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Studies on Nitro Sugars. VI.[1] Synthesis of Methyl 2-Deoxy-2-nitro-α-D-glucopyranoside Derivatives

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Synopsis. Oxidation of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-oximino-α-D-*arabino*-hexopyranoside (**5**) with trifluoroperoxyacetic acid afforded in 76% yield the corresponding 2-nitro-glucopyranoside (**6**) which has a twist-boat conformation in chloroform.

During the course of our synthetic studies[2,3] on nitro sugars by oxidation[4] of sugar oximes with trifluoroperoxyacetic acid, we have presented[5] the synthesis of benzyl 2-deoxy-3,4-*O*-isopropylidene-2-nitro-β-D-arabino- and ribopyranoside from the corresponding 2-oximino derivative. On their PMR spectroscopic conformational discussion, a slightly twisted 1*C* and a twist-boat conformation were elucidated, respectively.

In continuation of this study on 2-deoxy-2-nitropyranosides, we now describe the synthesis and the conformational discussion of methyl 2-deoxy-2-nitro-α-D-glucopyranoside derivatives.

On preparation of 2-nitro sugars in this manner, starting materials should have a free hydroxyl group at the C-2 position. 3-*O*-Benzyl-5,6-di-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose[6] (**1**) was heated under reflux in methanol containing 3% hydrogen chloride[7] to afford syrupy methyl 3-*O*-benzyl-α-D-glucopyranoside (**2**) which was easily converted to methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**3**) in 71% overall yield from **1** in the usual manner.

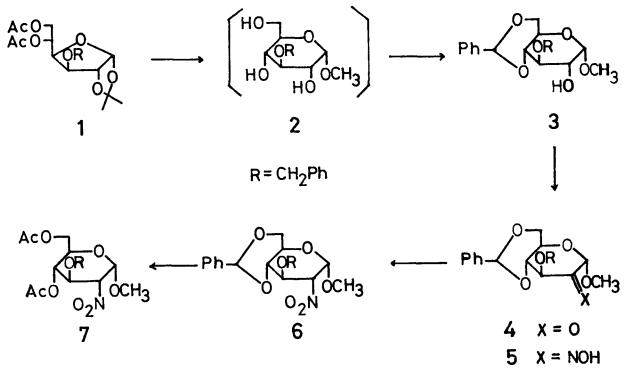
Assignment of α-D-glucopyranoside structure to **3** was based upon a specific rotation of +69.5° (acetone) and coupling constants, $J_{1,2}=3$ and $J_{2,3}=8$ Hz, on the PMR spectrum.

DMSO oxidation of **3** afforded in 54% yield amorphous powder of the corresponding 2-ulose (**4**), 1745 cm^{-1} ($\nu_{C=O}$), which was led to 2-oximino derivative (**5**) in 67% yield. Oxime **5** proved to be either single *syn*- or *anti*-form on the PMR spectrum (Table 1), although oxime is generally obtained as a mixture of them in such a reaction.

Oxidation of **5** with trifluoroperoxyacetic acid[8] at 42—43 °C gave selectively methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-nitro-α-D-glucopyranoside (**6**), 1560 cm^{-1} (ν_{asNO_2}), in 76% yield.

On the structural discussion of **6**, the configuration at the C-2 only might be determined because it is unchangeable at the anomeric and the C-3 position in such a oxidation. As shown in Table 1, coupling constants, $J_{2,3}=0$, $J_{3,4}=9$, and $J_{4,5}=8$ Hz which were obtained by the use of decoupling technics for deutrated **6**,[9] indicate that dihedral angles, ϕ_{23}, ϕ_{34}, and ϕ_{45}, are ~100, ~160, and ~170 °, respectively.

All the data, consequently, are consistent with D-gluco form which has a twist-boat conformation. Moreover, for completion of the configurational assignment, **6** was treated with acetic anhydride in the presence of concentrated sulfuric acid to give methyl 3-*O*-benzyl-2-deoxy-4,6-di-*O*-acetyl-2-nitro-α-D-glucopyranoside (**7**). The coupling constants, $J_{2,3}=9$, $J_{3,4}=10$, and $J_{4,5}=11$ Hz, indicate that H^2, H^3, H^4, and H^5 have diaxial relationship each other. Therefore diacetate **7** has obviously a *C*1 conformation, being different from the case of **6**.



Experimental

General. Melting points were determined in capillaries and are uncorrected. Specific rotations were measured with a Carl Zeiss photoelectric polarimeter. PMR spectra were recorded at 100 MHz with a JEOL spectrometer (Type JNM-4H-100) and tetramethylsilane as an internal standard. IR spectra were obtained with a Hitachi EPI-S2 instrument.

TABLE 1. PMR DATA FOR RING PROTONS (H^1–H^4) AND OTHER SUBSTITUENTS OF METHYL 3-*O*-BENZYL-α-D-GLUCOPYRANOSIDE DERIVATIVES (in $CDCl_3$)

Compound	Chemical shift (ppm)				Coupling constant (Hz)				Chemical shift (ppm)			
	H^1	H^2	H^3	H^4	J_{12}	J_{23}	J_{34}	J_{45}	$PhCH_2$	OCH_3	PhCH	OAc
3	4.72	4.25	?	?	3	8	?	?	4.83	3.57	5.50	—
5	5.82	—	4.54	?	—	—	10	?	4.80	3.39	5.53	—
6	5.22	4.61	4.63	?	3	0	9	8	4.86	3.36	5.59	—
7	5.17	5.05	4.60	4.53	3	9	10	11	4.70	3.34	—	2.04 1.96

Methyl 3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (3). To a suspension of 3-*O*-benzyl-5,6-di-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose[6] (**1**) (20 g) and anhydrous methanol (125 ml), was added acetyl chloride (6 ml)[7] slowly. After refluxed for 6 h, the reaction mixture was cooled to room temperature and poured into saturated sodium bicarbonate solution with stirring. Removal of inorganic substances by using ethanol and evaporation of the solvent gave syrup (16.7 g, negative Fehling test) which was stirred vigorously with benzaldehyde (50 ml) in the presence of zinc chloride (10 g) for 14 h. Work up in the usual manner gave crude solid which was recrystallized from ethanol to give fine crystals (13.4 g, 71%): mp 180—180.5 °C, $[\alpha]_D^{20}$ +69.5° (*c* 1, acetone). Found: C, 67.90; H, 6.60%. Calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50%.

Methyl 3-O-benzyl-4,6-O-benzylidene-α-D-arabino-hexopyranosid-2-ulose (4). After a mixture of **3** (0.74 g), distilled dimethyl sulfoxide (6 ml), and distilled acetic anhydride (4 ml) was stirred for 24 h at room temperature, the mixture was evaporated *in vacuo* below 60 °C. The solution of the residue in ethyl acetate (30 ml) was washed with water and evaporated to give yellowish solid which was reprecipitated from ethanol: amorphous powder 0.4 g (54%), 1745 cm^{-1} ($\nu_{C=O}$). Found: C, 67.79; H, 5.99%. Calcd for $C_{21}H_{22}O_6$: C, 68.07; H, 5.99 %.

Methyl 3-O-benzyl-4,6-3-O-benzylidene-2-oximino-α-D-arabino-hexopyranoside (5). A solution of **4** (1.3 g) in a mixture of pyridine (7 ml) and ethanol (7 ml) was heated under reflux in the presence of hydroxylamine hydrochloride (1 g) for 2 h. The mixture was evaporated *in vacuo* to give syrupy residue which was washed with water several times and put on a column (7.0×3.5 cm) of silica gel. After elution of benzene (100 ml), oxime **5** was eluted with a solvent system 19 : 1 benzene–methanol. Removal of the solvent gave amorphous solid which was reprecipitated from ethanol to give **5** (0.9 g, 67%): mp 182—183 °C, $[\alpha]_D^{20}$ −54.3° (*c* 0.8, acetone), 3280 cm^{-1} (ν_{OH}). Found: C, 65.21; H, 6.02; N, 3.90%. Calcd for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02; N, 3.63%.

Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-nitro-α-D-glucopyranoside (6). To oxidizing reagent[8] prepared by mixing successively 90% hydrogen peroxide (0.25 ml), trifluoroacetic anhydride (1.5 ml), acetonitrile (5 ml), dibasic sodium phosphate (5.75 g), and urea (45 mg), was added a solution of **5** (1 g) in acetonitrile (40 ml) dropwisely with manual stirring. After the mixture was kept at 42—43 °C for 1 h, the solvent was removed *in vacuo* to give solid which was dissolved in chloroform and washed with water three times. Evaporation *in vacuo* gave crude product which chromatographed on a column of silica gel with benzene. The eluate that showed a single spot at R_f 0.71 on tlc in a solvent system 30 : 1 benzene–acetone, was evaporated *in vacuo* to give the product (0.9 g, 86%). Recrystallization from ethanol–petroleum ether gave **6** (0.79g, 76%): mp 121—122 °C, $[\alpha]_D^{20}$ +75.4° (*c* 1, acetone), 1560 cm^{-1} (ν_{asNO_2}). Found: C, 62.67; H, 6.04; N, 3.56%. Calcd for $C_{21}H_{23}O_7N$: C, 62.83; H, 5.78; N, 3.49%.

Methyl 3-O-benzyl-2-deoxy-4,6-di-O-acetyl-2-nitro-α-D-glucopyranoside (7). **6** (207 mg) was treated with acetic anhydride (500 mg) in the presence of concentrated sulfuric acid (6 mg) at room temperature. After 30 min, the red mixture was poured into sodium bicarbonate solution and extracted with dichloromethane. The extracts were washed with water and dried over sodium sulfate, and then was evaporated to give the product which was recrystallized from ethanol–petroleum ether: white needles (60 mg, 30%), mp 148—149 °C, $[\alpha]_D^{20}$ +96° (*c* 1, chloroform), 1555 cm^{-1} (ν_{asNO_2}). Found: C, 54.19; H, 5.65; N, 3.59%. Calcd for $C_{18}H_{23}O_9N$: C, 54.40; H, 5.83; N, 3.53%.

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