with barium methylate. After removal of the barium as barium sulfate, the solution was evaporated *in vacuo* and the residue recrystallized from ethanol and from a mixture of methanol and ether; 119 mg. (95%) of long needles VIII was obtained; m.p. 199–200°, $[\alpha]^{25}D$ +150 ± 4° (in methanol, *c* 0.77). The mixed m.p. with methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-glucopyranoside[3] (m.p. 192–193°) was 165–183°. *Anal.* Calcd. for $C_{11}H_{21}O_6N$: C, 50.18; H, 8.04; OCH_3, 35.36. Found: C, 50.08; H, 8.03; OCH_3, 35.17.

Forty-five milligrams of VIII was refluxed overnight with 2 ml. of methyl iodide and 200 mg. of silver oxide; after a new addition of both reagents, reflux was continued for one day. The silver residue was filtered and washed exhaustively with acetone, and the combined filtrates, evaporated *in vacuo*, left 45 mg. of residue. Purification was obtained by chromatography on alumina. Elution with various mixtures of benzene and ether gave crystalline fractions, which after recrystallization from a mixture of chloroform and pentane gave 27 mg. (57%) of methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-glucopyranoside (IX), as long needles; m.p. 152–153°, with solidification and remelting at 167–168°, $[\alpha]^{23}D$ +133 ± 3° (in chloroform, *c* 0.44). Admixture with authentic material[3,3] did not depress the melting point.

Acetylation of 41 mg. of VIII with acetic anhydride and pyridine in the usual manner gave the **3-*O*-acetyl derivative**; recrystallization from a mixture of ether and pentane afforded 39 mg. (82%) of short prisms; m.p. 109–110°, $[\alpha]^{25}D$ +102 ± 3° (in chloroform, *c* 1.05). *Anal.* Calcd. for $C_{13}H_{23}O_7N$: C, 51.14; H, 7.59. Found: C, 51.13; H, 7.55.

Methyl 2-Acetamido-2-deoxy-4,6-di-*O*-methyl-α-D-glucopyranoside (VIII) from V.—To a solution of 125 mg. of sirupy V in 5 ml. of 90% methanol 3 g. of 2.5% sodium amalgam was added and the mixture was shaken overnight. The solution was saturated with carbon dioxide, the precipitated sodium bicarbonate was dissolved by addition of water and the mercury was filtered and washed with water and ethanol. The combined filtrates were evaporated to dryness *in vacuo*, extracted with acetone and filtered through a double layer of celite and Darco G-60. After evaporation *in vacuo*, the residue was crystallized from a mixture of methanol, ether and pentane, or from acetone and ether, affording 67 mg. (80%), m.p. 198–200°, $[\alpha]^{24}D$ +144 ± 2° (in methanol, *c* 0.92). In admixture with the compound obtained from VII described above, the m.p. was not depressed.

4,6-Di-*O*-methyl-D-glucosamine Hydrochloride (2-Amino-2-deoxy-4,6-di-*O*-methyl-D-glucose Hydrochloride) (X).—A solution of 120 mg. of VIII in 5 ml. of 3 *N* hydrochloric acid was heated for three hours on the water-bath, and after cooling was diluted with 10 ml. of water. The solution was evaporated *in vacuo*, the residue dissolved in methanol and the solution filtered through Darco G-60 and subsequently evaporated *in vacuo*. The colorless sirup obtained X was kept in a desiccator for several days over calcium chloride and soda lime; the yield was quantitative; $[\alpha]^{24}D$ +88 ± 1° (in water, *c* 1.83). *Anal.* Calcd. for $C_8H_{18}O_5NCl$: C, 39.43; H, 7.44; Cl, 14.55; OCH_3, 25.47. Found: C, 39.46; H, 7.41; Cl, 14.67; OCH_3, 25.53.

2-Deoxy-2-(2′-hydroxynaphthylidenamino)-4,6-di-*O*-methyl-D-glucose (XI).—A solution of 53 mg. of X in 1.0 ml. of water was treated as previously described[3] with 115 mg. of 2-hydroxynaphthaldehyde and 25 mg. of sodium acetate; purification was obtained by chromatography on silicic acid. Elution with mixtures of ethyl acetate and acetone and with pure acetone gave 69 mg. (90%) of crystalline fractions. The crystallization from a mixture of methanol, ether and pentane afforded 46 mg. (61%) of yellow prismatic needles XI, m.p. 192–194° (with slight decomposition) moistening at 180°; $[\alpha]^{26}_{5461}$ +296 ± 3° (at the equilibrium in methanol, *c* 0.80). *Anal.* Calcd. for $C_{19}H_{23}O_6N$: C, 63.14; H, 6.41. Found: C, 63.04; H, 6.40.

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BOSTON, MASSACHUSETTS

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6-*O*-Methyl-D-glucosamine Hydrochloride (2-Amino-2-deoxy-6-*O*-methyl-D-glucose Hydrochloride)[1]

BY ROGER W. JEANLOZ

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6-*O*-Methyl-D-glucosamine hydrochloride (2-amino-2-deoxy-6-*O*-methyl-D-glucose hydrochloride) has been prepared in crystalline form *via* two independent routes and transformed to the crystalline N-(2′-hydroxynaphthylidene) derivative.

In recent papers from this Laboratory[2a,b] syntheses of various methylated glucosamines have been reported for the purpose of studying their separation and identification.

The present paper describes the preparation of 6-*O*-methyl-D-glucosamine hydrochloride (2-amino-2-deoxy-6-*O*-methyl-D-glucose hydrochloride) (X) by two independent routes as shown in the accompanying diagram. One of the syntheses proceeds with benzoyl derivatives to protect positions 3 and 4 (II to IV). Such intermediates are unfortunately not crystalline and their stability under the conditions of methylation is subject to doubt. The over-all yield in the final product VII is good however and such a route is recommended for preparative purposes. The synthesis *via* the benzyl derivatives (V and VI) which are known for their stability was undertaken to provide additional proof of the structure of the methyl 2-acetamido-2-deoxy-6-*O*-methyl-α-D-glucopyranoside (VII) obtained *via* the benzoyl derivatives. Such a synthesis gives comparatively low yields in the preparation of the methyl 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-triphenylmethyl-α-D-glucopyranoside[3] used for the preparation of V and in the reductive splitting of the benzyl groups to prepare VII from VI.

Preparation of VIII from VII constitutes proof that position 5 was not methylated As VII is different from methyl 2-acetamido-2-deoxy-3-*O*-

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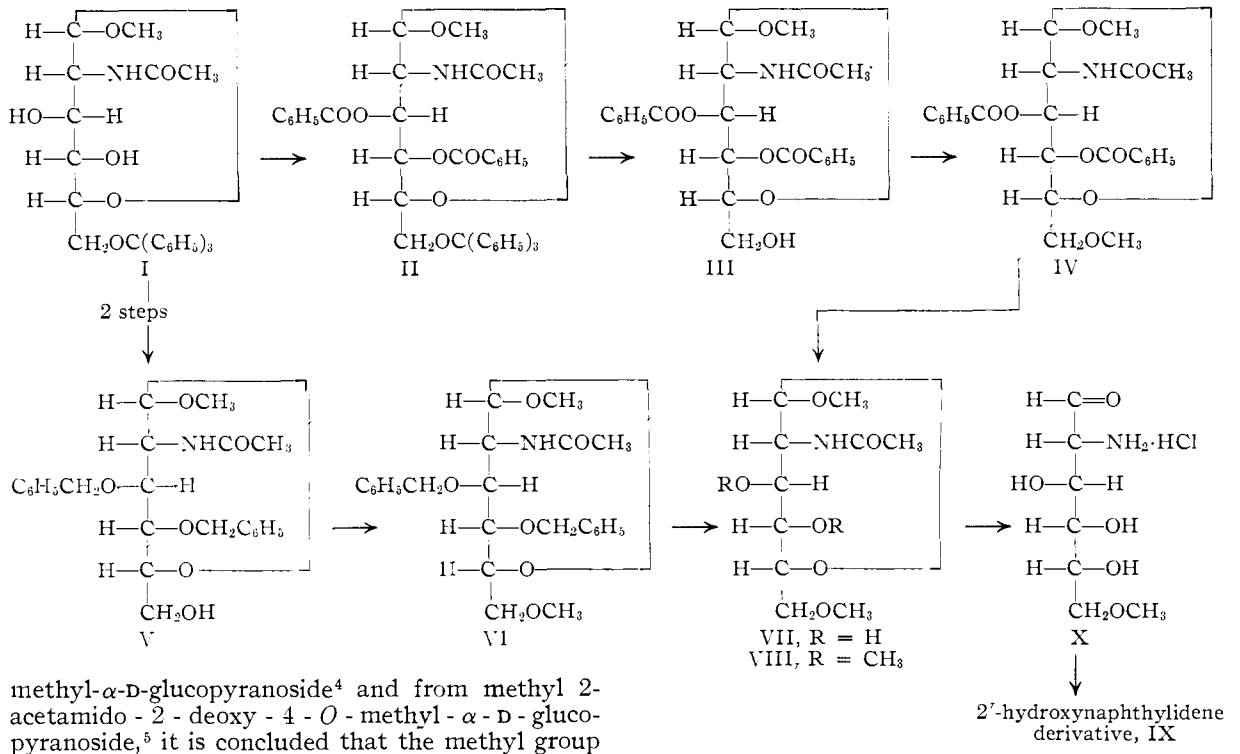
(2) (a) R. W. Jeanloz, THIS JOURNAL, **74**, 4597 (1952); (b) R. W. Jeanloz, *ibid.*, **76**, 555 (1954).

(3) Unpublished, manuscript in preparation.



methyl-α-D-glucopyranoside[4] and from methyl 2-acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranoside,[5] it is concluded that the methyl group is actually located in position 6. Additional evidence is obtained by periodate oxidation of VII which indicates the same consumption of oxidant as that of the methyl 2-acetamido-2-deoxy-α-D-glucopyranoside.[6]

The crystalline hydrochloride obtained through hydrolysis of VII showed a mutarotation from a +92° to a +68° value, and it was assumed to be in the α-form. Characterization was obtained, as previously, by preparing the easily recrystallized Schiff base with 2-hydroxynaphthaldehyde.[2,7]

Experimental[2b]

Methyl 2-Acetamido-3,4-di-*O*-benzoyl-2-deoxy-6-*O*-triphenylmethyl-α-D-glucopyranoside (II).—A solution of 2.0 g. of dry methyl 2-acetamido-2-deoxy-6-*O*-triphenylmethyl-α-D-glucopyranoside (I)[2a] in 20 ml. of anhydrous pyridine was cooled at −20° and 1.5 ml. of benzoyl chloride was slowly added. The mixture was kept at 0° for 24 hours, then diluted with chloroform. The solution was washed four times with ice-cold saturated sodium bisulfate solution, three times with ice-cold saturated sodium bicarbonate solution, then with water, dried over sodium sulfate and after filtration evaporated *in vacuo*. The sirupy residue was dissolved in benzene; hexane was added to turbidity and the mixture chromatographed on alumina. Pure benzene and mixtures of benzene and ether 19:1 and 9:1 eluted 2.75 g. (95%) of a colorless glass, $[\alpha]^{26}D$ +3 ± 1° (in chloroform, *c* 4.22). *Anal.* Calcd. for $C_{42}H_{39}O_8N$: C, 73.56; H, 5.74; N, 2.04. Found: C, 73.55; H, 5.78; N, 2.01.

Methyl 2-Acetamido-3,4-di-*O*-benzoyl-2-deoxy-α-D-glucopyranoside (III).—A solution of 2.75 g. of II in 50 ml. of glacial acetic acid was heated on the water-bath and 30 ml. of water was added slowly. After 30 minutes heating, the mixture was cooled and evaporated *in vacuo*. The last traces of acetic acid were removed by addition of dry toluene followed by evaporation *in vacuo*, and the sirupy residue was chromatographed on silicic acid. Benzene eluted 0.99 g. (95%) of triphenylcarbinol, whereas III was eluted as a colorless glass by ethyl acetate (1.77 g., 100%), $[\alpha]^{23}D$ −21 ± 1° (in chloroform, *c* 3.32). *Anal.* Calcd. for $C_{23}H_{25}O_8N$: C, 62.29; H, 5.68. Found: C, 62.31; H, 5.64.

Methyl 2-Acetamido-3,4-di-*O*-benzoyl-2-deoxy-6-*O*-methyl-α-D-glucopyranoside (IV).—To a solution of 1.18 g. of III in 20 ml. of methyl iodide was added 1 g. of silver oxide. The mixture was vigorously shaken for 24 hours and 1 g. of silver oxide added. After another shaking for 24 hours, the silver residue was filtered, extracted with acetone and the combined filtrates were evaporated *in vacuo;* the sirupy residue was dissolved in benzene and chromatographed on silicic acid. Elution with ether and mixtures of ether and ethyl acetate gave 925 mg. (76%) of a colorless glass IV, $[\alpha]^{24}D$ −8 ± 1° (in chloroform, *c* 0.95). *Anal.* Calcd. for $C_{24}H_{27}O_8N$: C, 63.01; H, 5.95; OCH_3, 13.57. Found: C, 63.05; H, 5.81; OCH_3, 13.76.

Methyl 2-Acetamido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-methyl-α-D-glucopyranoside (VI).—One hundred and sixty-four milligrams of methyl 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (V) (m.p. 195–197°)[3] was refluxed overnight with 10 ml. of methyl iodide and 500 mg. of silver oxide, then for 5 hours with a new addition of 200 mg. of silver oxide. After filtration, the silver residue was washed exhaustively with acetone and the combined filtrates after evaporation *in vacuo*, gave a crystalline residue. Crystallization from a mixture of acetone, ether and pentane gave 129 mg. (76%) of long needles; m.p. 197–198°, $[\alpha]^{23}D$ +99 ± 2° (in chloroform, *c* 0.74). *Anal.* Calcd. for $C_{24}H_{31}O_6N$: C, 67.11; H, 7.28; OCH_3, 14.45. Found: C, 67.24; H, 7.42; OCH_3, 14.56.

In admixture with the starting material V, the m.p. was depressed to 172–188°.

Methylation of 400 mg. of V dissolved in 20 ml. of acetone was carried out with 6.4 ml. of 30% sodium hydroxide and 2.4 ml. of methyl sulfate, both added in 12 portions, at 55° with vigorous stirring for 3 hours. After addition of 10 ml. of water, the temperature was raised for a few minutes to 100°. After cooling, the solution was diluted with 100 ml. of water, the precipitated product was filtered, dried in a desiccator and recrystallized from a mixture of acetone, ether and pentane. The yield was 340 mg. (83%) of VI, melting at 196–197°, and showing no depression in admixture with the product described above.

Methyl 2-Acetamido-2-deoxy-6-*O*-methyl-α-D-glucopyranoside (VII). (a) From IV.—A solution of 705 mg. of IV in 10 ml. of methanol and 2.5 ml. of 0.4 *N* barium methylate was left overnight at 0°. The solution was then filtered

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through a column of Dowex-50 in the acid form, previously washed with methanol. Evaporation of the methanolic solution *in vacuo* and recrystallization from a mixture of methanol and ether afforded 372 mg. (97%) of long needles; m.p. 189–191°, $[\alpha]^{28}D$ +143 ± 1° (in methanol *c*, 0.72). *Anal.* Calcd. for $C_{10}H_{19}O_6N$: C, 48.18; H, 7.68; OCH_3, 24.90. Found: C, 48.10; H, 7.84; OCH_3, 25.10. In admixture with methyl 2-acetamido-2-deoxy-α-D-glucopyranoside, the m.p. was depressed to 165–177°.

(b) From VI.—To a solution of 530 mg. of VI in 20 ml. of 97% ethanol was added rapidly 3 g. of sodium in small pieces[8]; more ethanol was added during the reaction to keep the product in solution. After cooling and dilution with water the solution was neutralized with CO_2, and concentrated to dryness *in vacuo*. The residue was extracted with acetone, which after evaporation gave 20 mg. of starting material, m.p. 194–195°.

The mother liquors were acetylated with acetic anhydride and pyridine, then chromatographed on silicic acid. Elution with mixtures of ether and ethyl acetate 19:1 and 9:1 gave after recrystallization 115 mg. of starting material (total of starting material recovery, 135 mg.).

Elution with mixtures of ether and ethyl acetate 4:1 and 2:1 gave crystalline **methyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-6-*O*-methyl-α-D-glucopyranoside**, which after recrystallization from a mixture of ether and pentane afforded 150 mg. of elongated prismatic crystals. The yield was 37% or 50% after deduction of the recovered starting material; m.p. 126–127°, $[\alpha]^{27}D$ +97 ± 2° (in chloroform, *c* 0.78). *Anal.* Calcd. for $C_{14}H_{23}O_8N$: C, 50.44; H, 6.95. Found: C, 50.25; H, 6.82.

One hundred and thirty milligrams of VI was dissolved in 5 ml. of glacial acetic acid and reduced catalytically with hydrogen in presence of 30 mg. of platinum oxide at room temperature and atmospheric pressure.[9] After no more hydrogen was absorbed, the platinum was filtered, the solution evaporated *in vacuo* and 16 mg. of VI was obtained, m.p. 191–193°. The mother liquors were acetylated and purified by chromatography as described above, giving 20 mg. of methyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-6-*O*-methyl-α-D-glucopyranoside and a total yield of 40%.

A solution of 71 mg. of methyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-6-*O*-methyl-α-D-glucopyranoside in 2 ml. of methanol was catalytically deacetylated with barium methylate. After removal of the barium ions with Dowex-50, the solution was evaporated and the residue, crystallized from a mixture of methanol and ether, gave 51.5 mg. (97%) of VII; m.p. 189–191, $[\alpha]^{28}D$ +144 ± 1° (in methanol, *c* 1.04). In admixture with the product obtained from IV no depression of the m.p. was observed.

Periodate oxidation of VII was carried out under conditions similar to those used for methyl 2-acetamido-2-deoxy-α-D-glucopyranoside[7]: 2.5 moles of sodium periodate was added for each mole of sugar and the oxidation performed at 5° and *p*H 4.5. After 24 and 48 hours, respectively, 0.83 and 1.02 moles of oxidant were consumed.

Thirty-seven milligrams of VII was refluxed overnight with 5 ml. of methyl iodide and 200 mg. of silver oxide; after a new addition of 200 mg. of silver oxide, reflux was continued for one day. The silver residue was filtered and washed with acetone. The filtrates gave after evaporation 35 mg. of residue which was purified by chromatography on alumina. Crystallization from a mixture of chloroform and pentane gave 25 mg. (61%) of methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-glucopyranoside (VIII) as long needles; m.p. 153–154°, $[\alpha]^{24}D$ +124 ± 3° (in chloroform, *c* 1.25). Admixture with authentic material[2,10] did not depress the melting point.

6-*O*-Methyl-D-glucosamine Hydrochloride (2-Amino-2-deoxy-6-*O*-methyl-D-glucose Hydrochloride) (X).—A solution of 220 mg. of VII in 5 ml. of 3 *N* hydrochloric acid was heated for three hours on the water-bath. After cooling and dilution with a few ml. of water, the solution was evaporated *in vacuo* and the residue left overnight in a desiccator in presence of calcium chloride and soda lime. After solution in methanol and treatment with charcoal, 168 mg. (83%) of prismatic needles was obtained by addition of acetone. Recrystallization from methanol and acetone did not change the m.p. 185 to 195° with decomposition.

The compound showed mutarotation from $[\alpha]^{25}D$ +92° (after 10 minutes) to $[\alpha]^{25}D$ +68 ± 2° (after 24 hours) (in water, *c* 1.00). *Anal.* Calcd. for $C_7H_{16}O_5NCl$: C, 36.61; H, 7.02; Cl, 15.44; OCH_3, 13.51. Found: C, 36.52; H, 7.14; Cl, 15.31; OCH_3, 13.32.

2-Deoxy-2-(2′-hydroxynaphthylidenamido)-6-*O*-methyl-D-glucose (IX).—A solution of 46 mg. of X in 1.0 ml. of water was treated as previously described[2] with 90 mg. of 2-hydroxynaphthaldehyde and 60 mg. of $CH_3COONa \cdot 3H_2O$; purification was obtained by chromatography. Elution with mixtures of ethyl acetate and acetone and with pure acetone gave 71 mg. of crystalline fractions. The crystallization from a mixture of methanol and acetone afforded 49 mg. (70%) of yellow rectangular plates, m.p. 205–207° with a slight decomposition; $[\alpha]^{24}_{5461}$ +222 ± 3° (at the equilibrium, in methanol, *c* 1.05). *Anal.* Calcd. for $C_{18}H_{21}O_6N$: C, 62.24; H, 6.09. Found: C, 62.21; H, 6.16.

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