0.17 to +56.3° (144 hr.) was observed.

Zemplén and Mester[2], and Korytnyk and Mills[3] reported on the preparation of so called "unstable chlorides" from fully acetylated aldopyranoses by treatment with aluminum chloride in cold chloroform. When a similar procedure was applied to II at room temperature, a 92.7% yield of 2, 4, 6-tri-*O*-acetyl-1-β-chloro-3-carbobenzoxyamino-3-deoxy-D-glucose (III) was obtained. As detailed below, the specific rotation of III changed very slowly from −3.5 to +55° in dried chloroform during 192 hr.

An attempt to prepare an α-glycoside from III proved to be practical. When shaken with methanol in the presence of silver carbonate and anhydrous calcium carbonate by the procedure of Wolfrom[4], methyl 2, 4, 6-tri-*O*-acetyl-3-carbobenzoxyamino-3-deoxy-α-D-glucopyranoside (IV) was obtained in 67.3% yield.

2, 3, 4-Tri-*O*-acetyl-6-carbobenzoxyamino-1-β-chloro-1, 6-dideoxy-D-glucopyranose (VII) and the corresponding methyl α-glycoside (VIII) have been synthesized by an analogous route outlined in the following Chart B:

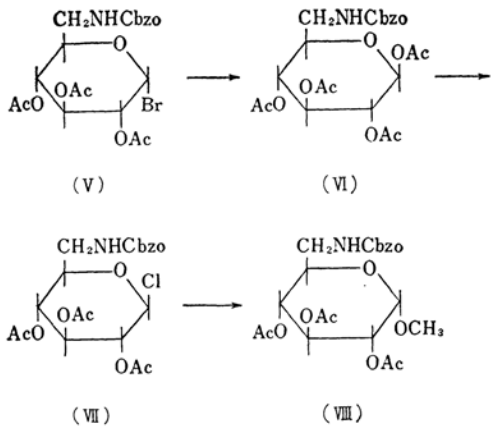

Chart B

2, 3, 4-Tri-*O*-acetyl-6-carbobenzoxyamino-1-β-chloro-1, 6-dideoxy-D-glucopyranose (VII) was obtained in an 89.5% yield and, when subjected to the procedure of Wolfrom mentioned above, VII gave an α-glycoside, methyl 2, 3, 4-tri-*O*-acetyl-6-carbobenzoxyamino-1, 6-dideoxy-D-glucopyranoside (VIII) in 61% yield.

Infrared spectra of the acetochloro derivatives (III, VII) showed absorption near 890 cm^{-1} which is characteristic of β-configuration, while the methylglycosides (IV, VIII) showed absorptions near 840 cm^{-1}, indicating that the methylglycosides have α-configuration as expected from the solvolytic mechanism. Moreover, determination of specific rotation of the above-mentioned derivatives consisted with the spectroscopic results, as shown in Table I, where these data are shown together with the calculated values using Hudson's rules modified by Korytnyk[5].

The agreement between the observed and calculated values of the glycosides (IV, VIII) is not so good, but the results seem to be allowable. The observed differences probably are to be ascribed to concomitance of β-anomer and an orthoester derivative, which are rather often the main product of the Koenigs-Knorr reaction. When the glycoside (IV) was deacetylated with methanolic ammonia and then catalytically reduced to remove the carbobenzoxyl group, there was obtained a mixture of methyl 3-amino-3-deoxy-α-D-glucoside and 3-amino-3-deoxy-D-glucose, which were identified by paper chromatography. The former was a main product and identified by comparison with an authentic specimen obtained by methanolysis of kanamycin. The formation of 3-amino-3-deoxy-D-glucose probably indicates the concomitance of orthoester derivative in the glycoside (IV), provided that the glycosidic linkage is stable enough in the above-mentioned series of reactions. Since the methyl α-glycoside was obtained as a main product, it is probable that, in the case of acetochloro derivatives of

2) G. Zemplén and L. Mester, *Acta Chim. Acad. Sci., Hungary*, **4**, 73 (1954).
3) W. Korytnyk and J. A. Mills, *J. Chem. Soc.*, **1959**, 636.
4) M. L. Wolfrom, A. O. Pittet and I. C. Gillam, *Proc. Nat. Acad. Sci.*, **47**, 700 (1961).
5) W. Korytnyk, *J. Chem. Soc.*, **1959**, 650.

3-carbobenzoxyamino-3-deoxyglucose and 6-carbobenzoxyamino-6-deoxyglucose, the replacement reaction[6] took place more rapidly than the interconversion of isomeric halides.

It should be noted also that the reaction of 1, 3, 4, 6-tetra-*O*-acetyl-2-carbobenzoxyamino-2-deoxy-D-glucose (IX) with aluminum chloride by a similar procedure to that used for the preparation of III and VII afforded 4, 5-(3, 4, 6-tri-*O*-acetyl-D-glucopyrano)-2-oxazolone which had been described by Konstas et al.[7]

Experimental

1, 2, 4, 6-Tetra-*O*-acetyl-3-carbobenzoxyamino-3-deoxy-β-D-glucopyranose (II).—A mixture of 3.0 g. of 2,4,6-tri-*O*-acetyl-1-α-bromo-3-carbobenzoxyamino-1,3-dideoxy-D-glucopyranose (I) prepared by our method[1] and 2.0 g. of well dried silver acetate in 100 ml. of benzene was refluxed for 8 hr. and cooled. A small quantity of active charcoal was added to the resulting mixture, followed by filtration. The filtrate was concentrated under reduced pressure and the residue was recrystallized from isopropanol to yield 2.17 g. (77%) of 1,2,4,6-tetra-*O*-acetyl-3-carbobenzoxyamino-3-deoxy-β-D-glucopyranose, m. p. 165.5~166°C, $[\alpha]_D^{7.5}$ +17.5° (*c* 0.87, $CHCl_3$). The infrared spectrum of the product in Nujol contains absorption bands at 3350 (νNH), 1757 (νC=O in OAc), 1713 (νC=O in Cbzo), 1550 (δNH), 1231, 1215 (νC-O in OAc), 898 (type 2b of pyranose ring), 775, 738, 696 (phenyl).

Found: C, 54.46; H, 5.64; N, 3.08. Calcd. for $C_{22}H_{27}NO_{11}$ (481.5): C, 54.88; H, 5.67; N, 2.91%.

2, 4, 6-Tri-*O*-acetyl-1-β-chloro-3-carbobenzoxyamino-1, 3-dideoxy-D-glucopyranose (III).—A mixture of 0.25 g. of 1,2,4,6-tetra-*O*-acetyl-3-carbobenzoxyamino-3-deoxy-β-D-glucopyranose (II) and 0.3 g. of freshly prepared aluminum chloride in 5 ml. of chloroform was shaken at room temperature for 40 min. After addition of 60 ml. of benzene, the resulting mixture was washed with each 8 ml. of ice water thrice. The benzene-layer was dried over sodium sulfate and evaporated to dryness under reduced pressure and the residue was recrystallized from ether-petroleum ether and then ether to yield 0.22 g. (92.7%) of colorless crystals of 2,4,6-tri-*O*-acetyl-1-β-chloro-3-carbobenzoxyamino-1,3-dideoxy-D-glucopyranose, m. p. 151~151.5°C, $[\alpha]_D^{15}$ −3.5° (initial) → +55° (final, 192 hr.) (*c* 0.85, $CHCl_3$). The infrared spectrum of the product in potassium bromide contains absorption bands at 3160 (νNH), 1763 (νC=O in OAc), 1715 (νC=O in Cbzo), 1545 (δNH), 1228 (νC-O in OAc), 890 (type 2b of pyranose ring), 774, 738, 696 (phenyl).

Found: C, 52.50; H, 5.04; N, 3.08; Cl, 7.30. Calcd. for $C_{20}H_{24}NO_9Cl$ (458.0): C, 52.35; H, 5.27; N, 3.08; Cl, 7.76%.

Methyl 2, 4, 6-Tri-*O*-acetyl-3-carbobenzoxyamino-3-deoxy-α-D-glucoside (IV).—A mixture of 60 mg. of silver carbonate prepared by the procedure of Wolfrom et al.[4] and 400 mg. of anhydrous calcium sulfate in 4 ml. of anhydrous methanol was shaken in dim light for 15 min. at room temperature. To the suspension were added 0.15 g. of 2,3,4-tri-*O*-acetyl-1-β-chloro-3-carbobenzoxyamino-1,3-dideoxy-D-glucopyranose (III), 10 mg. of silver perchlorate and a small quantity of anhydrous calcium sulfate and the mixture was shaken in dim light for 3.5 hr. at room temperature. After removal of silver salts by filtration, the solvent was removed by evaporation under reduced pressure and the residue was dissolved in chloroform and allowed to stand overnight. After removal of an insoluble matter by filtration the filtrate was evaporated to give a crystalline residue, which was recrystallized from isopropanol-hexane to yield 0.1 g. (67.3%) of crystals of methyl 2,4,6-tri-*O*-acetyl-3-carbobenzoxyamino-3-deoxy-α-D-glucopyranoside, m. p. 129~130°C, $[\alpha]_D^{15}$ +75.6° (*c* 0.91, $CHCl_3$). The infrared spectrum of the product in chloroform contains absorption bands at 3350 (νNH), 1753 (νC=O in OAc), 1730 (shoulder) 1523 (δNH), 1210 (νC-O in OAc), 847 (type 2a pyranose ring), 695 cm^{-1} (phenyl).

Found: C, 55.83; H, 5.76; N, 3.15. Calcd. for $C_{21}H_{27}NO_{10}$ (453.5): C, 55.77; H, 5.76; N, 3.07%.

A sample of 20 mg. of the above product was dissolved in 4 ml. of methanol saturated with ammonia and allowed to stand overnight in a refrigerator and evaporated to dryness under reduced pressure. The residue was taken up in about 4 ml. of aqueous methanol and 40 mg. of paladium chloride-charcoal catalyst was added to the solution. pH of the mixture was adjusted to about 2 with dilute hydrochloric acid and hydrogenated at room temperature for 3 hr. As the reaction mixture gradually became alkaline, a small quantity of dilute hydrochloric acid was repeatedly added to adjust pH to about 2. After removal of the catalyst by filtration, the solution was evaporated to dryness under reduced pressure. The residue was dissolved in 0.4 ml. of water and subjected to paper chromatography, using two solvent systems. The spots were identified by coloration with ninhydrin and silver-ammonia. The solvent system butanol-pyridine-acetic acid-water (6 : 4 : 1 : 3) gave two spots of R_f 0.43 and 0.30 which were identical with the spots of authentic specimen of methyl 3-amino-3-deoxy-D-α-glucoside (R_f 0.43) obtained by methanolysis of kanamycin and a synthetic specimen of 3-amino-3-deoxy-D-glucose[8] (R_f 0.30). The solvent system butanol-acetic acid-water (10 : 2 : 5) gave two spots of R_f 0.23 and 0.14, which were identical with the spots of the above-mentioned specimens (R_f 0.23, 0.15).

1, 2, 3, 4-Tetra-*O*-acetyl-6-carbobenzoxyamino-6-deoxy-β-D-glucopyranose (VI).—A mixture of 0.3 g. of 2,3,4-tri-*O*-acetyl-1-bromo-6-carbobenzoxyamino-1,6-dideoxy-D-glucopyranose (V) prepared by our method[1] and 0.2 g. of silver acetate in 10 ml. of benzene was refluxed for 8 hr. and then worked up

6) The anomeric replacement by the Koenigs-Knorr reaction was discussed in detail by H. L. Frush and H. S. Isbell, *J. Research Natl. Bur. Standards*, **27**, 413 (1941); E. Pascu, *Advances in Carbohydrates Chemistry*, **1**, 78 (1945); and R. U. Lemieux, ibid., **9**, 1 (1954).

7) S. Konstas, A. I. Photake and L. Zervas, *Chem. Ber.*, **92**, 1288 (1959).

8) Y. Ito, S. Koto and S. Umezawa, This Bulletin, **35**, 16 (1962).

in a similar manner to that used for the compound II. The crude product was recrystallized from ethanol repeatedly to yield 0.18 g. (63.6%) of 1,2,3,4-tetra-*O*-acetyl-6-carbobenzoxyamino-6-deoxy-β-D-glucopyranose, m. p. 144~145°C, $[\alpha]_D^{12}$ +10.2° (*c* 1.6, $CHCl_3$). The infrared spectrum of the product in Nujol contains absorption bands at 3385, 1760, 1745, 1550, 1240, 1212, 892, 774, 736, 700 cm^{-1}.

Found: C, 55.22; H, 5.75; N, 3.18. Calcd. for $C_{22}H_{27}NO_{11}$ (481.5): C, 54.88; H, 5.67; N, 2.91%.

2, 3, 4-Tri-*O*-acetyl-6-carbobenzoxyamino-1-β-chloro-1, 6-dideoxy-D-glucopyranose (VII). — This material was prepared from 0.33 g. of 1,2,3,4-tetra-*O*-acetyl-6-carbobenzoxyamino-6-deoxy-β-D-glucopyranose and 0.42 g. of aluminum chloride by the method used for the preparation of compound III. The crude product was recrystallized from ether-petroleum ether and then from benzene-ether to yield 0.28 g. (89.5%) of colorless crystals of 2,3,4-tri-*O*-acetyl-6-carbobenzoxyamino-1-β-chloro-1,6-dideoxy-D-glucopyranose, m. p. 158~158.5°C (decomp.), $[\alpha]_D^{15}$ +0.17° (initial) → +56.3° (final, 144 hr.) (*c* 1.7, $CHCl_3$). The infrared spectrum of the product in potassium bromide contains absorption bands at 3235, 1753, 1728, 1520, 1252, 1220, 901, 772 751, 696 cm^{-1}.

Found: C, 52.58; H, 5.29; N, 2.95; Cl, 7.36. Calcd. for $C_{20}H_{24}NO_9Cl$ (458.0): C, 52.35; H, 5.27; N, 3.08; Cl, 7.76%.

Methyl 2,3,4-Tri-*O*-acetyl-6-carbobenzoxyamino-6-deoxy-α-D-glucopyranoside (VIII). — A mixture of 60 mg. of silver carbonate prepared by the method of Wolfrom et al.[4] and 300 mg. anhydrous calcium sulfate in 4 ml. of anhydrous methanol was shaken in dim light for 15 min. at room temperature. To the suspension was added 0.124 g. of 2,3,4-tri-*O*-acetyl-6-carbobenzoxyamino-1-β-chloro-1,6-dideoxy-D-glucopyranose and 10 mg. of silver perchlorate and the mixture was shaken in dim light for 2 hr. and then worked up in a similar manner to that used for the compound IV. The crude product was dissolved in isopropanol and *n*-hexane was added to the solution to yield a syrup, which was triturated with *n*-hexane to yield 0.075 g. (61%) of a crystalline powder of methyl 2,3,4-tri-*O*-acetyl-6-carbobenzoxyamino-6-deoxy-α-D-glucopyranoside, $[\alpha]_D^{15}$ +81° (*c* 0.91, $CHCl_3$). The infrared spectrum of the product in chloroform contains absorption bands at 3460, 1758, 1735, 1520, 1233, 1213, 847, 697 cm^{-1}.

Found: C, 55.30; H, 6.22; N, 3.10. Calcd. for $C_{21}H_{27}NO_{10}$ (453.5): C, 55.77; H, 5.76; N, 3.07%.

1, 3, 4, 6-Tetra-*O*-acetyl-2-carbobenzoxyamino-2-deoxy-D-β-glucose (IX).—A mixture of 350 mg. of 2,4,6-tri-*O*-acetyl-1-bromo-2-carbobenzoxyamino-1,2-dideoxy-α-D-glucopyranose[9] and 245 mg. of silver acetate in 25 ml. of benzene was refluxed for 7 hr. and then worked up in a similar manner to that used for the compound II. The crude product was recrystallized from isopropanol-hexane to yield 250 mg. of the title compound, m. p. 147~148°C. Repeated recrystallization raised the m. p. to 150~150.5°C[10], $[\alpha]_D^{23}$ +28.1° (*c* 1.4, $CHCl_3$).

Found: C, 54.98; H, 5.70; N, 2.96. Calcd. for $C_{22}H_{27}NO_{11}$ (481.2): C, 54.88; H, 5.67; N, 2.91%.

Formation of Oxazolone Derivative from Tetra-acetyl Derivative of 2-Carbobenzoxyamino-2-deoxy-D-glucose.—A mixture of 630 mg. of 1,3,4,6-tetra-*O*-acetyl-2-carbobenzoxyamino-2-deoxy-D-glucose and 630 mg. of freshly prepared aluminum chloride in 9.5 ml. of chloroform was shaken at room temperature for 40 min. After addition of 150 ml. of benzene, the resulting mixture was washed with water and the benzene-layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. Trituration of the residue with ether-petroleum ether yielded crystals of 4,5-(3,4,6-tri-*O*-acetyl-D-glucopyrano)-2-oxazolone; yield 450 mg. (75%). Recrystallization from benzene gave m. p. 170.5~174°C[11].

Found: N, 4.08. Calcd. for $C_{13}H_{17}NO_9$ (331.3): N, 4.02%.

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9) L. Zervas and S. Konstans, *Chem. Ber.*, 93, 435 (1960).
10) Reported m. p. 151.5~152°C. W. H. Bromund and R. M. Herbst, *J. Org. Chem.*, 10, 267 (1945).
11) Reported m. p. 174~175°C. S. Konstas, A. I. Photake and L. Zervas, loc. cit.