# SYNTHESIS AND HYDROBORATION OF A 3-*C*-METHYLENE DERIVATIVE OF 2-AMINO-2-DEOXY-D-GLUCOSE

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## ABSTRACT

Opening of the epoxide ring of methyl 3,3′-anhydro-2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-(hydroxymethyl)-α-D-allopyranoside (**1**) with sodium iodide, in the presence of acetic anhydride and *p*-toluenesulfonic acid, gave methyl 3-*O*-acetyl-2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-(iodomethyl)-α-D-allopyranoside (**2**). Reduction of **2** with powdered zinc in buffered *N*,*N*-dimethylformamide gave methyl 2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methylene-α-D-*ribo*-hexopyranoside (**3**) in 92% yield. Treatment of **1** with zinc in acetic acid containing sodium iodide afforded **3** directly in 90% yield. Hydroboration–oxidation of **3** gave a mixture of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-glucopyranoside (**6**), and the corresponding 3-deoxy-3-*C*-(hydroxymethyl) derivatives (**4**). Chromatographic separation of the isomers afforded one of the 3-deoxy-3-*C*-(hydroxymethyl) 3-epimers as a pure oil, and **6** as an impure oil. Acetylation of the former with acetic anhydride in pyridine gave the 3-deoxy-3-*C*-(acetoxymethyl) derivative (**5**), and acetylation of **6** with acetic anhydride containing *p*-toluenesulfonic acid gave crystalline methyl 3-*O*-acetyl-2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-glucopyranoside (**7**).

## INTRODUCTION

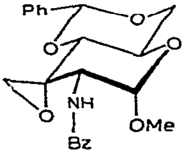
Ring opening of spiro-epoxide derivatives of amino sugars by various nucleophiles presents a simple route for the synthesis of branched-chain amino sugars[1]. Several amino sugars bearing functionalized, branched chains have been synthesized by this approach. Known branched-chain amino sugars[1,2], in which the nitrogen atom does not occur at the branching point, usually have an oxygen atom attached to the carbon atom bearing the branched side-chain. It is of interest, therefore, to examine possible syntheses of this type of branched-chain amino sugar that possesses a hydrogen atom, and no oxygen substituent, at the branching point.

The hydroboration–oxidation reaction[3] has been applied successfully for the anti-Markownikov addition of the elements of water to several types of unsaturated sugar[4–8]. Hydroboration of a *C*-methylene branched-chain amino sugar has not been described previously, and seemed of interest for the synthesis of the desired branched-chain amino sugars.

This report describes the synthesis and hydroboration–oxidation of methyl 2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methylene-α-D-*ribo*-hexopyranoside (**3**).

## DISCUSSION AND RESULTS

Attempts to convert the spiro-epoxide (**1**) into the 3-deoxy-3-*C*-(hydroxymethyl) derivative directly, were unsuccessful. Thus, reduction of **1** with a 4:1 mixture[9] of aluminum chloride and lithium aluminum hydride, under the conditions recently used[10] for the conversion of a piperidine spiro-oxirane to a *C*-hydroxymethyl derivative, gave a complex mixture of products. Reduction[11] with diborane gave similar results. Attempted ring opening and rearrangement of the epoxide with lithium perchlorate[12], or zinc[13], to the 3-deoxy-3-*C*-formyl derivative, afforded mainly unchanged starting material.



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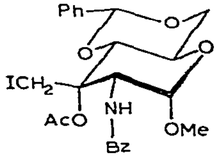

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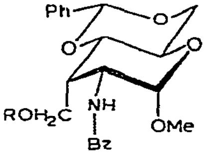

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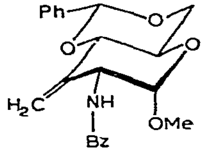
5 R = Ac



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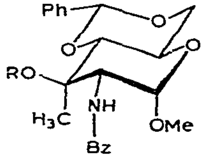

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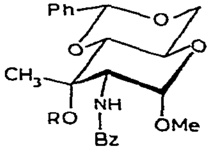

8 R = H
9 R = Ac

Ring opening of the epoxide **1** with sodium iodide, in the presence of excess *p*-toluenesulfonic acid in acetic anhydride, readily afforded methyl 3-*O*-acetyl-2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-(iodomethyl)-α-D-allopyranoside (**2**). *p*-Toluenesulfonic acid could promote opening of the oxirane, as well as catalyze acetylation of the intermediate tertiary 3-hydroxy group thus generated. Nucleophilic attack on **1** has been shown[1] to occur at the methylene carbon atom, to give an axial hydroxy group. The expected axial orientation of the 3-acetoxy group of **2** was confirmed by the presence of a 3-proton singlet at $\tau$ 7.87 in the n.m.r. spectrum. Axial acetoxy groups of pyranose acetates usually[1,2] resonate below $\tau$ 7.90.

Reduction of **2** with zinc powder in *N*,*N*-dimethylformamide gave methyl

2-benzamido-4,6-*O*-benzylidene-3-*C*-methylene-α-D-*ribo*-hexopyranoside (3) in nearly quantitative yield. Direct reduction[14] of **1** to **3** was effected with a mixture of sodium iodide and zinc powder in buffered acetic acid. The two-step procedure is advantageous, since it allows isolation of the intermediate 3-*C*-(iodomethyl) derivative (3), which may be used for further elaboration of the branched side-chain. The n.m.r. spectrum of the exocyclic methylene derivative (3), showed no acetoxy-proton signal, and its i.r. spectrum had no ester-carbonyl absorption below 5.88 μm, but showed a strong absorption peak at 6.07 μm due to the exocyclic methylene group.

Hydroboration of **3** in tetrahydrofuran, followed by oxidation with alkaline hydrogen peroxide, gave a mixture of products that ran as two spots on t.l.c. Separation of the components by preparative-layer chromatography afforded the faster-moving component in 24% yield, and the slower-moving component in 45% yield; none of the products could be crystallized.

The mass spectrum of the faster-moving component showed a molecular-ion peak of *m/e* 399, and a peak of *m/e* 369, representing the loss of formaldehyde from the molecular ion, suggesting that the product has the 3-*C*-(hydroxymethyl) structure, **4**. The n.m.r. spectrum was compatible with structure **4**. Acetylation of **4** with acetic anhydride in pyridine gave an oil that showed one spot on t.l.c. The structure of the 3-*C*-(acetoxymethyl) derivative (**5**) is consistent with the presence of a molecular ion peak at *m/e* 441 in its mass spectrum, and an absorption peak at 5.76 μm in the i.r., and is confirmed by the n.m.r. data. An unambiguous assignment of the configuration at *C*-3 could not be made with the data presently available.

The slower-moving component from the mixture of hydroboration products of **3** showed one spot on t.l.c.; its n.m.r. spectrum showed a single, 3-proton, tertiary-*C*-methyl signal at τ 8.59, a 3-proton *O*-methyl singlet at τ 6.57, and a benzylic proton singlet at τ 4.40, consistent with structure **6**. An additional *O*-methyl signal at τ 6.63, and a singlet at τ 4.52 for a benzylic proton, indicated that the product consisted of a 2:1 mixture of **6** and a compound that did not have a *C*-methyl group. The mass spectrum of the mixture showed a molecular ion of *m/e* 399. The mobility of the mixture on t.l.c. was markedly different from that of the known[2] methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-allopyranoside (**8**).

Acetylation of the mixture with acetic anhydride containing *p*-toluenesulfonic acid afforded 42% of crystalline acetate **7**. The acetate moved as a single spot on t.l.c., and had spectral properties in agreement with **7**. Since axial acetoxy groups of pyranose acetates usually resonate below τ 7.90, and equatorial ones usually[1,15] above τ 7.90, the acetyl signal observed at τ 8.02 in the n.m.r. spectrum of **7** suggests that **7** contains an equatorial acetoxy group. The corresponding 3-*C*-methyl-3-*O*-acetylalloside[2] (**8**) gave an acetyl proton signal at τ 7.89. Comparison of physical properties and spectral data of **7** and **9** therefore allows assignment of the *gluco*-configuration to **6** and **7**.

The relatively high proportion (*ca.* 30%) of the tertiary alcohol **6** obtained from the hydroboration of **3** is a consequence of the electron-withdrawing effect of the benzyloxy substituent at C-4, which is allylic with respect to the exocyclic double bond of **3**. For the same reason, hydroboration of allyl ethers[16] and 2*H*-dihydropyran[17] gave yields of 19–32% of Markownikov hydration products, apart from the expected products of hydroxylation at the least-substituted carbon atom. It has been shown[18] that approach of diborane to methylenecyclohexanes is from the least-hindered, equatorial side, and the alcohols obtained corresponded to pure *cis*-addition of the elements of water to the double bond. Preferential approach of borane from the outside of the fold formed by the exocyclic methylene group and the pyran ring of **3** should, therefore, be expected, since axial approach of borane to **3** would also lead to a severe 1,3-interaction with the $\alpha$-methoxy group. Thus, only one tertiary alcohol (**6**), of the *gluco*-configuration, was obtained, and the configuration of the 3-deoxy-3-*C*-(hydroxymethyl) derivative (**4**) is probably as shown. Confirmation of the latter assignment could not be made by first-order analysis of the n.m.r. spectra of **4** and **5**, or from calculations[19] of molecular rotation.

Attempts are being made to establish the nature of the contaminant of **6** obtained in the hydroboration, and to confirm the configurational assignment of **4** and **5**.

## EXPERIMENTAL

*General.* — Melting points were taken in capillary tubes in a Büchi silicone bath apparatus, and are corrected. I.r. spectra were determined for KBr discs in the case of solid products, and as films in the case of liquids, with a Perkin–Elmer 257 grating spectrophotometer. N.m.r. spectra were recorded in chloroform-*d* on a Varian A-60A spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained with an AEI MS-9 mass spectrometer. Optical rotations were determined with a Perkin–Elmer 141 polarimeter. Thin-layer chromatograms were run on precoated, silica gel F plates (Merck), and spots were detected by examination under 254 nm u.v. light. Preparative-layer chromatograms were run on precoated, preparative, silica gel plates (Merck). A 9:1 mixture of benzene and acetone was used as the mobile phase for all chromatograms. Microanalyses were performed by Dr. Franz Pascher, Bonn, Western Germany.

*Methyl 3-O-acetyl-2-benzamido-4,6-O-benzylidene-2-deoxy-3-C-(iodomethyl)-α-D-allopyranoside* (**2**). — A mixture of 2.4 g (6 mmoles) of **1**, 5 g of sodium iodide, 1.14 g (6 mmoles) of *p*-toluenesulfonic acid, 25 ml of butanone, and 15 ml of acetic anhydride was stirred for 18 h under reflux. The cooled mixture was poured into 500 ml of saturated, ice-cold sodium hydrogen carbonate solution, and stirred for 1 h. The mixture was extracted with chloroform (4 × 25 ml), and the combined extracts were washed consecutively with saturated aqueous sodium hydrogen carbonate (2 × 200 ml), 2% aqueous sodium thiosulfate (100 ml), and finally with water (200 ml). The dried (magnesium sulfate) extract was evaporated below 35° *in vacuo* to leave a yellowish syrup that crystallized from 10 ml of hot 90% ethanol on cooling. Recrystallization of the product from aqueous ethanol gave 1.77 g (52%) colorless crystals that showed one spot on t.l.c., and that had m.p. 167–168°, $[\alpha]_D^{20}$ +129° (*c* 0.88, chloroform).

*Anal.* Calc. for $C_{24}H_{26}INO_7$: C, 50.81; H, 4.62; N, 2.47. Found: C, 50.89; H, 4.46; N, 2.41.

*Methyl 2-benzamido-4,6-O-benzylidene-2,3-dideoxy-3-C-methylene-α-*D-ribo-*hexopyranoside* (**3**). — (*a*) A stirred mixture of 4.03 g (7.1 mmoles) of **2**, and 15 g of zinc dust in 50 ml of *N,N*-dimethylformamide was refluxed for 4 h. The mixture was filtered, and the residue was washed with 25 ml of hot *N,N*-dimethylformamide. The cooled filtrate was diluted with 500 ml of water, and the resulting white precipitate was collected on a filter. Two recrystallizations of the dried product from 95% aqueous ethanol gave 2.51 g (92%) of colorless, silky needles that showed one spot on t.l.c.; m.p. 221–222°, $[\alpha]_D^{20}$ $-34°$ (*c* 2.25, chloroform).

*Anal.* Calc. for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.43; H, 6.08; N, 3.66.

(*b*) To a stirred solution of 480 mg (1.2 mmoles) of **1** in 15 ml of glacial acetic acid was added 4 g of sodium iodide, 1.5 g of sodium acetate trihydrate, and 1 ml of water. Four 150-mg portions of zinc dust were added at 15-min intervals to the stirred mixture at 0°. Stirring was continued for 1 h at 0°, and for 1 h at ambient temperature. The remaining zinc was filtered off and washed on the filter with 20 ml of chloroform. The filtrate was diluted with 100 ml of water, and the aqueous layer was extracted with chloroform (4 × 10 ml). The combined chloroform extracts were washed with cold, 5% aqueous potassium carbonate, and water. Evaporation of the dried (magnesium sulfate) extract gave a white solid. Two recrystallizations from aqueous ethanol gave 410 mg (90%) of colorless needles, which proved identical with **3**, described in (*a*).

*Hydroboration–oxidation of* **3**. — To a solution of 1.14 g (3 mmoles) of **3** in 25 ml of anhydrous tetrahydrofuran was added 25 ml of M borane in tetrahydrofuran. The mixture was stirred at room temperature for 2 h, and then cooled in ice, and diluted with 20 ml of tetrahydrofuran. Excess borane was decomposed by slow addition of 5 ml 50% aqueous tetrahydrofuran. After addition of 2 ml of 2M potassium hydroxide, and 10 ml of 30% hydrogen peroxide, the mixture was stirred at room temperature for 15 h, and then diluted with 500 ml of ice–water, and extracted with chloroform (6 × 15 ml). The extract was washed with water (2 × 50 ml), and the dried (magnesium sulfate) organic layer was evaporated to give 940 mg of a colorless syrup that showed two major spots on t.l.c. The mixture was separated on twelve preparative-layer chromatograms. The faster-moving component was obtained as a colorless oil (290 mg, 24% overall), that could not be crystallized. The product (**4**) showed one spot ($R_F$ ~0.46) on t.l.c., and had $[\alpha]_D^{28}$ $+65.9°$ (*c* 2.07, chloroform); n.m.r. data: τ 6.59 (3-proton singlet, OMe), 4.46 (1-proton singlet, benzylic H).

*Anal.* Calc. for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.15; H, 6.59; N, 3.53.

The slower-moving component (**6**) was obtained as a colorless oil (540 mg, 45% overall) that could not be crystallized. The product showed one spot on t.l.c. ($R_F$ ~0.3), and had $[\alpha]_D^{28}$ $+27.5°$ (*c* 1.72, chloroform).

*Methyl 3-O-acetyl-2-benzamido-4,6-O-benzylidene-2-deoxy-3-C-methyl-α-*D-

*glucopyranoside* (7). — A solution of 400 mg (1 mmole) of **5** in 6 ml of acetic anhydride, containing 190 mg (1 mmole) of *p*-toluenesulfonic acid monohydrate, was stirred for 12 h at ambient temperature. The mixture was then poured into 200 ml of ice-cold, saturated, aqueous sodium hydrogen carbonate, stirred for 1 h, and extracted with chloroform (5 × 10 ml). The dried (magnesium sulfate) extract was evaporated *in vacuo*, and the syrup remaining was crystallized from aqueous ethanol. Recrystallization from aqueous ethanol and then from acetone–petroleum ether, gave 170 mg (42%) of colorless crystals that moved as a single spot on t.l.c.; m.p. 196–197°, $[\alpha]_D^{28}$ +55° (*c* 1.82, chloroform); *m/e* 441 (Found 441.175535, Calc. for $C_{24}H_{27}NO_2$: 441.178738) $[M]^+$, *m/e* 381 (Found 381.156221, Calc. for $C_{22}H_{23}NO_5$ 381.157612) $[M\text{–}HOAc]^+$; n.m.r. data: $\tau$ 8.39 (3-proton singlet, C-Me), 8.02 (3-proton singlet, -OAc), 6.57 (3-proton singlet, OMe), 4.38 (1-proton singlet, benzylic H).

*Anal.* Calc. for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.33; H, 6.18; N, 3.22.

*Methyl 3-*C*-(acetoxymethyl)-2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-*D-ribo*-hexopyranoside* (5). — A solution of 200 mg (0.5 mmoles) of **4**, in a mixture of pyridine (2.5 ml) and acetic anhydride (1 ml) was kept for 12 h at room temperature. The mixture was evaporated to dryness *in vacuo*, and small portions of toluene were evaporated several times from the remaining oil. The product was precipitated twice from ethanol with petroleum ether, and dried *in vacuo*. The colorless oil (160 mg, 73%) thus obtained could not be crystallized, but showed one spot on t.l.c., and had $[\alpha]_D^{28}$ +51.4° (*c* 1.78, chloroform); *m/e* 441 $[M]^+$; n.m.r. data: $\tau$ 8.12 (3-proton singlet, OAc), 6.56 (3-proton singlet, OMe), 4.42 (1-proton singlet, benzylic H).

*Anal.* Calc. for $C_{24}H_{27}NO_7 \cdot H_2O$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.68; H, 6.39; N, 2.90.

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## REFERENCES

1 J. H. Jordaan and S. Smedley, *Carbohyd. Res.*, 16 (1971) 177.
2 B. R. Baker and D. H. Buss, *J. Org. Chem.*, 31 (1966) 217.
3 H. C. Brown, *Hydroboration*, Benjamin, New York, 1962.
4 H. Paulsen and H. Behre, *Carbohyd. Res.*, 2 (1966) 80.
5 M. L. Wolfrom, K. Matsuda, F. Komitsky, Jr., and T. E. Whiteley, *J. Org. Chem.*, 28 (1963) 3551.
6 H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Amer. Chem. Soc.*, 86 (1964) 74.
7 J. Lehmann, *Carbohyd. Res.*, 2 (1966) 1.
8 A. Rosenthal and M. Sprinzl, *Can. J. Chem.*, 47 (1969) 4477.
9 M. N. Rerick and E. L. Eliel, *J. Amer. Chem. Soc.*, 84 (1962) 2356.
10 K. Mashimo and Y. Sato, *Chem. Pharm. Bull.* (Tokyo), 18 (1970) 353.
11 D. J. Pasto, C. C. Cumbo, and J. Hickman, *J. Amer. Chem. Soc.*, 88 (1966) 2201.
12 B. Rickborn and R. M. Gerkin, *J. Amer. Chem. Soc.*, 90 (1968) 4193.

13 E. Ghera, *J. Org. Chem.*, 35 (1970) 660.
14 J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, (1959) 112.
15 F. W. Lichtenthaler and P. Emig, *Tetrahedron Lett.*, (1967) 577.
16 H. C. Brown and O. J. Cope, *J. Amer. Chem. Soc.*, 86 (1964) 1801.
17 G. Zweifel and J. Plamondon, *J. Org. Chem.*, 35 (1970) 898.
18 J. Klein and D. Lichtenberg, *J. Org. Chem.*, 35 (1970) 2654.
19 R. U. Lemieux and J. C. Martin, *Carbohyd. Res.*, 13 (1970) 139.