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Nucleosides. 124. 3-Amino-3-deoxyhexopyranosyl Nucleosides. 7. 1-(3-Deoxy-3-Nitro- β -D-glucopyranosyl) Uracil and Its Galactopyranosyl Isomer¹

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NUCLEOSIDES. 124. 3-AMINO-3-DEOXYHEXOPYRANOSYL NUCLEOSIDES. 7.
1-(3-DEOXY-3-NITRO- β -D-GLUCOPYRANOSYL)URACIL
AND ITS GALACTOPYRANOSYL ISOMER.¹

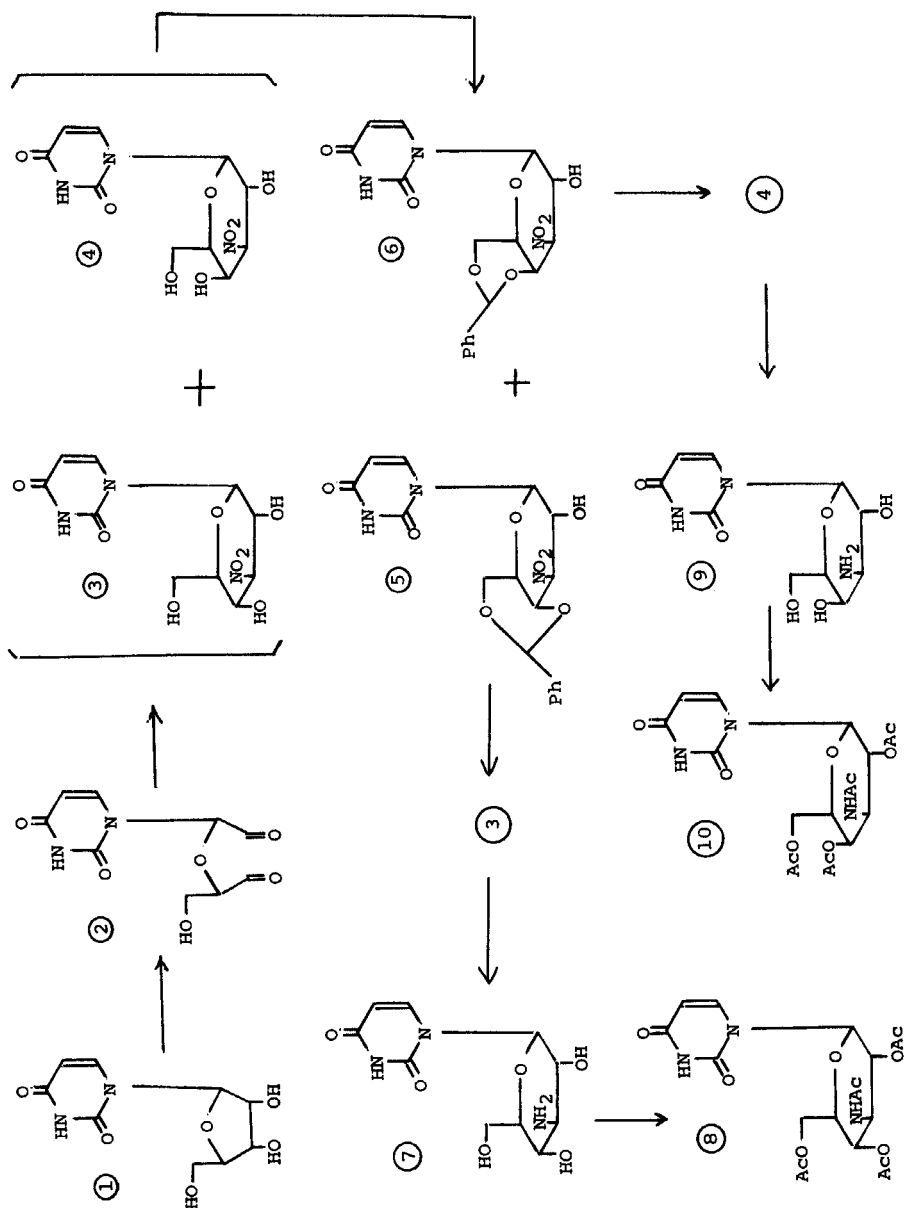
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Abstract: Crystalline 1-(3-deoxy-3-nitro- β -D-glucopyranosyl)uracil (3), originally prepared by nitromethane condensation of "uridine dialdehyde," was found to contain the galactosyl isomer (4). Each isomer was obtained in pure form by 4',6'-O-benzylidenation of the mixture of 3 and 4, followed by chromatographic separation and subsequent O-debenzylidenation. The structure of each isomer was established by chemical conversion of the isomer into the corresponding known 3'-acetamido-2',4',6'-tri-O-acetyl derivative.

The nucleoside, 1-(3-deoxy-3-nitro- β -D-glucopyranosyl)uracil (3) was originally reported by Watanabe, *et al.*,² who prepared it in about 60% yield by condensation of "uridine dialdehyde" (2) with nitromethane. The structure of the product was assigned to the gluco configuration (3) on the basis of its chemical conversion into the 3'-amino-nucleoside (7) from which, eventually, methyl 3-acetamido-2,4,6-tri-O-acetyl-3-deoxy- α -D-glucopyranoside was obtained. The nitro product had the melting point (175-176°C) which was not altered after repeated recrystallization. It was analyzed correctly and the ¹H NMR spectrum (60 MHz) did not indicate the presence of other isomers.

During our recent studies on the chemistry of nitro-sugar nucleosides, the 4',6'-O-benzylidene nucleoside (5) was needed. This nitro-nucleoside was prepared by condensation of 2 with MeNO₂ followed by treatment with α,α -dimethoxytoluene in presence of acid. We found the two benzylidenated products in the reaction mixture in a proportion of ~4:1. The starting nitro-nucleoside was therefore re-examined by ¹H NMR (100 MHz) which showed that it also was a 4:1 mixture of two components, as estimated by the integra-



tion of double peaks for H-5 and H-6 signals. Attempts to separate these components by silica-gel chromatography were unsuccessful. Even application of analytical HPLC (μ Bondapak C18) using MeOH:H₂O with proportions from 100:0 to 20:80 did not separate these two nucleosides. The 4',6'-O-benzylidene products, however, were separated to afford two crystalline products on a silica gel column. The major product was O-debenzylidenated and then reduced to 3'-amino-3'-deoxy- β -D-glucopyranosyluracil (7)^{2,3} which was further peracetylated to the known crystalline tetraacetate (8).² The minor product was also O-debenzylidenated to a crystalline 3'-nitro-nucleoside. After reduction and peracetylation, the known galactosyl nucleoside (10)⁴ was obtained. These experiments established the structure of the major nitro-methane condensation product to be the gluco derivative (3) and the minor product to the galacto nucleoside (4). Thus, for the first time, these 3'-nitro nucleosides were isolated and characterized in the pure state.

EXPERIMENTAL

General. Melting points were determined on a Thomas-Hoover Capillary apparatus and are corrected. ¹H NMR spectra were obtained on a JEOL-PFT-100 Spectrometer, and Me₄Si was the internal standard for organic solvents and Me₃Si(CH₂)₃SO₃Na (external) for D₂O. TLC was performed on Uniplates (Analtech, Newark, Del.) and column chromatography on silica gel G60 (70-230 mesh, ASTM, Merck).

1-(4,6-O-Benzylidene-3-deoxy-3-nitro- β -D-glucopyranosyl)uracil (5) and 1-(4,6-O-Benzylidene-3-deoxy-3-nitro- β -D-galactopyranosyl)uracil (6). A mixture of the nitronucleosides⁵ (9.0 g, 30 mmol), α,α -dimethoxytoluene (6 mL) and TsOH·H₂O (300 mg) in DMF was heated at 50-55°C with stirring under reduced pressure (ca. 20 mm Hg). After 16 h, α,α -dimethoxytoluene (1 mL) and TsOH·H₂O (100 mg) were added, and the mixture stirred for another 8 h under reduced pressure at 50-55°C. The mixture was diluted with AcOEt (100 mL) and the organic layer was washed with saturated NaHCO₃ solution (50 mL), H₂O (50 mL) x 3, and dried (Na₂SO₄). After evaporation of the solvent, the residue was triturated with n-C₆H₁₄ (50 mL x 3), dissolved in CHCl₃ and chromatographed (30 x 5 cm) using CHCl₃-MeOH (40:1) as the eluent. The major component was eluted from the column first, followed by the minor component. Each fraction was evaporated and the residue recrystallized from MeOH. From the first fraction, 9 g (77%) of compound 5: mp 258-259°C was obtained. ¹H NMR (DMSO-d₆): δ 3.84 (2H, m, H-6',6"), 4.32 (3H, m, H-2',4',5'), 5.26 (1H, t, H-3', J_{2',3'} = J_{3',4'} =

10.1 Hz), 5.68 (1H, s, PhCH=), 5.74 (1H, d, H-1', $J_{1',2'} = 7.9$ Hz), 5.82 (1H, d, H-5, $J_{5,6} = 8.2$ Hz), 6.50 (1H, d, 2'-OH, exchangeable), 7.39 (5H, s, Ph), 7.87 (1H, d, H-6, $J_{5,6} = 8.2$ Hz), 11.44 (1H, broad s, NH, exchangeable).

Anal. Calcd. for $C_{17}H_{17}N_3O_8$: C, 52.18; H, 4.38; N, 10.74. Found: C, 52.30; H, 4.49; N, 10.71.

From the second fraction, compound 6 (1 g, 8.6%) was obtained: mp 243-244°C. ^1H NMR (DMSO- d_6): δ 4.02 (1H, s, H-5'), 4.14 (2H, s, H-6',6"), 4.46 (1H, m, H-2'), 4.82 (1H, broad s, H-4'), 5.37 (1H, dd, H-3', $J_{2',3'} = 9.8$ Hz, $J_{3',4'} = 3.7$ Hz), 5.68 (1H, s, PhCH=), 5.72 (1H, d, H-1', $J_{1',2'} = 9.2$ Hz), 5.76 (1H, d, H-5, $J_{5,6} = 8.2$ Hz), 6.22 (1H, d, 2'-OH), 7.39 (5H, s, Ph), 7.61 (1H, d, H-6, $J_{5,6} = 8.2$ Hz), 11.45 (1H, broad s, NH).

Anal. Calcd. for $C_{17}H_{17}N_3O_8 \cdot H_2O$: C, 49.88; H, 4.68; N, 10.26. Found: C, 50.25; H, 4.50; N, 10.05. The presence of water in the analytical sample was detected by ^1H NMR.

1-(3-Deoxy-3-nitro- β -D-glucopyranosyl)uracil (3). Compound 5 (391 mg, 1 mmol) was dissolved in 90% $\text{CF}_3\text{CO}_2\text{H}$ (5 mL), and the solution stirred for 2 h at room temperature, then evaporated to dryness in vacuo. The solid residue was triturated with benzene (10 mL \times 3) and then recrystallized from H_2O to give 210 mg (70%) of compound 3: mp 176° (sintered), 202-203°C (eff.), single spot on TLC (CHCl_3 -MeOH, 5:1 v/v) and ^1H NMR did not indicate the presence of any impurity. ^1H NMR (DMSO- d_6): δ 3.3-4.0 (4H, m, H-4',5',6',6"), 4.10 (1H, m, H-2'; became a triplet upon addition of D_2O , $J_{1',2'} = J_{2',3'} = 9.4$ Hz), 5.63 (2H, m, H-3', 6'-OH; became a triplet for 1H upon addition of D_2O , $J_{2',3'} = J_{3',4'} = 9.4$ Hz), 5.58 (1H, d, H-1', $J_{1',2'} = 9.4$ Hz), 5.69 (1H, dd, H-5, $J_{5,6} = 8.3$ Hz, $J_{3,5} = 0.5$ Hz), 5.98 (1H, d, OH), 6.22 (1H, d, OH). 7.81 (1H, d, H-6, $J_{5,6} = 8.3$ Hz), 11.39 (1H, bs, NH).

1-(3-Deoxy-3-nitro- β -D-galactopyranosyl)uracil (4). In a similar manner as above, 260 mg (86%) of 4 was obtained from 391 mg (1 mmol) of 6 after recrystallization from water: mp 173-174° (sinter), 224-225°C (eff.), single spot on TLC (CHCl_3 -MeOH, 5:1 v/v) and ^1H NMR did not indicate the presence of any impurity. ^1H NMR (DMSO- d_6): δ 3.30-3.45 (2H, m, H6',6"), 3.85 (1H, t, H-5'), 4.25 (1H, dd, H-4'; becomes d upon addition of D_2O , $J_{3',4'} = 3.4$ Hz), 4.41 (1H, m, H-2'; becomes t upon addition of D_2O , $J_{1',2'} = J_{2',3'} = 9.5$ Hz), 4.86 (1H, t, 6'-OH), 5.10 (1H, dd, H-3', $J_{2',3'} = 9.5$, $J_{3',4'} = 3.4$ Hz), 5.51 (1H, d, OH), 5.57 (1H, d, H-1', $J_{1',2'} = 9.5$ Hz), 5.75 (1H, dd, H-5; becomes d upon addition of D_2O , $J_{5,6} = 8.3$, $J_{3,5} = 0.5$ Hz), 6.06 (1H, d, OH), 7.85 (1H, d, H-6, $J_{5,6} = 8.3$ Hz), 11.36 (1H, bs, NH).

1-(3-Amino-3-deoxy- β -D-glucopyranosyl)uracil (7). To a solution of crystalline 3 (500 mg, 1.7 mmol) in 100 mL of 40% aqueous EtOH was added activated Raney Ni (1 g, wet weight). The mixture was shaken in hydrogen for 1 h at room temperature at an initial pressure of 3 atmospheres. The catalyst was removed by filtration through a Celite pad and washed with EtOH (20 mL) and water (10 mL). The filtrate and washings were combined, concentrated in vacuo and the solid residue recrystallized from EtOH to give 425 mg (94%) of 7: mp 227-230°C (eff.). ^1H NMR (DMSO- d_6): δ 2.75 (1H, t, H-3', $J_{2',3'} = J_{3',4'} = 8.8$ Hz), 5.34 (1H, d, H-1', $J_{1',2'} = 9.2$ Hz), 5.62 (1H, d, H-5, $J_{5,6} = 8.2$ Hz), 7.64 (1H, d, H-6, $J_{5,6} = 8.2$ Hz). 1-(3-Amino-3-deoxy- β -D-galactopyranosyl)uracil (9). In a similar manner, compound 9 (53 mg, 99%) was obtained from 60 mg of 4: mp 120°C (sinter), 264-268°C (eff.).

1-(3-Acetamido-2,4,6-tri-O-acetyl-3-deoxy- β -D-glucopyranosyl)uracil (8). A mixture of 7 (272 mg, 1 mmol), Ac_2O (2 mL) and pyridine (5 mL) was stirred overnight at room temperature. MeOH (5 mL) was added and the mixture was concentrated in vacuo to dryness. The residue was recrystallized from EtOH to give 390 mg (quantitative yield) of the tetraacetate 8: mp 253-254°C, (Lit.² mp 253-254°C). ^1H NMR (DMSO- d_6): δ 1.76 (3H, s, NAc), 1.89 (3H, s, OAc), 1.99 (3H, s, OAc), 2.01 (3H, s, OAc), 4.08-4.27 (3H, m, H-5', 6', 6''), 4.42 (1H, q, H-3', $J_{2',3'} = J_{3',4'} = J_{3',\text{NH}} = 9.7$ Hz), 4.95 (1H, t, H-2' (4'), $J_{1',2'} = J_{2',3'} = 9.7$ Hz), 5.07 (1H, t, H-4' (2'), $J_{3',4'} = J_{4',5'} = 10.0$ Hz), 5.72 (1H, d, H-5, $J_{5,6} = 8.2$ Hz), 5.92 (1H, d, H-1', $J_{1',2'} = 9.6$ Hz), 7.56 (1H, d, H-6, $J_{5,6} = 8.2$ Hz), 7.89 (1H, d, 3'-NH), 11.42 (1H, bs, 3-NH).

1-(3-Acetamido-2,4,6-tri-O-acetyl-3-deoxy- β -D-galactopyranosyl)uracil (10). In a similar manner, compound 9 was peracetylated to give crystalline 10: mp 156-158°C. (Lit.⁴ mp 156°C). The ^1H NMR spectrum of this sample was identical with that of the tetraacetate of 3'-aminogalactopyranosyluracil⁴ which was prepared via condensation of peracetylated 3-aminogalactosyl bromide with 2,4-dimethoxypyrimidine by the Hilbert-Johnson procedure.

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