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Note

Acetalation of 2-acetamido-4,6-(*R*)-*O*-benzylidene-2-deoxy-D-glucitol*

CHRISTOPHE MORIN

Laboratoire de Chimie appliquée aux Corps Organisés, Muséum National d'Histoire Naturelle, 63, Rue de Buffon, 75005 Paris (France)

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Synthetic uses of accessible carbohydrates rely more often than not on the chemical differentiation of their various hydroxyl groups, and such processes have been extensively applied to the cyclic forms of 2-amino-2-deoxy-D-glucose. In contrast, acyclic 2-amino-2-deoxy-D-glucose or 2-amino-2-deoxy-D-glucitol derivatives are comparatively rare and, furthermore, do not allow full differentiation of the hydroxyl groups[1–9]. During the course of another project, a need arose for a 2-amino-2-deoxy-D-glucitol derivative having HO-5 free and the other groups variously protected. As none of the compounds described in the literature[1–9] suited our purpose, we explored the preparation of the desired derivative.

As simultaneous protection of primary and secondary hydroxyl groups occurs in terminal acetals of alditols, our target became a mixed 1,3:4,6-diacetal of an *N*-protected 2-amino-2-deoxy-D-glucitol. This solution would leave HO-5 free, as desired. However, the direct acetalation of 2-acetamido-2-deoxy-D-glucitol has been shown to yield 5,6- and 3,4:5,6-acetals[1,2]. Therefore, advantage was taken of benzylidenation of the readily available 2-acetamido-2-deoxy-D-glucose[10], which is known to give the 4,6-acetal[11,12] **1**. Reduction of the aldehyde group of **1** then gave a 4,6-acetal of 2-acetamido-2-deoxy-D-glucitol, namely **2**. The ^{13}C-n.m.r. chemical shifts of the backbone carbon atoms of the new triol **2** appeared as expected, when compared with known values for 2-acetamido-2-deoxy-D-glucitol[13]. The acetal carbon resonance (δ = 102.2 p.p.m.), however, was downfield from the proposed range of values for 1,3-dioxane acetals[14,15]. A detailed ^{1}H-n.m.r. analysis was therefore performed on the triacetate **3** derived from **2**. Full spectral assignments with double-resonance experiments, subspectral analysis, and simulation of the non-first-order systems, could only be made at 250 MHz. Three conclusions were drawn: (*a*) One CHOAc group was adjacent to a methylene group; this result

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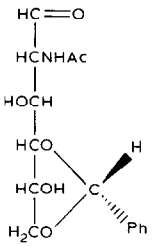
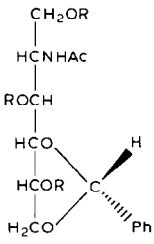
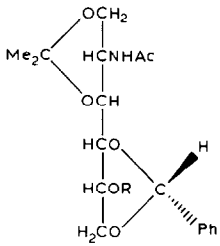
excluded a dioxolane type of acetal, thereby demonstrating the proposed structure **3** and hence structures **1** and **2**; (*b*) the observed coupling constants for H-5 ($J_{4,5}$ 10.2, $J_{5,6}$ 5.4, $J_{5,6'}$ 10.5 Hz) indicated the 5-OAc group and the C-3 side chain to be *trans*-diequatorial in the most stable conformation; (*c*) as a single acetal was present, the phenyl group was equatorially oriented, as a normal value (δ = 5.48 p.p.m.) was found for the (axial) benzylic hydrogen atom[15–18]. Therefore the absolute configuration of the acetal is established as *R*.



1



2 R = H
3 R = Ac

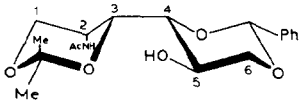


4 R = H
5 R = Ac

Isopropylidenation of **2** proved difficult because most of the standard reaction-conditions failed: acetone with such acid catalysts as sulfuric acid, *p*-toluenesulfonic acid, copper sulfate, ferric chloride, or zinc bromide; 2,2-dimethoxypropane or 2-methoxypropene in *N,N*-dimethylformamide with *p*-toluenesulfonic acid or sulfuric acid as catalysts; 1:1 acetone–2,2 dimethoxypropane with copper(II) sulfate (a system shown effective in a related case[19]). Although, in a few instances, some product was formed in low yield (typically ~10%), the starting material was generally far from being consumed, a result presumably attributable to its very low solubility (even in *N,N*-dimethylformamide). Heating was detrimental to the reaction itself. However, the use of a large excess of 2,2-dimethoxypropane, together with a catalytic amount of sulfuric acid, allowed isolation of an isopropylidene acetal in good yield, although the mixture was heterogeneous.

In view of possible acetal migration under acid catalysis[20], a detailed spectral analysis proved necessary. ^{13}C-N.m.r. spectroscopy disclosed the ring size of both acetals. A normal value (δ = 101.2 p.p.m.) was found for the 6-membered-ring benzylidene acetal[14,15]. The quaternary carbon atom of the isopropylidene acetal resonated at 99.9 p.p.m., which is a value expected for the chair conformation of such 1,3-dioxane acetals[21–23]. Furthermore, the chemical shifts of the methyl groups were separated by 10.9 p.p.m. which is within the range of predicted values for such dioxanes[22,23]. Therefore it was concluded that both acetals were 6-membered. However, the location of the isopropylidene (1,3- *vs.* 3,5-acetal) had to be established, especially as the latter (3,5-acetal) should be more stable[20,24]. That **4** was indeed the correct structure could best be demonstrated with the acetylated de-

rivative **5**. Close comparison of the ^{1}H-n.m.r. spectra of acetates **3** and **5** revealed that the chemical shifts and shapes of the signals of H-5, H-6, and H-6′ were almost identical. First-order analysis of the benzylidene acetal-ring resonances for **5** yielded coupling constants similar to those previously calculated for **3**. This result rules out a 3,5-isopropylidene acetal (which would then bear a primary acetate group) and establishes the proposed structure **5**, and hence **4**. No fused 3,5:4,6-diacetal was therefore obtained. It is reasonable to assume that **4** is kinetically formed[20,25] and then to consider the most probable chair-conformations of the two rings (**4a**). The 4,6-benzylidene acetal would have all substituents equatorial, and the 1,3-isopropylidene acetal would presumably have the bulky substituent at C-3 equatorial as well. Thus, acetal migration from **4a** would involve inversion of the 1,3-isopropylidene chair so as to bring the HO-5 group into proximity. However, this process did not take place. It is of related interest to note that, whereas 12 products were recognized in the direct acetalation of D-glucitol[26], no fused 3,5:4,6-fused ring structures could be identified[23,27,28].



4a

Thus, in 4 steps from 2-amino-2-deoxy-D-glucose, a chemically differentiated 2-amino-2-deoxyglucitol derivative having HO-5 free was obtained.

EXPERIMENTAL

General methods. — Melting points were determined with a Köfler or Reichert apparatus and are uncorrected. Microanalyses were performed by the Centre de Microanalyse de l'Université P. et M. Curie, Paris. ^{1}H- and ^{13}C-N.m.r. spectra were recorded in $CDCl_3$ (unless otherwise noted) with tetramethylsilane as the internal standard ($\delta = 0$) with the following spectrometers: Varian EM-360, Bruker WP-80, and Bruker WM-250 for ^{1}H, and Bruker WP-80 for ^{13}C. Chemical shifts are expressed in parts per million (p.p.m.) and coupling constants in Hz. The abbreviations s, d, t, m denote singlet, doublet, triplet, and multiplet, respectively. Mass spectra were recorded with a Thomson THN 208 apparatus. I.r. spectra were obtained with a Perkin–Elmer 157 G spectrophotometer. Optical rotations were determined with a Perkin–Elmer 141 polarimeter. Column chromatography was effected with silica gel 60 or 60H (Merck).

2-Acetamido-4,6-(R)-O-benzylidene-2-deoxy-D-glucitol (**2**). — Finely ground 2-acetamido-4,6-(*R*)-*O*-benzylidene-2-deoxy-D-glucose[11,12] (71.0 g; 229.5 mmol) was suspended in methanol (500 mL) in a 2-L beaker. An excess of sodium borohydride was added portionwise during 5 h with constant stirring (caution: foaming)

and appropriate cooling so as to keep the temperature below 30°. The initially thick mixture became gradually fluid, and finally gave a translucid liquid upon completion of the reaction. The pH was then adjusted to 7.0 by slow addition of concentrated aqueous sodium hydrogenphosphate. The mixture was set aside overnight in the cold. The supernatant solution was then separated from the semicrystalline mass and the latter was extracted three times with warm (50°) methanol. The methanolic extracts were then combined with the supernatant solution and evaporated under diminished pressure without heating. The dry, solid residue was extracted 5 times with methanol (~300 mL). The combined methanolic phases were evaporated to dryness. The solid residue was washed twice with dichloromethane and was then taken up in methanol. After filtration, evaporation of the methanol gave pure **2** (70.5 g, 98.6%), m.p. 89° (softens), 165–166° (fully melts), $[\alpha]_D^{23}$ −38.5° (*c* 0.91, methanol); ^{13}C-n.m.r. (CD_3OD): δ 22.6 ($CO\underline{C}H_3$), 55.5 (C-2), 61.7 and 62.4 (C-1 and C-5), 67.8 (C-3), 72.2 (C-6), 83.8 (C-4), 102.2 (*C*HPh), 127.3, 128.8, 129.6, and 139.2 (Ph), and 173.4 (*C*O); *m/z* 311 (M^+), 310, 280, 233, 179, 174, 144, 132, 120, 114, 105, 103, 91 (100), 79, 77, 73, 72, 60, and 43.

Anal. Calc for $C_{15}H_{21}NO_6$: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.76; H, 6.65; N, 4.24.

*2-Acetamido-1,3,5-tri-*O*-acetyl-4,6-(*R*)-*O*-benzylidene-2-deoxy-*D*-glucitol* (**3**). — Under standard acetylation conditions (acetic anhydride–pyridine) at room temperature, triacetate **3** was obtained as the sole product from **2**. After quenching the mixture with ice, the aqueous layer was extracted with dichloromethane. Drying and evaporation of the organic layer provided crude **3**. Column chromatography (dichloromethane–methanol 99:1) afforded pure **3**, which crystallized slowly, m.p. 176–178°, $[\alpha]_D^{22}$ +18.9° (*c* 1.0 dichloromethane), ν_{max} ($CHCl_3$) 3430 (NH), 1735 (acetate CO), and 1760 cm^{-1} (amide CO); ^{1}H-n.m.r. (250 MHz): δ 3.62 (t, 1 H, $J_{6,6'}$ 10.4, $J_{5,6'}$ 10.5 Hz, H-6'), 4.01 (dd, 1 H, $J_{4,5}$ 10.2, $J_{3,4}$ 2.2 Hz, H-4), 4.10 (AB part of an ABX system, 1 H, $J_{1,1'}$ 11.7, $J_{1',2}$ 5.4 Hz, H-1'), 4.14 (AB part of an ABX system, 1 H, $J_{1,1'}$ 11.7, $J_{1,2}$ 4.7 Hz, H-1), 4.36 (dd, 1 H, $J_{6,6'}$ 10.4, $J_{5,6}$ 5.4 Hz, H-6), 4.64 (dd, 1 H, $J_{NH,2}$ 8.7, $J_{2,3}$ 5.8 Hz, H-2), 4.90 (M part of an ABMX system, 1 H, $J_{4,5}$ 10.2, $J_{5,6}$ 5.4, $J_{5,6'}$ 10.5 Hz, H-5), 5.33 (dd, 1 H, H-3), 5.47 (s, 1 H, C*H*Ph), and 5.91 (d, 1 H exch. with D_2O, NH).

Anal. Calc. for $C_{21}H_{27}NO_9$: C, 57.66; H, 6.22; N, 3.20. Found: C, 57.51; H, 6.03; N, 3.19.

*2-Acetamido-4,6-(*R*)-*O*-benzylidene-2-deoxy-1,3-*O*-isopropylidene-*D*-glucitol* (**4**). — Compound **2** (3.11 g, 10 mmol) was finely ground and suspended in 2,2-dimethoxypropane (25 mL) with stirring. Two drops (~40 mg) of concentrated sulfuric acid were added, which gave a few orange spots on the surface of undissolved material. The mixture became much thicker within 20 min. After 2 h, two additional drops of sulfuric acid were added with vigorous stirring. The next day, the mixture was much more fluid and stirring was continued for a further 2 days. Solid sodium hydrogencarbonate (~1 g) was then added and, after stirring for 1 h, most of the 2,2-dimethoxypropane was removed under diminished pressure. Di-

chloromethane was added and the organic layer was washed with water, dried, and evaporated under diminished pressure. Chromatography of the crude extract (3.3 g) on silica gel 60H, eluting with ethyl acetate, afforded pure **4** as a white foam (2.65 g, 75%; this yield decreased, however, to 55% on a 20-fold scale); $[\alpha]_D^{27}$ −46° (*c* 0.5 dichloromethane); ^{1}H-n.m.r.: δ 1.42 and 1.46 (s, 3 H each, C*Me*$_2$), 1.85 (s, 3 H, COC*H*$_3$), 4.4–5.3 (complex pattern, 8 H, H-1–H-6′), 5.4 (s, 1 H, C*H*Ph), 6.65 (d, 1 H, $J_{NH,2}$ 8 Hz), and 7.25–7.55 (m, 5 H, aromatic); ^{13}C-n.m.r.: δ 18.5 (C*Me*$_2$), 23.1 (CO*C*H$_3$), 29.4 (C*Me*$_3$), 47.0 (C-2), 62.0 (C-5), 64.8 (C-1), 69.0 (C-3), 71.6 (C-6), 81.8 (C-4), 99.9 (*C*Me$_2$), 101.2 (*C*HPh), 126.2, 128.1, 128.9, 137.8, (aromatic), and 170.7 (CO); *m/z* 351, 333, 230, 202, 150, 144, 108, 85 (100), 60, and 43.

Anal. Calc. for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.18; H, 7.29; N, 4.22.

*2-Acetamido-5-*O*-acetyl-4,6-(*R*)-*O*-benzylidene-2-deoxy-1,3-*O*-isopropylidene-*D*-glucitol* (**5**). — Acetylation of compound **4** under standard acetylation conditions gave, after quenching with ice, extraction of the aqueous layer with dichloromethane, and evaporation of the solvents, crude **5**. Purification by column chromatography (49:1 dichloromethane–methanol) gave pure **5**. An analytical sample was obtained by recrystallisation from toluene–cyclohexane; m.p. 120–122°, $[\alpha]_D^{27}$ −12.1° (*c* 1.08, dichloromethane); ν_{max} ($CHCl_3$: 1730 (acetate CO), and 1655 cm^{-1} (amide CO); ^{1}H-n.m.r.: δ 1.40 and 1.45 (s, 3 H, C*Me*$_2$), 1.69 (s, 3 H, NCOCH$_3$), 2.08 (s, 3 H, OCOC*H*$_3$), 3.59 (t, 1 H, $J_{6,6'}$ 10.3, $J_{5,6'}$ 10.3 Hz, H-6′), 3.8–4.3 (m, 5 H, H-1–H-4), 4.37 (dd, 1 H, $J_{5,6}$ 5.25 Hz, H-6), 5.21 (m, 1 H, $J_{4,5}$ 10.4 Hz, H-5), 5.44 (s, 1 H, C*H*Ph), and 7.30–7.55 (m, 5 H, aromatic).

Anal. Calc. for $C_{20}H_{27}NO_7$: C, 61.05; H, 6.92; N, 3.56. Found: C, 60.83; H, 7.03; N, 3.70.

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