Branched-Chain Deoxy Nitro and Amino Sugar Derivatives from Ketose

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(Received September 22, 1976)

The nitromethane addition to 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-*erythro*-pentofuranos-3-ulose (**1**) proceeded smoothly to give the corresponding branched-chain sugar (**2**), which on acetylation afforded (**3**) followed by elimination of acetic acid in presence of a base catalyst, resulted in the formation of the corresponding nitro olefin (**4**). The nitro olefin when subjected to borohydride reduction gave 5-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-3-(nitromethyl)-α-D-ribofuranose (**5**), which on catalytic hydrogenation followed by acetylation yielded the 3-(acetamidomethyl)-5-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (**6**). By the study of the NMR spectra of 3-deoxy derivatives (**5**) and (**6**), their D-ribo configurations were established.

The synthesis of various branched-chain carbohydrates was the aim of several investigators in recent years.[1,2] These syntheses usually utilise the required oxo sugars as intermediates, which then condense with diazomethane,[3] organolithium compounds,[1,4] Grignard reagents,[1,4,5] sulfur ylides,[6] and phosphorane.[7,8]

The synthesis of amino sugars by the method of nitromethane-sugar dialdehyde[9] has been modified,[10] by using nitroethane to afford branched-chain amino deoxy sugars, in which branching is on the carbon atom having the amino group.

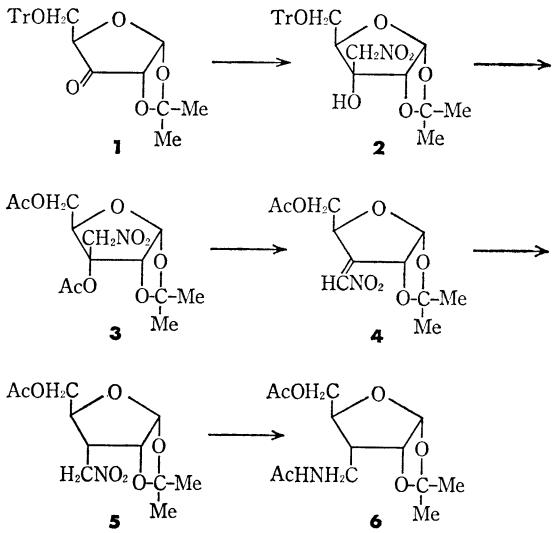
A recent method[8] described the synthesis of deoxy sugars having a nitrile or an amino group on the branched-chain. The synthesis of branched-chain nitro sugars[11] was carried out by the addition of nitryl iodide to a branched-chain unsaturated sugars, whereas Michael addition of nitro-alkanes to unsaturated nitro sugars produced branched-chain dinitro sugar derivatives.[12] The nitromethane method[9] has now been applied to oxo sugar to produce sugar derivatives with a nitro group on the branch, which could be readily converted into deoxy sugars having a nitro or an amino group on the branched-chain. This mehtod and others[13] led to the direct introduction of a functionalized one-carbon branch into carbohydrates.

Results and Discussion

The reaction of 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-*erythro*-pentofuranos-3-ulose[14] (**1**) with a suspension of the sodium salt of nitromethane (prepared by careful addition of sodium hydride to nitromethane)in nitromethane afforded 1,2-*O*-isopropylidene-3-(nitromethyl)--5-*O*-trityl-α-D-ribofuranose (**2**) in 76% yield.
Its NMR spectrum showed the existence of an exchangeable proton (3-OH) and an AB quartet of the two methylene protons of the branch. The IR spectrum showed the presence of a nitro group.

Acetylation of **2** with acetic anhydride in the presence of *p*-toluenesulfonic acid resulted in acetolysis of the 5-trityl ether in addition to acetylation of the 3-hydroxyl group, to produce 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-3(nitromethyl)-α-D-ribofuranose (**3**).

β-Acetoxynitroalkanes are useful precursors for α-nitroalkene synthesis, since they easily undergo base-catalyzed elimination of acetic acid.[15] Thus, treatment of **3** with anhydrous sodium carbonate in dry benzene readily gave the nitro olefin (**4**), which was then reduced



using sodium borohydride in aqueous acetonitrile,[16] to give the corresponding branched-chain deoxy nitro sugar (**5**) in a good overall yield. The 1,2-*O*-isopropylidene group, as expected, controlled the reaction sterically. From the NMR data of **5**, the configuration at C-3 was deduced. It showed a doublet at τ 4.14 (H-1) and a triplet at 5.19 (H-2), indicating that it was also coupled to H-3 . Since there was no coupling between H-2 and H-3 in 1,2-*O*-isopropylidene -α-D-xylo-furanose,[17] the product should have the deoxy-D-ribo configuration.

Catalytic reduction of **5** followed by acetylation afforded 3-(acetamidomethyl)-5-*O*-acetyl-3-doxy-1,2-*O*-isopropylidene-α-D-ribofuranose (**6**). Its NMR spectral data also confirmed the deoxy-D-ribo configuration.

This series of reactions describes the synthesis of functionalized branched-chain deoxy sugars from a branched-chain sugar with inversion of configuration at the center of branching, which is achieved by the steric influence of the 1,2-*O*-isopropylidene group.

Experimental

Melting points were determined with a Fischer-Jones apparatus and were uncorrected. NMR spectra were observed on a Varian HA-100 spectrometer using TMS as an internal standard. IR spectra were recorded with a Unican SP 200 spectrometer. Optical rotations were determined with a Perkin-Elmer 141 recording polarimeter. Solutions were concentrated on a rotary evaporator at below 20 °C under

reduced pressure.

1,2-O-Isopropylidene-3-(nitromethyl)-5-O-trityl-α-D-ribofuranose (2). A suspension of sodium hydride (0.15 g) in nitromethane (10 ml) was added dropwise to a cooled (Dry Ice bath below −20 °C) and stirred solution of 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-*erythro*-pentofuranos-3-ulose[14] (1.1 g) in nitromethane (10 ml). The reaction mixture was stirred for one additional hour at room temperature and neutralized with glacial acetic acid, and the solvent was evaporated. The residue was dissolved in water (60 ml) and extracted with chloroform (3×50 ml), washed with water and dried. The syrup obtained on evaporation of the extract was crystallised from acetone–hexane to give the title compound **2** (0.9 g, *Y*= 76%); mp 120—122 °C, $[\alpha]_D^{20}$ +29° (*c* 1, $CHCl_3$), IR ν_{max}^{KBr} 3450 (OH), 1560 cm^{-1} (NO_2); NMR ($CHCl_3$): τ 3.98 (1H, d, $J_{1,2}$ 4.0 Hz); 5.13 (2H, d), 5.88 (4H, t, $J_{4,5}$ 5 Hz); 6.68 (5H, m); 5.59 (CH_2NO_2, q, $J_{a,b}$ 12.5 Hz); 8.40, 8.60 (CMe_2, s); 6.83 (OH, s, disappeared on deuteration with D_2O).

Found: C, 68.5; H, 5.7; N, 3.0%. Calcd for $C_{28}H_{29}NO_7$: C, 68.4; H, 5.9; N, 2.8%.

3,5-Di-O-acetyl-1,2-O-isopropylidene-3-(nitromethyl)-α-D-ribofuranose (3). A solution of **2** (0.6 g) in acetic anhydride (6 ml) was stirred overnight at room temperature in the presence of anhydrous *p*-toluenesulfonic acid (0.1 g). The reaction mixture was then slowly poured onto an aqueous solution of sodium hydrogencarbonate and the gummy product was decanted, washed several times with cold water and dissolved in chloroform, which was washed with water and dried (Na_2SO_4). On evaporation of the dried chloroform, compound **3** was obtained as a pale yellow syrup (0.4 g); IR ν_{max} 1760 (OAc); 1510 cm^{-1} (NO_2).

Found: C, 45.1; H, 4.8; N, 4.6%. Calcd for $C_{12}H_{16}NO_9$: C, 45.3; H, 5.0; N, 4.4%.

5-O-Acetyl-3-deoxy-1,2-O-isopropylidene-3-(nitromethyl)-α-D-ribofuranose (5). Powdered potassium carbonate (0.5 g) was added to a solution of **3** (1.8 g) in dry benzene (25 ml) and the suspension was stirred magnetically for 6 h at room temperature. The mixture was filtered using Celite pad and the filtrate was evaporated to give **4** as yellow viscous syrup. It was dissolved in acetonitrile (25 m), cooled in an ice bath, stirred. To this was added a solution of sodium borohydride (0.2 g) in water (2 ml). After one hour stirring, the reaction mixture was diluted with water (100 ml) and extracted with chloroform (4×25 ml). The extracts were washed with water and dried (Na_2SO_4). On evaporation, the residue obtained (0.8 g, *Y*=58%) was crystallised from acetone–hexane, mp 127—129 °C; $[\alpha]_D^{20}$ +62° (*c* 1, $CHCl_3$), IR ν_{max}^{KBr} 1750 (OAc), 1565 cm^{-1} (NO_2), NMR ($CDCl_3$): τ 4.14 (1H, d, $J_{1,2}$ 4.0 Hz); 5.14 (2H, t); 7.32 (3H, m); 5.70—6.07 (3-proton, m, 4H, 5H); 5.39 (CH_2NO_2, q); 8.52, 8.72 (CMe_2, 2 s); 7.96 (Ac, s).

Found: C, 48.2; H, 6.3; N, 4.9%. Calcd for $C_{11}H_{17}NO_7$: C, 48.0; H, 6.2; N, 5.1%.

3-(Acetamidomethyl)-5-O-acetyl-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (6). A solution of **5** (0.14 g) in ethanol (20 ml) was reduced with hydrogen in the presence of platinum oxide (0.1 g) at room temperature under atmospheric pressure for 2 h, during which the calculated amount of hydrogen was consumed. The reaction mixture was filtered and evaporated to give the corresponding amine as a syrup. It was dissolved in dry pyridine (2 ml) and acetic anhydride (2 ml) was added, and the solution was stirred for 2 h. The reaction mixture was then poured onto ice, and extracted with chloroform (4× 20 ml). The extracts were then washed with cold dilute hydrochloric acid, aqueous sodium hydrogencarbonate and water, and dried (Na_2SO_4). On evaporation of the dried extract compound **6** was obtained as a syrup, (0.11 g, *Y*= 82%) $[\alpha]_D^{20}$+57° (*c* 1, $CHCl_3$); IR ν_{max} 3450 (NH), 1750 (OAc), 1680, 1525 cm^{-1} (NHAc); NMR ($CDCl_3$): τ 4.20 (1H, *d*, $J_{1,2}$ 4.0 Hz); 5.34 (2H, t); 3.74 (NH, broad);7.93, 8.04 (Ac, two s); 8.50, 8.70 (CMe_2, two s).

Found: C, 54.4; H, 7.6; N, 4.7%. Calcd for $C_{13}H_{21}NO_6$: C, 54.3; H, 7.4; N, 4.9%.

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