extracted with ethyl acetate to give 0.260 g. more of the di-acid X, m.p. 256–258° (total yield 23.1%).

In another run the lactol (VI, R = OH) was isolated by chromatography of the crude amorphous acidic material on acetic acid washed alumina. The lactol (VI, R = OH) was eluted with chloroform and crystallized from methanol–ether as colorless prisms, m.p. 178–179°, $[\alpha]^{24}D$ +27° (chloroform).

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.35; H, 8.93. Found: C, 69.40; H, 9.18.

The infrared spectrum showed a single carbonyl band at 5.69 μ characteristic of a five-membered lactone.

Preparation of Tetrahydropyridazone (VIII).—To the pyridazinone (VII, R = C_8H_{17}) (200 mg.) dissolved in 20 ml. of ether was added 2 ml. of a 0.9 *M* lithium aluminum hydride solution and after one minute the excess hydride was decomposed with ethyl acetate. Ethyl acetate (50 ml.) and a solution of 3 g. of Rochelle salt in 20 ml. of water were then added, the layers separated, and the aqueous layer extracted with chloroform. The combined extracts were washed with water, saturated sodium chloride solution and concentrated. The crystalline residue was triturated with ether and the colorless crystals filtered off to give 78 mg. (39%) of the tetrahydropyridazone (VIII). For analysis a sample was recrystallized from benzene–ether, m.p. 274–276°, $[\alpha]^{24}D$ +104.2° (chloroform).

Anal. Calcd. for $C_{25}H_{44}ON_2$: C, 77.26; H, 11.41. Found: C, 77.09; H, 11.34.

Preparation of Keto Acid II (R = OH).—Testosterone (4.0 g.) was dissolved in 40 ml. of ethyl acetate and 40 ml. of acetic acid and ozonized (2 molar equivalents) at −10°. The resulting colorless solution was diluted with 25 ml. of water and 4 ml. of 30% hydrogen peroxide and allowed to stand three days. After addition of ether, the organic layer was washed six times with 50-ml. portions of water and then extracted with 160 ml. of 1 *N* sodium hydroxide in five portions. The basic extracts were acidified, and the precipitate again extracted into ether. The ether extracts were washed with water, saturated sodium chloride solution, dried over magnesium sulfate and concentrated leaving a crystalline solid. Recrystallization from acetone–ether gave 3.20 g. (75%) of the keto acid, m.p. 197–199°. Recrystallization from acetone–water gave an analytical sample, m.p. 204–205.5°, $[\alpha]^{24}D$ −30.0° (chloroform). Further recrystallization from acetone did not raise the m.p. although Bolt[2] reported 206.5–207° for this compound.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.17; H, 9.32.

Reductive Cleavage of the Ozonide of Diphenylethylene Ketone (V).—Diphenylethylene ketone (0.95 g.) (regenerated from the 2,4-dinitrophenylhydrazone) was dissolved in 40 ml. of ethyl acetate and 30 ml. of methanol and ozonized (2.5 molar equivalents) at −10°. Zinc (3 g.) and 20 ml. of 75% acetic acid were added to the resulting ice-cold solution and the mixture was stirred for 15 minutes. The zinc was filtered off and the solvents removed under vacuum. The residue was taken up in ether and water, the layers separated, the organic layer washed with water, 5% sodium bicarbonate solution, water, dried over magnesium sulfate and concentrated leaving 1.00 g. of colorless oil which could not be induced to crystallize.

This oil (0.10 g.) was treated with an alcoholic sulfuric acid solution containing 0.10 g. of 2,4-dinitrophenylhydrazine. An orange-red precipitate (90 mg.) so obtained was chromatographed on 9.0 g. of neutral alumina. Benzophenone 2,4-dinitrophenylhydrazone was eluted first with 50% benzene–ligroin and recrystallized from chloroform–ethanol as orange-red prisms, m.p. 242–242.5°.

A second compound was obtained by elution with 20% chloroform–benzene and recrystallization from chloroform–benzene gave yellow fluffy crystals, m.p. 166–168° (35 mg.). Recrystallization again from chloroform–ligroin gave orange clusters, m.p. 213–214°, apparently another crystalline form. Analysis indicated it was a bis-2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{37}H_{56}O_8N_8$: C, 60.38; H, 6.86. Found: C, 60.36; H, 6.95.

LOS ANGELES, CALIFORNIA

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

4,6-Di-*O*-methyl-D-glucosamine Hydrochloride (2-Amino-2-deoxy-4,6-di-*O*-methyl-D-glucose Hydrochloride)[1,2]

BY ROGER W. JEANLOZ

RECEIVED MAY 7, 1953

4,6-Di-*O*-methyl-D-glucosamine hydrochloride (2-amino-2-deoxy-4,6-di-*O*-methyl-D-glucose hydrochloride) has been prepared *via* two independent routes and transformed to the crystalline N-(2′-hydroxynaphthylidene) derivative.

Synthesis of the various methylated 2-amino-2-deoxy-D-glucopyranoses has been undertaken[3] with the purpose of using them as reference compounds in the elucidation of the structure of complex natural polysaccharides by the methylation procedure.

Synthesis of 2-amino-2-deoxy-4,6-di-*O*-methyl-D-glucose was of special interest, since this compound should result from the degradation of methylated hyaluronic acid[4] if a 1,3-glucuronido–glucosamine linkage exists. Evidence for such a linkage has been advanced as a result of periodate oxidation studies[5] and definitely established by study of a degradation product.[6]

Synthesis of the dimethyl compound has been accomplished *via* two routes starting from methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[7] (I) as shown in the accompanying diagram.

Protection of the hydroxyl group in position 3 was obtained by benzoylation (III) or tosylation

(1) Studies on hyaluronic acid and related substances VIII. This is publication No. 142 of the Robert W. Lovett Memorial Foundation for the Study of Crippling Diseases, Harvard Medical School, Boston, Massachusetts. This investigation has been supported by research grants from Eli Lilly and Company and from the National Institute of Arthritis and Metabolic Diseases, of the National Institutes of Health, Public Health Service.

(2) Presented before the Division of Sugar Chemistry at the 122nd Meeting of the American Chemical Society, Atlantic City, New Jersey, September, 1952.

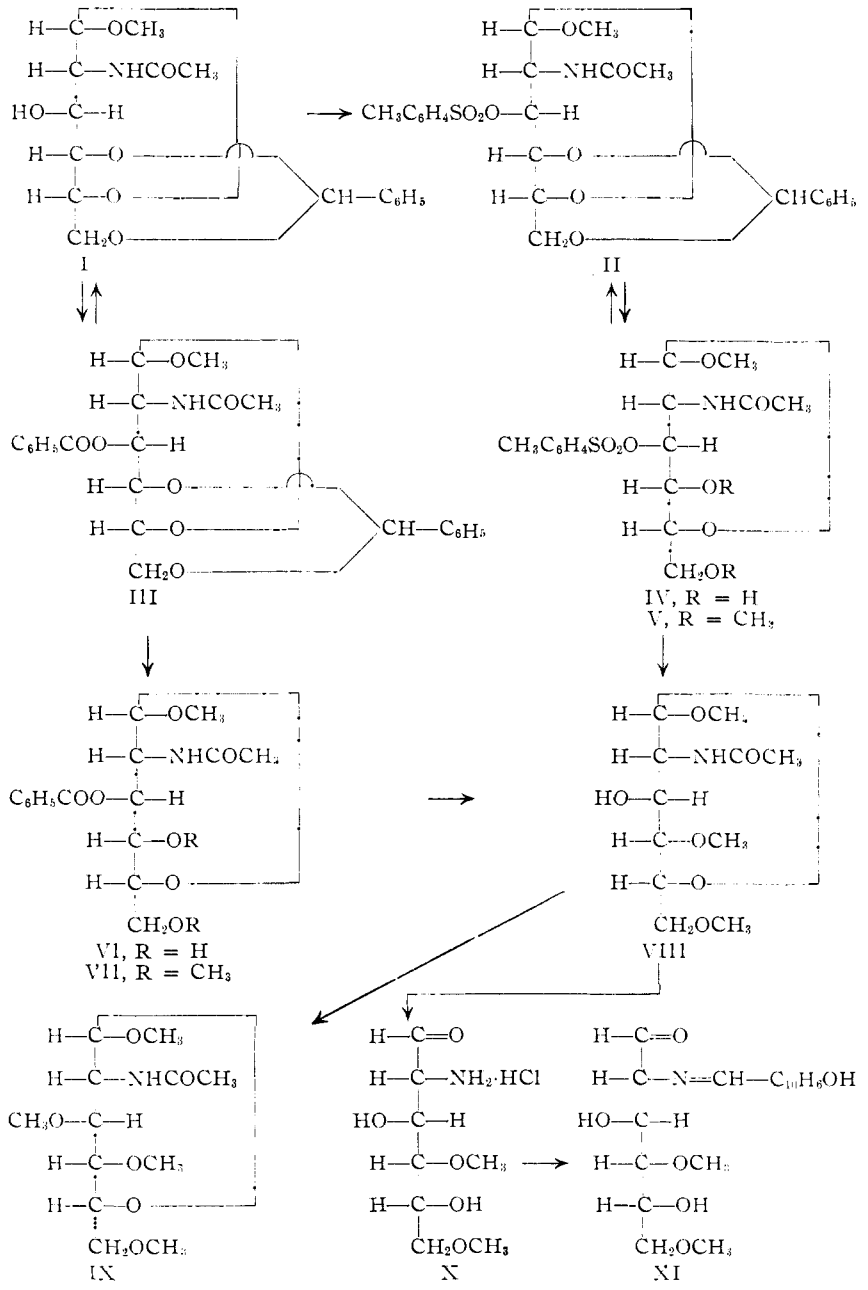
(3) R. W. Jeanloz, THIS JOURNAL, **74**, 4597 (1952).

(4) R. W. Jeanloz, *J. Biol. Chem.*, **197**, 141 (1952); *Helv. Chim. Acta*, **35**, 262 (1952).

(5) R. W. Jeanloz, *Experientia*, **6**, 52 (1950); R. W. Jeanloz and E. Forchielli, *J. Biol. Chem.*, **190**, 537 (1951).

(6) B. Weissmann and K. Meyer, THIS JOURNAL, **74**, 4729 (1952).

(7) A. Neuberger, *J. Chem. Soc.*, 50 (1941).



(II). In both reactions secondary products were isolated, not completely identified as yet.

In the sequence using the benzoyl derivatives, the methyl 2-acetamido-3-*O*-benzoyl-2-deoxy-α-D-glucopyranoside (VI) could not be crystallized. However, the preparation of the crystalline 4,6-di-*O*-acetyl derivative in an 84% yield, showed VI to be homogeneous. Methylation to the 4,6-di-*O*-methyl derivative VII gave a relatively low yield (52%) even after methylation of the mother liquor and chromatography. It is very likely that some migration of the benzoyl group occurred during the methylation. The over-all yield from I to VIII using the benzoyl intermediates was 32%.

In the sequence using the tosyl derivative, removal of the benzylidene group to give crystalline IV concurred with the formation of a relatively large amount of a more polar material, not as yet identified. The material obtained by methylation could not be crystallized and the content in methoxyl of the sirup purified by chromatography was low. The over-all yield from I to VIII using the tosyl intermediates was 23%.

Preparation of the known methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-glucopyranoside[8] from VIII constitutes proof that position 5 was not methylated. While there is a possibility of benzoyl groups migrating during the methylation procedure, tosyl groups are stable under such conditions. As both sequences of reaction gave the same final product, it is highly probable that position 3 remained protected and the methylation took place in positions 4 and 6.

Hydrolysis of VIII gave a sirup which has resisted all attempts to crystallize it up to the present. Thus characterization of the di-*O*-methyl-D-glucosamine was obtained by preparing the easily recrystallized Schiff base with 2-hydroxynaphthaldehyde.[3,9]

Experimental

Melting points were taken with a Fisher–Johns apparatus equipped with a microscope and correspond to "corrected melting point." Chromatograms were made with the flowing method, using an alumina, Alorco (grade F-20, 80–200 mesh), washed with acetic acid, then with distilled water to a *p*H above 5.5, dried and activated at 200° *in vacuo* for 24 hours. The silicic acid used for chromatogram was "Silica Gel Davison" (grade 923-08-08-276; 100–200 mesh) without pretreatment. The sequence of eluants was hexane, benzene, ether and methanol individually or in binary mixtures for alumina and hexane, benzene or chloroform, ether, ethyl acetate, acetone and methanol for silicic acid. Rotations were determined in semimicro tubes, with a length of 100 or 200 mm., using a Rudolph Photoelectric Polarimeter Attachment, Model 200; the chloroform used was A.R. grade and contained approximately 0.75% of ethanol. Microanalyses were carried out by Dr. K. Ritter, Basel, Switzerland.

Methyl 2-Acetamido-3-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (III).—To a solution of 2.0 g. of crude dry methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[7] (I) in 10 ml. of anhydrous pyridine, was added a solution of 1.5 ml. of benzoyl chloride in 10 ml. of anhydrous pyridine; both solutions had been previously cooled at −20°. The mixture was left at 0° overnight,

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

(9) Z. E. Jolles and W. T. J. Morgan, *Biochem. J.*, **34**, 1183 (1940).

then diluted with 300 ml. of chloroform and washed twice with ice-cold water, thrice with ice-cold dilute sulfuric acid, thrice with ice-cold saturated sodium bicarbonate solution, thrice with water and dried over sodium sulfate. After filtration, the solution was concentrated *in vacuo* to a sirup, which was dissolved in hot benzene. By cooling 0.45 g. crystallized with a m.p. of 284–286°. The mother liquor was chromatographed on alumina. Mixtures of benzene–ether and pure ether eluted 1.75 g. of crystalline fractions; recrystallization from mixtures of benzene and hexane, or acetone, ether and pentane afforded 1.70 g. (65%) of fine needles III, melting at 212–216°; $[\alpha]^{27}D$ +8 ± 2° (in chloroform, *c* 1.04). *Anal.* Calcd. for $C_{23}H_{25}O_7N$: C, 64.62; H, 5.90; N, 3.28. Found: C, 64.90; H, 5.86; N, 3.52. Mixtures of ether and ethyl acetate eluted 0.55 g. of a compound identical with that having a m.p. of 284–286° described above (total weight 1.0 g., 37%). This compound was much more insoluble than III and was recrystallized from methanol; m.p. 293–295°; $[\alpha]^{26}D$ −102 ± 2° (in chloroform, *c* 0.73). The analysis showed the same elementary composition as III. *Anal.* Calcd. for $C_{23}H_{25}O_7N$: C, 64.62; H, 5.90. Found: C, 64.66, 64.75; H, 5.68, 5.77.[10] Catalytic debenzoylation of III, m.p. 210–214°, gave a material melting at 258–260°, which did not depress the m.p. in admixture with pure methyl 2-acetamido-4,6-*O*-benzylidene-α-D-glucopyranoside (I).[11]

Methyl 2-Acetamido-3-*O*-benzoyl-2-deoxy-α-D-glucopyranoside (VI).—A solution of 1.60 g. of III in 60 ml. of glacial acetic acid was heated on the water-bath and 40 ml. of water was slowly added. After 30 minutes the solution was cooled and evaporated *in vacuo*. The benzaldehyde was removed by addition of water and evaporation *in vacuo*, and the remaining sirup dried by addition of toluene and evaporation. Separation of traces of benzoic acid was obtained by chromatography on silicic acid. Sirupy VI was eluted in an almost quantitative yield by mixture of ethyl acetate and acetone; $[\alpha]^{26}D$ +99 ± 2° (in chloroform, *c* 2.93). *Anal.* Calcd. for $C_{16}H_{21}O_7N$: C, 56.63; H, 6.24; OCH_3, 9.14. Found: C, 56.59; H, 6.33; OCH_3, 9.00.

Acetylation of 47 mg. of VI with acetic anhydride and pyridine in the usual manner gave the **4,6-di-*O*-acetyl derivative**. Crystallization from a mixture of ether and pentane afforded 49 mg. (84%) of long needles; m.p. 140–141°, $[\alpha]^{25}D$ +52 ± 2° (in chloroform, *c* 0.80). *Anal.* Calcd. for $C_{20}H_{25}O_9N$: C, 56.73; H, 5.95. Found: C, 56.71; H, 6.01.

Methyl 2-Acetamido-3-*O*-benzoyl-2-deoxy-4,6-di-*O*-methyl-α-D-glucopyranoside (VII).—To a solution of 0.73 g. of VI in 2 ml. of acetone was added 20 ml. of methyl iodide and 1 g. of silver oxide. After refluxing overnight, 1 g. of silver oxide was added and the reflux continued for one day. The silver residue was filtered and washed exhaustively with acetone, and the combined filtrates were evaporated *in vacuo* in a residue which was chromatographed on silicic acid. Elution with mixtures of ether and ethyl acetate gave crystalline fractions. The crystallization from a mixture of acetone, ether and pentane afforded 250 mg. of heavy prisms VII; m.p. 115–116°, $[\alpha]^{25}D$ +63 ± 2° (in chloroform, *c* 1.46). *Anal.* Calcd. for $C_{18}H_{25}O_7N$: C, 58.84; H, 6.86; OCH_3, 25.34. Found: C, 58.69; H, 6.79; OCH_3, 25.40.

The non-crystalline fractions were methylated and chromatographed as described previously and an additional crop of VII, weighing 100 mg. was obtained. The mother liquor was then debenzoylated and acetylated, affording 125 mg. of methyl 2-acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-methyl-α-D-glucopyranoside (see below) corresponding to 65 mg. of VII. Thus, the total yield of VII was 415 mg. or 52%. The remaining sirupy fractions were not examined.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (II).—To an ice-cold solution of 2.00 g. I in 20 ml. of dry pyridine was added 1.80 g. (1.5 moles) of *p*-toluenesulfonyl chloride. The solution was kept at 0° for 3 days, the excess chloride was decomposed by addition of ice and the solution extracted with chloroform. The chloroform layer washed thrice with cold 2 *N* sulfuric acid followed by saturated sodium bicarbonate and then water, was dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silicic acid. Elution with mixtures of benzene and ether 4:1 and 2:1 afforded 28 mg. (0.7%) of crystals melting at 215–225° (see below): elution with a mixture of benzene and ether 1:1, with ether and with mixtures of ether and ethyl acetate 49:1, 19:1, 9:1, 4:1 and 2:1 afforded crystalline fractions, which after recrystallization from a mixture of acetone, ether and pentane gave 1.51 g. (51%) of prismatic needles II; m.p. 192–194° with slight decomposition, $[\alpha]^{25}D$ −1 ± 1° (in chloroform, *c* 1.69). *Anal.* Calcd. for $C_{23}H_{27}O_8NS$: C, 57.85; H, 5.70; S, 6.72. Found: C, 57.92; H, 5.61; S, 6.72.

Elution with ethyl acetate, acetone and mixtures of acetone and methanol gave 0.62 g. (31%) of pure starting material.

In an experiment with the same amount of material, the solution was left two days at room temperature, then heated at 60° for 30 minutes. On chromatography, elution with mixtures of benzene and ether 4:1 and 2:1 gave 0.40 g. of crystalline fractions (11%), which after recrystallization from a mixture of chloroform and ether, melted at 235–237°; $[\alpha]^{24}D$ +34 ± 1° (in chloroform, *c* 1.89). Analysis showed the introduction of two tosyl groups. *Anal.* Calcd. for $C_{30}H_{33}O_{10}NS_2$: C, 57.04; H, 5.27; S, 10.15; $COCH_3$, 6.81. Found: C, 57.19; H, 5.43; S, 10.72; $COCH_3$, 7.47. The structure of methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-*p*-tolylsulfonyl-2-*N*-*p*-tolylsulfonylacetamido-α-D-glucopyranoside has been tentatively assigned to this compound. In addition 30% of pure II and 45% of crude starting material were obtained.

Methyl 2-Acetamido-2-deoxy-3-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (IV).—A solution of 1.85 g. of II in 36 ml. of glacial acetic acid was heated on the water-bath and 24 ml. of water was slowly added. After a half-hour, the solution was cooled and evaporated *in vacuo*. The benzaldehyde was removed by addition of water and evaporated *in vacuo*, and the remaining sirup dried by addition and evaporation of toluene. Purification was obtained by chromatography on silicic acid. Elution with mixtures of ethyl acetate and acetone 4:1,3:1 and 2:1 gave fractions (1.12 g.), which crystallized after evaporation of the solvent. The crystallization from a mixture of acetone and ether afforded 1.00 g. (66%) of typical pentagonal prisms IV; m.p. 158–160°, $[\alpha]^{26}D$ +77 ± 1° (in chloroform, *c* 0.86). *Anal.* Calcd. for $C_{16}H_{23}O_8NS$: C, 49.34; H, 5.95; S, 8.23. Found: C, 49.35, 49.50; H, 6.07, 5.93; S, 8.07.

Elution with mixtures of acetone and methanol gave 0.28 g. of sirupy material, which was not further investigated.

Acetylation of 37 mg. of IV with acetic anhydride and pyridine in the usual manner gave the **4,6-di-*O*-acetyl derivative**. Crystallization from a mixture of acetone, ether and pentane afforded 42 mg. (92%) of short and heavy prisms; m.p. 152–153°, $[\alpha]^{29}D$ +72 ± 3° (in chloroform, *c* 0.84). *Anal.* Calcd. for $C_{20}H_{27}O_{10}NS$: C, 50.73; H, 5.75; S, 6.77. Found: C, 50.82; H, 5.73; S, 6.74.

Forty-six milligrams of IV was shaken overnight with 0.5 ml. of benzaldehyde and 100 mg. of freshly fused zinc chloride. Ice was added and the mixture was extracted with hexane to remove the excess of benzaldehyde. The mixture was then extracted with chloroform and the chloroform layer was washed with saturated sodium bicarbonate, water and then dried over sodium sulfate. After evaporation of the solvent *in vacuo*, the crystalline residue was recrystallized from a mixture of acetone, ether and pentane, affording 33 mg. (58%) of II melting at 183–186° and not depressing the m.p. in admixture with authentic II.

Methyl 2-Acetamido-2-deoxy-4,6-di-*O*-methyl-3-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (V).—One hundred and fifty milligrams of IV was refluxed for two days with 3 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*, were chromatographed on silicic acid. Elution with mixtures of ether and ethyl acetate 1:1 and with pure ethyl acetate gave 141 mg. (87%) of an hygroscopic sirup; $[\alpha]^{28}D$ +69 ± 2° (in chloroform, *c* 1.55). *Anal.* Calcd. for $C_{18}H_{27}O_8NS$: C, 51.78; H, 6.52; OCH_3, 22.3. Found: C, 50.99; H, 6.96; OCH_3, 19.5.

Methyl 2-Acetamido-2-deoxy-4,6-di-*O*-methyl-α-D-glucopyranoside (VIII) from VII.—A solution of 175 mg. of VII in 2 ml. of methanol was catalytically debenzoylated at 0°

(10) The elementary composition and the negative rotation seem to indicate that this may be the β-form. Further investigation is underway.

(11) Neuberger[7] recorded for I m.p. 255°; we observed 260–262°.

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

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

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.