alumina. Mixtures of benzene and ether 19:1 and 9:1 eluted crystalline fractions. Crystallization from a mixture of acetone, ether and pentane gave 485 mg. (66%) of **methyl 2-O-acetyl-4,6-O-benzylidene-3-O-p-tolylsulfonyl-α-D-glucopyranoside (XX)**, as stout prisms, m.p. 124–125°, $[\alpha]^{24}D$ +26 ± 2° (in chloroform, *c* 0.51).[26] *Anal.* Calcd. for $C_{23}H_{26}O_9S$: C, 57.73; H, 5.48; S, 6.70. Found: C, 57.93; H, 5.58; S, 6.53. From the mother liquors, 8 mg. (1%) of shiny platelets, m.p. 157–159°, were obtained. In admixture with methyl 3-O-acetyl-4,6-O-benzylidene-2-O-p-tolylsulfonyl-α-D-glucopyranoside (XVIII) described above no depression of the m.p. was observed.

Elution with 4:1, 2:1 and 1:1 mixtures of ether and benzene gave crystalline fractions. After crystallization from a mixture of acetone, ether and pentane, 125 mg. (25%) was obtained, melting at 133–134° and showing no depression in admixture with the starting material.

(26) Bourne, *et al.*,[3] reported a yield of 49%, m.p. 120–121°, $\alpha^{25}D$ +23.1° (in chloroform, *c* 0.78).

Action of Pyridinium Chloride on Methyl 3-O-Acetyl-4,6-O-benzylidene-α-D-glucopyranoside (IV).—A solution of 0.1 ml. of anhydrous pyridine in 5 ml. of dry ether was saturated with dry hydrogen chloride. After removal of the ether and excess hydrogen chloride, 5 ml. of anhydrous pyridine and 200 mg. of IV were added. After one day at room temperature, ice was added and the product was isolated as described above. Recrystallization from a mixture of ether and pentane gave 190 mg. (95%) of starting material, m.p. 176–177°.

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[CONTRIBUTION FROM THE ROBERT W. LOVETT MEMORIAL LABORATORIES FOR THE STUDY OF CRIPPLING DISEASES, MASSACHUSETTS GENERAL HOSPITAL, AND THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

4-O-Methyl-D-glucosamine Hydrochloride (2-Amino-2-deoxy-4-O-methyl-D-glucose Hydrochloride)[1]

BY ROGER W. JEANLOZ AND CHARLES GANSSER[2]

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The synthesis of 4-O-methyl-D-glucosamine hydrochloride (2-amino-2-deoxy-4-O-methyl-D-glucose hydrochloride), a reference substance for structural studies of glucosamine-containing substances, is described. It was obtained in a sirupy state, starting from methyl 2-acetamido-2-deoxy-6-O-triphenylmethyl-α-D-glucopyranoside and from methyl 2-acetamido-3-O-tolylsulfonyl-α-D-glucopyranoside. It was transformed into the crystalline *N*-acetyl and *N*-(2'-hydroxynaphthylidene) derivatives.

In a previous paper[3] describing the methylation of methyl 2-acetamido-2-deoxy-6-O-triphenylmethyl-α-D-glucopyranoside (IV), a crystalline compound was isolated in addition to the known methyl 2-acetamido-2-deoxy-3-O-methyl-6-O-triphenylmethyl-α-D-glucopyranoside and methyl 2-acetamido-2-deoxy-3,4-di-O-methyl-6-O-triphenylmethyl-α-D-glucopyranoside. The structure of a methyl 2-acetamido-2-deoxy-4-O-methyl-6-O-triphenylmethyl-α-D-glucopyranoside (III) was ascribed to this product on the basis of its elementary analysis, of its mode of preparation, and because it was possible to prepare a monoacetyl derivative. It was of interest to ascertain this structure by an independent synthesis and at the same time synthesize the still unknown 4-O-methyl-D-glucosamine hydrochloride (VII), to complete the series of the known monomethyl derivatives of 2-amino-2-deoxy-D-glucopyranose.

The first attempt to obtain a 4-O-methyl-derivative, using as starting material a compound in which positions 3 and 6 were protected during methylation by methylsulfonyl groups, was unsuccessful, because such groupings could not be removed subsequently by reductive splitting.[4]

Another experiment in which the methylation of the methyl 2-acetamido-2-deoxy-3-O-p-tolylsulfonyl-6-O-triphenylmethyl derivative was attempted did not give conclusive results (see Experimental part).

Finally, the following route as shown in the accompanying diagram was successful: Controlled p-toluenesulfonylation of methyl 2-acetamido-2-deoxy-3-O-p-tolylsulfonyl-α-D-glucopyranoside (I)[5] gave, in excellent yield, the sirupy 3,6-di-O-p-tolylsulfonyl derivative II, characterized by a crystalline 4-O-acetyl derivative. Methylation with methyl iodide and silver oxide produced the sirupy 4-O-methyl derivative V. It was purified from the starting material by acetylation followed by chromatography. Although this product could not be obtained in crystalline form, and showed a rotation slightly different from the rotation of the product prepared by p-toluenesulfonylation of methyl 2-acetamido-2-deoxy-4-O-methyl-α-D-glucopyranoside (VI), it analyzed correctly and was used as such. Splitting of the p-tolylsulfonyl groups was accomplished by reduction and afforded in a 73% yield a crystalline methyl 2-acetamido-2-deoxy-4-O-methyl-α-D-glucopyranoside (VI) identical in all respects with the crystalline product obtained by weak acid hydrolysis of methyl 2-acetamido-2-deoxy-4-O-methyl-6-O-triphenylmethyl-α-D-glucopyranoside (III). Additional evidence for the identity of both compounds was obtained

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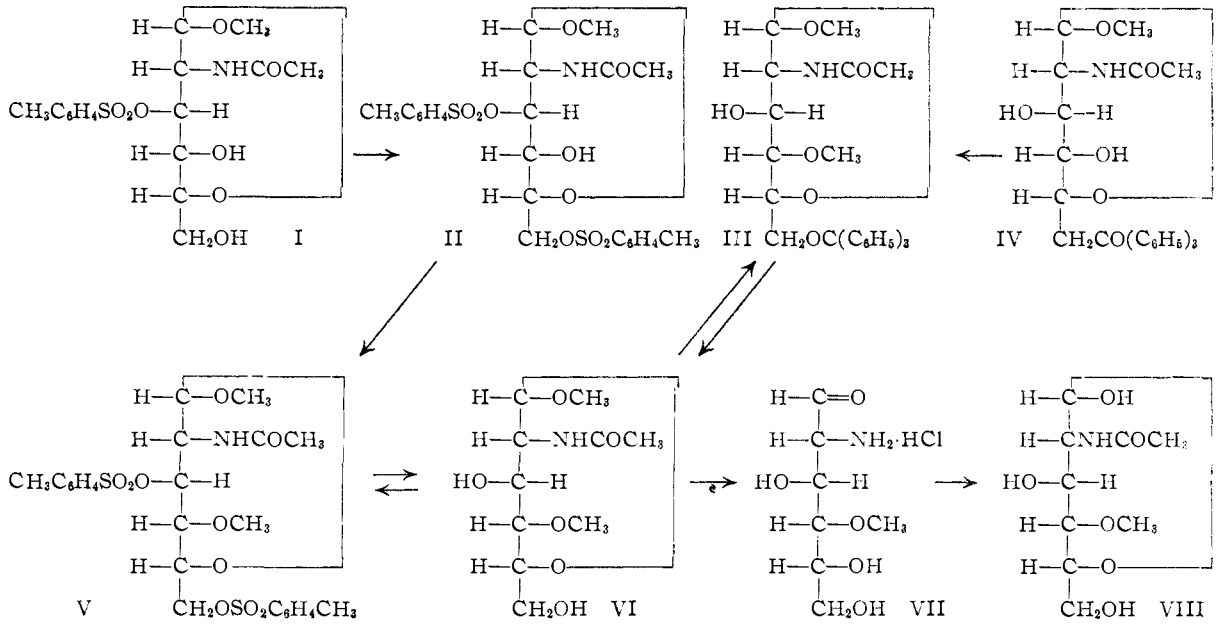
(2) Fellow of the Swiss Foundation "Stiftung für Stipendien auf dem Gebiete der Chemie."

(3) R. W. Jeanloz, THIS JOURNAL, **74**, 4597 (1952).

(4) R. W. Jeanloz and C. T. Bothner-By, unpublished.

(5) R. W. Jeanloz, THIS JOURNAL, **76**, 555 (1954).



by preparing III using as starting material the glycoside VI obtained through the route of the *p*-tolylsulfonyl derivatives. Attempts to characterize VI in preparing a crystalline 3,6-*O*-diacetyl derivative, were unsuccessful. Two different methods of preparation gave sirupy products, showing an identical rotation but with quite incorrect elementary analysis. The synthesis of methyl 2-acetamido-2-deoxy-3,4-6-tri-*O*-methyl-α-D-glucopyranoside[3,6] starting from VI showed that no shifting of the ring had occurred during methylation. Hydrolysis of VI gave the sirupy 2-amino-2-deoxy-4-*O*-methyl-D-glucosamine hydrochloride (VII), which was transformed into the crystalline N-acetyl (VIII) and N-(2′-hydroxynaphthylidene) (IX) derivatives.

Experimental[7]

Methyl 2-Acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranoside (VI) from III.—A solution of 105 mg. of methyl 2-acetamido-2-deoxy-4-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (III)[3] in 4 ml. of glacial acetic acid was heated on the water-bath and 3 ml. of water was added dropwise. After one hour, the solution was cooled and diluted with 15 ml. of water. The triphenylcarbinol (47 mg.) was filtered off and the solution evaporated to dryness *in vacuo*. The crystalline residue, recrystallized from cold ethanol and from a mixture of ethanol and ether gave 43 mg. (85%) of elongated needles, m.p. 232–233°, $[\alpha]^{24}D$ +158 ± 5° (in methanol, *c* 0.58). *Anal.* Calcd. for $C_{10}H_{19}O_6N$: C, 48.18; H, 7.68. Found: C, 48.06; H, 7.84.

Methyl 2-Acetamido-2-deoxy-3,6-di-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (II).—To a solution of 500 mg. of methyl 2-acetamido-2-deoxy-3-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside[5] (I), in 1.5 ml. of dry pyridine was added 280 mg. (1.15 moles) of *p*-toluenesulfonyl chloride dissolved in 2.5 ml. of dry pyridine, both solutions having previously been cooled at −20°. The solution was kept at 0° overnight and at room temperature for one day; then the excess chloride was decomposed by addition of ice and the solution extracted with chloroform. The chloroform layer was washed three times each with ice-cold water, ice-cold 2 *N* sulfuric acid, saturated sodium bicarbonate solution, and water, dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silicic acid. Elution with mixtures of ether and ethyl acetate afforded a quantitative yield of II as a colorless sirup; $[\alpha]^{24}D$ +62 ± 2° (in chloroform, *c* 1.30). *Anal.* Calcd. for $C_{23}H_{29}O_{10}NS_2$: C, 50.82; H, 5.38; S, 11.80. Found: C, 50.98; H, 5.50; S, 11.66.

Acetylation of 82 mg. of II with acetic anhydride and pyridine in the usual manner gave the **4-*O*-acetyl derivative** which was purified by chromatography on silicic acid. Elution with pure ether and mixtures of ether and ethyl acetate gave crystalline fractions which after recrystallization from a mixture of acetone, ether and pentane afforded 62 mg. (80%) of prisms, m.p. 142°, $[\alpha]^{21}D$ +78 ± 2° (in chloroform, *c* 0.96). *Anal.* Calcd. for $C_{25}H_{31}O_{11}NS_2$: C, 51.27; H, 5.34. Found: C, 51.41; H, 5.47.

Methyl 2-Acetamido-2-deoxy-4-*O*-methyl-3,6-di-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (V) from II.—Five hundred and five milligrams of II was refluxed for one day with 10 ml. of methyl iodide and 300 mg. of silver oxide; after another addition of 200 mg. of silver oxide, reflux was continued for another day. The silver residue was filtered and washed exhaustively with acetone, and the filtrate, evaporated *in vacuo*, was dissolved in benzene and chromatographed on silicic acid. Elution with mixtures of ether and ethyl acetate gave 430 mg. of a hygroscopic sirup. It was acetylated with acetic anhydride and pyridine in the usual manner to transform the unreacted II into its crystalline 4-*O*-acetyl derivative. After repeated evaporation *in vacuo* with toluene the remaining sirup was chromatographed on silicic acid. Elution with mixtures of ether and ethyl acetate (9:1 and 4:1) gave 412 mg. (80%) of V, as a colorless glass, $[\alpha]^{24}D$ +75 ± 2° (in chloroform, *c* 1.10). *Anal.* Calcd. for $C_{24}H_{31}O_{10}NS_2$: C, 51.69; H, 5.60; OCH_3, 11.13. Found: C, 51.60; H, 5.77; OCH_3, 11.04. The crystalline acetyl derivative of II was eluted with a mixture of ether and ethyl acetate 2:1.

From VI.—To a solution of 48 mg. of VI in 0.5 ml. of anhydrous pyridine was added 120 mg. of *p*-toluenesulfonyl chloride. After standing one day at 0° and another day at room temperature, ice was added and the solution was extracted with chloroform. The extract was washed with 2 *N* sulfuric acid, then with saturated sodium bicarbonate, and water and was dried over sodium sulfate. After removal of the solvent by distillation *in vacuo*, the sirupy residue was chromatographed on silicic acid. Elution with mixtures of benzene and ether afforded a first peak of substance, weighing 21 mg. (19%) which could not be induced to crystallize; $[\alpha]^{26}D$ +68 ± 2° (in chloroform, *c* 2.09). *Anal.* Calcd. for $C_{24}H_{31}O_{10}NS_2$: C, 51.69; H, 5.60; S, 11.33. Found: C, 51.99; H, 5.44; S, 11.33. The more polar fractions, some being partially crystalline, were not further investigated.

Methyl 2-Acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranoside (VI) from V.—To a solution of 275 mg. of V in 10 ml. of 90% methanol, 14 g. of 2.5% sodium amalgam was

(6) W. O. Cutler, W. N. Haworth and S. Peat, *J. Chem. Soc.*, 1979 (1937).

(7) See ref. 5 and R. W. Jeanloz and D. A. Jeanloz, THIS JOURNAL, **79**, 2579 (1957).

added and the mixture was shaken overnight. After addition of water, the solution was saturated with carbon dioxide, the mercury was filtered off through a layer of Celite and Darco G-60, and washed with methanol. The filtrate was evaporated to dryness *in vacuo*, dried by co-distillation with dry toluene, and the residue was extracted with acetone. After evaporation *in vacuo*, the crystalline residue was recrystallized from a mixture of methanol and ether, affording 90 mg. (73%) of prismatic needles, m.p. 232–233°, $[\alpha]^{22}D$ +157 ± 2° (in methanol, *c* 1.16). *Anal.* Calcd. for $C_{10}H_{19}O_6N$: C, 48.18; H, 7.68; OCH_3, 24.90. Found: C, 48.05; H, 7.60; OCH_3, 24.69. In admixture with the material described above, the m.p. was not depressed.

Acetylation of 50 mg. of VI with acetic anhydride and pyridine in the usual manner, gave, after chromatography on silicic acid, 58 mg. (87%) of the **3,6-di-O-acetyl** derivative as a homogeneous peak, eluted with mixtures of chloroform and ether. It failed to crystallize and showed $[\alpha]^{25}D$ +79 ± 2° (in chloroform, *c* 2.93). *Anal.* Calcd. for $C_{14}H_{23}O_8N$: C, 50.44; H, 6.96. Found: C, 51.27; H, 6.85.

Acetylation of 50 mg. of VI was carried out by heating with 2 ml. of acetic anhydride and 100 mg. of fused sodium acetate for 4 hours on the water-bath. After dilution with water, the solution was extracted with chloroform. After washing with water, the extract was dried over sodium sulfate, the solvent was removed by distillation *in vacuo* and the residue chromatographed on silicic acid, as described above. A quantitative yield of the sirupy **3,6-di-O-acetyl** derivative was obtained, $[\alpha]^{25}D$ +77 ± 2° (in chloroform, *c* 2.22). *Anal.* Calcd. for $C_{14}H_{23}O_8N$: C, 50.44; H, 6.96. Found: C, 51.43; H, 7.20.

Methylation of VI with dimethyl sulfate and sodium hydroxide[8] in the usual manner gave the methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-glucopyranoside. Purification was obtained by chromatography on silicic acid. Elution with mixtures of acetone and methanol (19:1) afforded a crystalline material. On recrystallization from a mixture of chloroform and pentane, long prismatic needles were obtained (yield about 40%), m.p. 166–168° (sublimation at 150°) $[\alpha]^{20}D$ +122 ± 4° (in chloroform, *c* 2.23). In admixture with authentic material,[3,6] the m.p. was not depressed.

Methyl 2-Acetamido-2-deoxy-4-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (III) from VI.—A solution of 50 mg. of VI obtained from V and 115 mg. of triphenylchloromethane (2.0 equivalents) in 4.5 ml. of dry pyridine was left at 47° for 6 days. The pyridine was evaporated *in vacuo* at room temperature and the residue dried in a desiccator over calcium chloride and potassium hydroxide. After a new addition of 57 mg. of triphenylchloromethane (1.0 equivalent) and of 3.0 ml. of dry pyridine, the solution was left at 100° for four hours, the excess chloride decomposed by addition of ice and the solution extracted with chloroform. The chloroform layer was washed three times each with ice-cold saturated potassium bisulfate solution, sodium bicarbonate and water, dried over sodium sulfate and evaporated *in vacuo*. The residue was dissolved in benzene and chromatographed on silicic acid. Elution with mixtures of ethyl acetate and acetone afforded 36 mg. (36%) of crystalline fractions. Recrystallization from a mixture of acetone and ether gave 22 mg. (22%) of prisms (III), m.p. 210–212°, $[\alpha]^{24}D$ +59 ± 2° (in chloroform, *c* 0.81). In admixture with the material previously described[3] the m.p. was not depressed.

4-O-Methyl-D-glucosamine Hydrochloride (2-Amino-2-deoxy-4-O-methyl-D-glucose Hydrochloride) (VII).—A solution of 200 mg. of VI in 5 ml. of 3 *N* hydrochloric acid was heated for three hours on the steam-bath. After cooling it was diluted with 15 ml. of water, and the solution was evaporated *in vacuo*. The residue was dissolved in methanol, the solution was filtered through Celite and Darco G-60, and evaporated *in vacuo*. The colorless hygroscopic sirup (VII) was kept in a desiccator for several days over soda lime and obtained in a quantitative yield: $[\alpha]^{24}D$ +90 ± 2° (in water, *c* 1.70), $[\alpha]^{28}D$ + 108 ± 2° (in methanol, *c* 1.19). *Anal.* Calcd. for $C_7H_{16}O_5NCl$: C, 36.61; H, 7.02; Cl, 15.44; OCH_3, 13.51. Found: C, 36.43; H, 7.16; Cl, 15.30; OCH_3, 13.40.

2-Acetamido-2-deoxy-4-O-methyl-α-D-glucopyranose (VIII).—To a solution of 72 mg. of VII in 1 ml. of absolute methanol was added 58 mg. of silver acetate and 0.7 ml. of acetic anhydride. The mixture was left at 0° overnight, at room temperature for three hours, refluxed for five minutes, and filtered through Celite. The silver residue was washed with methanol and then with 1 ml. of hot water, and one drop of 0.1 *N* hydrochloric acid was added to the filtrate. After two hours the solution was filtered through Celite and Darco G-60 and the filtrate evaporated *in vacuo*. The residue was crystallized from a mixture of methanol and ether, and gave 41 mg. (56%) of prisms, m.p. 211–215° dec. The compound showed mutarotation from $[\alpha]^{24}D$ +79° (after 16 minutes) to $[\alpha]^{22}D$ +69 ± 2° (after 24 hours, in water, *c* 1.02). *Anal.* Calcd. for $C_9H_{17}O_6N$: C, 45.95; H, 7.28. Found: C, 45.77; H, 7.39.

2-Deoxy-2-(2′-hydroxynaphthylidenamino)-4-O-methyl-D-glucopyranose (IX).—A solution of 60 mg. of VII in 3 ml. of water was treated as previously described[3] with 110 mg. of 2-hydroxynaphthaldehyde and 30 mg. of sodium acetate trihydrate. The product was purified by chromatography on silicic acid. Elution with mixtures of ethyl acetate and acetone gave crystalline fractions. Recrystallization from a mixture of monomethyl glycol, methanol and ether gave 46 mg. (53%) of yellow, prismatic needles, m.p. 218–219° dec., $[\alpha]^{22}_{5461}$ +305 ± 10° (in methanol, at equilibrium, *c* 0.14). *Anal.* Calcd. for $C_{18}H_{21}O_6N$: C, 62.24; H, 6.09. Found: C, 62.28; H, 6.18.

Methyl 2-Acetamido-2-deoxy-3-O-*p*-tolylsulfonyl-6-O-triphenylmethyl-α-D-glucopyranoside.—To a solution of 550 mg. of methyl 2-acetamido-2-deoxy-3-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside[5] (I) in 5 ml. of dry pyridine was added 400 mg. (1.05 moles) of triphenylchloromethane. After standing overnight at room temperature, the solution was heated at 100° for 2 hours. After cooling, ice was added, and the solution was extracted with chloroform. The organic phase was washed three times each, at 0° with a saturated solution of potassium bisulfate, at room temperature with a saturated solution of sodium bicarbonate and with water, then dried over sodium sulfate. After evaporation *in vacuo*, the residue was dissolved in benzene and chromatographed on silicic acid. Elution with mixtures of benzene and ether 2:1 and 1:1 and with pure benzene gave 600 mg. (67%) of a colorless sirup; $[\alpha]^{28}D$ +42 ± 2° (in chloroform, *c* 1.46). *Anal.* Calcd. for $C_{35}H_{37}O_8NS$: C, 66.54; H, 5.90; S, 5.08. Found: C, 66.43; H, 5.94; S, 5.24.

Acetylation of 43 mg. of the above sirup with acetic anhydride and pyridine in the usual manner gave, after purification by chromatography and recrystallization from a mixture of ether and pentane, 36 mg. (80%) of the **4-O-acetyl derivative**, as prismatic needles, m.p. 145–148°, $[\alpha]^{24}D$ +75 ± 3° (in chloroform, *c* 1.26). *Anal.* Calcd. for $C_{37}H_{39}O_9NS$: C, 65.95; H, 5.83; S, 4.76. Found: C, 66.04; H, 5.82; S, 4.92.

Attempts to methylate methyl 2-acetamido-2-deoxy-3-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside with methyl iodide and silver oxide gave only the starting material, identified by its crystalline 4-*O*-acetyl derivative.

Acknowledgment.—The authors wish to thank Mrs. Shirley Butterworth for her technical assistance.

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(8) Attempts with methyl iodide and silver oxide alone or in presence of dimethylformamide[9] gave unsatisfactory results.

(9) R. Kuhn, *Angew. Chem.*, **67**, 32 (1955).