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Note

Synthesis of 2,4-di-*O*-benzyl-3-deoxy-3-[*N*-(2,4-dinitrophenyl)-*N*-methylamino]-α-D-xylopyranosyl chloride (a 1-halogeno gentosamine derivative)

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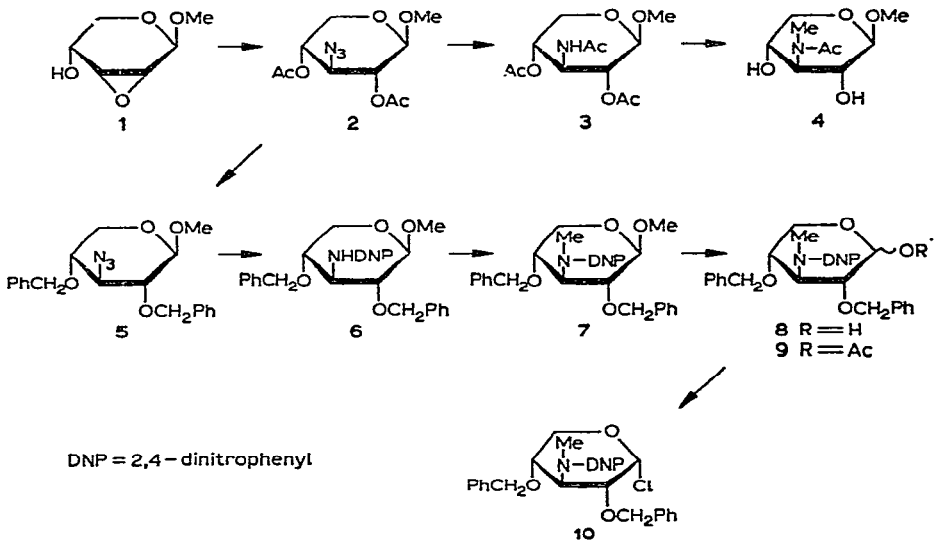
Gentosamine [3-deoxy-3-(methylamino)-D-xylose] is known as a component of gentamicin A, one of the numerous antibiotics that comprise the gentamicin complex. Maehr and Schaffner[1,2] isolated it as the methyl gentosaminides by methanolysis of gentamicin A, and elucidated the configuration synthetically. The present Note deals with the synthesis of a stable 1-halogeno gentosamine derivative bearing benzyl groups at O-2 and O-4. Treatment of methyl 2,3-anhydro-β-D-ribopyranoside[3] (**1**) in 2-methoxyethanol (methyl Cellosolve) with sodium azide, followed by acetylation, afforded (in over 90% yield) methyl 2,4-di-*O*-acetyl-3-azido-3-deoxy-β-D-xylopyranoside (**2**).

In order to obtain structural evidence, compound **2** was converted into methyl 3-acetamido-2,4-di-*O*-acetyl-3-deoxy-β-D-xylopyranoside (**3**) by reduction with Pd–C catalyst, followed by acetylation. *N*-Methylation of compound **3** by using methyl iodide and silver oxide in dry *N*,*N*-dimethylformamide (DMF), and subsequent *O*-deacetylation, afforded the known methyl *N*-acetylgentosaminide[2] (**4**). We therefore concluded that the initial product from **1** is methyl 2,4-di-*O*-acetyl-3-azido-3-deoxy-β-D-xylopyranoside (**2**).

Benzylation[4] of the *O*-deacetylated derivative of **2** with benzyl bromide in DMF gave methyl 3-azido-2,4-di-*O*-benzyl-3-deoxy-β-D-xylopyranoside (**5**) in good yield. Reduction of the azido group of **5** with zinc powder in 90% aqueous acetic acid, followed by (2,4-dinitrophenyl)ation, afforded methyl 2,4-di-*O*-benzyl-3-deoxy-3-(2,4-dinitrophenylamino)-β-D-xylopyranoside (**6**). Treatment of compound **6** with methyl iodide and silver oxide in dry DMF afforded methyl 2,4-di-*O*-benzyl-3-deoxy-3-[*N*-(2,4-dinitrophenyl)-*N*-methylamino]-β-D-xylopyranoside (**7**) in almost quantitative yield; as far as we are aware, *N*-methylation of the 2,4-dinitroanilino group has not hitherto been encountered in the carbohydrate field. Hydrolysis of **7** by mild heating with acetic acid–hydrochloric acid, followed by acetylation, afforded the 1-acetate (**9**). 1-*O*-Acetyl-2,4-di-*O*-benzyl-3-deoxy-3-[(*N*-2,4-dinitrophenyl)-*N*-methylamino]-D-xylopyranose (**9**) was treated with 6% hydrogen chloride in dry 1,4-dioxane, affording the chloride (**10**) in quantitative yield. Compound **10** was found to be the

α anomer, as its n.m.r. spectrum showed an anomeric proton signal at τ 3.78, with a spacing[5] of 3.5 Hz.



EXPERIMENTAL

General methods. — Melting points were determined on a Yanagimoto micro melting-point apparatus and are uncorrected. Specific rotations were determined with a Yanagimoto polarimeter OR-50. N.m.r. spectra were recorded at 60 MHz for solutions in chloroform-*d*. I.r. spectra were recorded with a Jasco IRA-1 spectrophotometer. Preparative chromatography was performed on 100-mesh silicic acid (Mallinckrodt Chem. Works) with the solvent systems specified.

Methyl 2,4-di-O-acetyl-3-azido-3-deoxy-β-D-xylopyranoside (**2**). — To a solution of methyl 2,3-anhydro-β-D-ribopyranoside[3] (**1**) (24.0 g) in methyl Cellosolve (500 ml) and water (100 ml) were added sodium azide (53 g) and ammonium chloride (25 g), and the mixture was stirred for 5 h at 120°. The inorganic salts were removed by filtration, and the filtrate was evaporated *in vacuo* to a syrup which was acetylated with acetic anhydride (90 ml) and pyridine (140 ml). The mixture was evaporated *in vacuo*, the residue extracted with chloroform, and the extract washed successively with 2M hydrochloric acid, M sodium carbonate, and water, and evaporated to a crystalline mass (42.5 g, 95%) which was recrystallized from ethanol to afford colorless plates having m.p. 64.5° and $[\alpha]_D^{25}$ −67.1° (*c* 1.0, chloroform); ν_{max}^{Nujol} 2150 (N_3), and 1770 and 1230 cm^{-1} (ester).

Anal. Calc. for $C_{10}H_{15}N_3O_6$: C, 43.95; H, 5.53; N, 15.35. Found: C, 44.09; H, 5.27; N, 14.98.

Methyl 3-acetamido-2,4-di-O-acetyl-3-deoxy-β-D-xylopyranoside (**3**). — The azido compound **2** (30.0 g) was dissolved in ethanol (500 ml) and acetic acid (9 ml);

5% Pd–C catalyst (16.0 g) was added, and hydrogen was bubbled through the mixture, with stirring, for 3 h at room temperature. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo*. The residual syrup was acetylated with acetic anhydride (30 ml) and pyridine (50 ml). The product was recrystallized from ether to give colorless needles; wt. 30.5 g (93%), m.p. 174–175.5°, $[\alpha]_D^{28}$ −60.2° (*c* 1.02, chloroform); ν_{max}^{Nujol} 3450 (NH), 1750 and 1250 (ester), and 1670 and 1560 cm^{-1} (amide).

Anal. Calc. for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84. Found: C, 50.11; H, 6.37; N, 4.96.

Methyl 3-deoxy-3-(N-*acetyl*-N-*methylamino*)-*β*-D-*xylopyranoside* (*methyl* N-*acetyl*-*β*-D-*gentosaminide*) (**4**). — To a stirred solution of **3** (34.0 g) in dry DMF (205 ml) and methyl iodide (40 ml) was added silver oxide (38.0 g) during 30 min. The suspension was stirred for 12 h at room temperature, and the silver salts were collected by filtration, and washed with DMF. The filtrate and washings were combined, evaporated *in vacuo*, the residue extracted with chloroform, and the extract evaporated to dryness. To a solution of the resulting syrup in methanol (100 ml) was added sodium metal (50 mg), and the mixture was kept for 10 min at room temperature, and then treated with Amberlite IRC-50 ion-exchange resin. The solution was evaporated *in vacuo* to a syrup which was crystallized from methanol–ether to give 15.5 g (62%) of **4**; after recrystallization from the same solvent mixture, this was obtained as colorless needles, m.p. 183°, $[\alpha]_D^{30}$ −58° (*c* 1.0, water); lit.[2] m.p. 183°, $[\alpha]_D^{25}$ −59.5° (*c* 0.8, water).

Anal. Calc. for $C_9H_{17}NO_5$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.26; H, 7.97; N, 6.45.

*Methyl 3-azido-2,4-di-*O-*benzyl-3-deoxy-β-*D-*xylopyranoside* (**5**). — Compound **2** (30.0 g) was *O*-deacetylated by sodium in methanol in the usual way. To a stirred solution of the product in DMF (300 ml), held at 0°, were added benzyl bromide (90 ml), barium oxide (85 g), and barium hydroxide octahydrate (40 g). The mixture was stirred for 2 h at 0°, and then for 14 h at room temperature. Dichloromethane (250 ml) was added, the suspension was filtered, and the solid was washed with dichloromethane. The filtrate and washings were combined, washed with water, dried (sodium sulfate), and evaporated *in vacuo* to a syrup which was chromatographed on a column of silicic acid (300 g) with benzene. Compound **5** was isolated as a colorless syrup (34 g, 84%), $[\alpha]_D^{15}$ −21.2° (*c* 0.82, acetone); ν_{max}^{Nujol} 2150 (N_3), and 740 and 690 cm^{-1} (phenyl).

Anal. Calc. for $C_{20}H_{23}N_3O_4$: C, 65.02; H, 6.28; N, 11.38. Found: C, 65.32; H, 6.02; N, 11.65.

*Methyl 2,4-di-*O-*benzyl-3-deoxy-3-*(*2,4-dinitrophenylamino*)-*β*-D-*xylopyranoside* (**6**). — To a stirred solution of **5** (10.0 g) in 90% aqueous acetic acid held at 2° was added zinc powder (15.0 g) in small amounts, and the mixture was stirred for 30 min at 0°. The precipitate was removed by filtration, and the filtrate was evaporated *in vacuo* below 50°, to give a syrup which was extracted with chloroform. The extract was successively washed with M sodium carbonate and water, dried (sodium sulfate),

and evaporated *in vacuo* to a syrup (8.2 g) which was used in the next reaction without further purification. To a stirred solution of the syrup and 1-fluoro-2,4-dinitrobenzene (5.4 g) in acetone (200 ml) were added sodium carbonate (5.5 g) and water (80 ml), the mixture was stirred for 24 h at room temperature, the acetone was evaporated off, and the aqueous solution was extracted with chloroform. The extract was washed with water, dried, and evaporated *in vacuo* to a syrup which crystallized from ethanol. Recrystallization from ethanol gave yellow needles, wt. 4.6 g (33%), m.p. 116°, $[\alpha]_D^{15}$ +16.1° (*c* 1.0, acetone); ν_{max}^{Nujol} 3350 (NH), 1615 and 1585 [2,4-$(NO_2)_2C_6H_4$], and 730 and 690 cm^{-1} (phenyl).

Anal. Calc. for $C_{26}H_{27}N_3O_8$: C, 61.29; H, 5.34; N, 8.25. Found: C, 61.40; H, 5.55; N, 8.05.

*Methyl 2,4-di-*O*-benzyl-3-deoxy-3-*[N-(*2,4-dinitrophenyl*)-N-*methylamino*]-β-*D*-xylopyranoside* (**7**). — To a stirred solution of **6** (5.0 g) in dry DMF (20 ml) and methyl iodide (7.0 g) was added silver oxide (3.4 g) at room temperature, and the mixture was stirred for 24 h. The silver salts were removed by filtration, the filtrate was evaporated *in vacuo*, and the residue was extracted with chloroform. The extract was washed with water, dried, and evaporated *in vacuo* to a syrup which was chromatographed on a column of silicic acid (50 g) with benzene. Compound **7** was obtained as an amorphous product; wt. 5.0 g (97%), $[\alpha]_D^{15}$ +34.5° (*c* 0.98, acetone); ν_{max}^{Nujol} 1610 and 1590 [2,4-$(NO_2)_2C_6H_4$], and 730 and 690 cm^{-1} (phenyl); n.m.r. data: τ 2.75 (phenyl), 6.41 (OCH_3), and 2.71 and 2.86 (NCH_3).

Anal. Calc. for $C_{27}H_{29}N_3O_8$: C, 61.94; H, 5.88; N, 8.03. Found: C, 61.82; H, 5.65; N, 7.76.

*2,4-Di-*O*-benzyl-3-deoxy-3-*[N-(*2,4-dinitrophenyl*)-N-*methylamino*]-*D*-xylopyranose* (**8**). — A solution of compound **7** (18.0 g) in a mixture of acetic acid (50 ml) and 6M hydrochloric acid (6.5 ml) was heated for 2.5 h at 86–90° with occasional shaking, poured onto ice–water, and extracted with chloroform. The extract was successively washed with M sodium carbonate and water, dried, and evaporated *in vacuo*. The residual syrup was chromatographed on silicic acid (100 g) with benzene, to afford **8** (14.1 g, 81%), m.p. 60–62.5°, $[\alpha]_D^{15}$ +48.5° (*c* 1.07, equil., chloroform); ν_{max}^{Nujol} 3400 (OH), 1610 and 1580 [2,4-$(NO_2)_2C_6H_4$], and 740 and 690 cm^{-1} (phenyl).

Anal. Calc. for $C_{26}H_{27}N_3O_8$: C, 61.29; H, 5.34; N, 8.25. Found: C, 61.20; H, 5.43; N, 8.25.

*1-*O*-Acetyl-2,4-di-*O*-benzyl-3-deoxy-3-*[N-(*2,4-dinitrophenyl*)-N-*methylamino*]-*D*-xylopyranose* (**9**). — Compound **8** (14.0 g) was acetylated with acetic anhydride–pyridine at room temperature; the product was obtained as an amorphous compound in quantitative yield, $[\alpha]_D^{15}$ +35.7° (*c* 1.0, acetone).

Anal. Calc. for $C_{28}H_{29}N_3O_9$: C, 60.97; H, 5.30; N, 7.62. Found: C, 61.17; H, 5.46; N, 7.56.

*2,4-Di-*O*-benzyl-3-deoxy-3-*[N-(*2,4-dinitrophenyl*)-N-*methylamino*]-α-*D*-xylopyranosyl chloride* (**10**). — A solution of compound **9** (3.5 g) in 6% hydrogen chloride in absolute 1,4-dioxane (115 ml) was kept for 7 days at 30–35° and then evaporated to dryness below 35°. Dry benzene was repeatedly added and evaporated. The

product was obtained as an amorphous compound; $[\alpha]_D^{15}$ +94.5° (*c* 0.7, benzene); n.m.r. data: τ 2.75 (phenyl), 3.78 (1 H, doublet, $J_{1,2}$ 3.5 Hz), and 7.75 (NCH_3).

Anal. Calc. for $C_{26}H_{26}ClN_3O_7$: C, 59.15; H, 4.96; N, 7.96. Found: C, 59.10; H, 5.16; N, 7.83.

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