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3,6-Di-*O*-methyl-D-galactosamine Hydrochloride (2-Amino-2-deoxy-3,6-di-*O*-methyl-D-galactose Hydrochloride)[1]

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The synthesis of 3,6-di-*O*-methyl-D-galactosamine hydrochloride (2-amino-2-deoxy-3,6-di-*O*-methyl-D-galactose hydrochloride), a reference compound for the determination of the structure of compounds containing D-galactosamine, is described. It was prepared from methyl 2-acetamido-2-deoxy-3-*O*-methyl-α-D-galactopyranoside and was characterized by its crystalline *N*-acetyl and *N*-(2-hydroxynaphthylidene) derivatives.

The synthesis of 3,6-di-*O*-methyl-D-galactosamine hydrochloride (IX) completes the series of the *O*-methyl ethers of 2-amino-2-deoxy-D-galactopyranose.[3-8] They are used as reference compounds in the elucidation of the chemical structure of natural products containing D-galactosamine by the methylation procedure.

At first, a route identical to the one followed in the synthesis of 3,6-di-*O*-methyl-D-glucosamine[9] was selected. However, side reactions already noticed in the glucosamine series became much more important, because of the change from an equatorial to an axial configuration of the hydroxyl group at C_4, when passing from the D-glucosamine to the D-galactosamine series.

Two pathways were studied for the preparation of the key compound, methyl 2-acetamido-4-*O*-benzoyl-2-deoxy-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (XIII). Direct methylation of methyl 2-acetamido-2-deoxy-6-*O*-triphenylmethyl-α-D-galactopyranoside (XV)[5] was expected to give only the 3-*O*-methyl ether IV, since the bulky trityl group would stabilize the molecule in the C_1 chair conformation[10] and consequently the hydroxyl group at position 4 would possess the less reactive axial conformation. This result was indeed obtained and the 3-*O*-methyl ether IV was isolated in a 53% yield. However, the 3,4-di-*O*-methyl ether XVI was also produced in a 32% yield, showing some reactivity of the axial hydroxyl group. A similar observation had been made in the methylation of 2-acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose.[6] The separation of both products was laborious, the properties of the bulky trityl group overwhelming the properties of the remainder of the molecule and decreasing the efficiency of absorption chromatography and fractional crystallization. An attempt was made to take advantage of the free hydroxyl group in the monomethyl ether IV, and to prepare directly the 4-*O*-benzoyl-3-*O*-methyl derivative XIII by benzoylation of the crude mixture resulting from the methylation of XV. However, it resulted not only in the formation of the 4-*O*-benzoyl ester XIII, but also in side reactions, with replacement of the acetamido group by a benzamido group in both monomethyl IV and dimethyl XVI ethers. The mixture obtained was complex and only a small amount of the expected methyl 2-acetamido-4-*O*-benzoyl-2-deoxy-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (XIII) could be isolated. Part of the mother liquors was debenzoylated and afforded small amounts of methyl 2-benzamido-2-deoxy-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (II) and of methyl 2-acetamido-2-deoxy-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (IV). Detritylation of the remaining part gave methyl 2-acetamido-4-*O*-benzoyl-2-deoxy-3-*O*-methyl-α-D-galactopyranoside (XIV), methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranoside (XVIII) and methyl 2-benzamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranoside (XIX).

The second pathway started from the known methyl 2-acetamido-2-deoxy-3-*O*-methyl-α-D-galactopyranoside (III).[3] The 6-*O*-triphenylmethyl derivative IV was prepared and the remaining hydroxyl group at C_4 was benzoylated. The main product of the benzoylation was the crystalline methyl 2-acetamido-4-*O*-benzoyl-2-deoxy-3-*O*-

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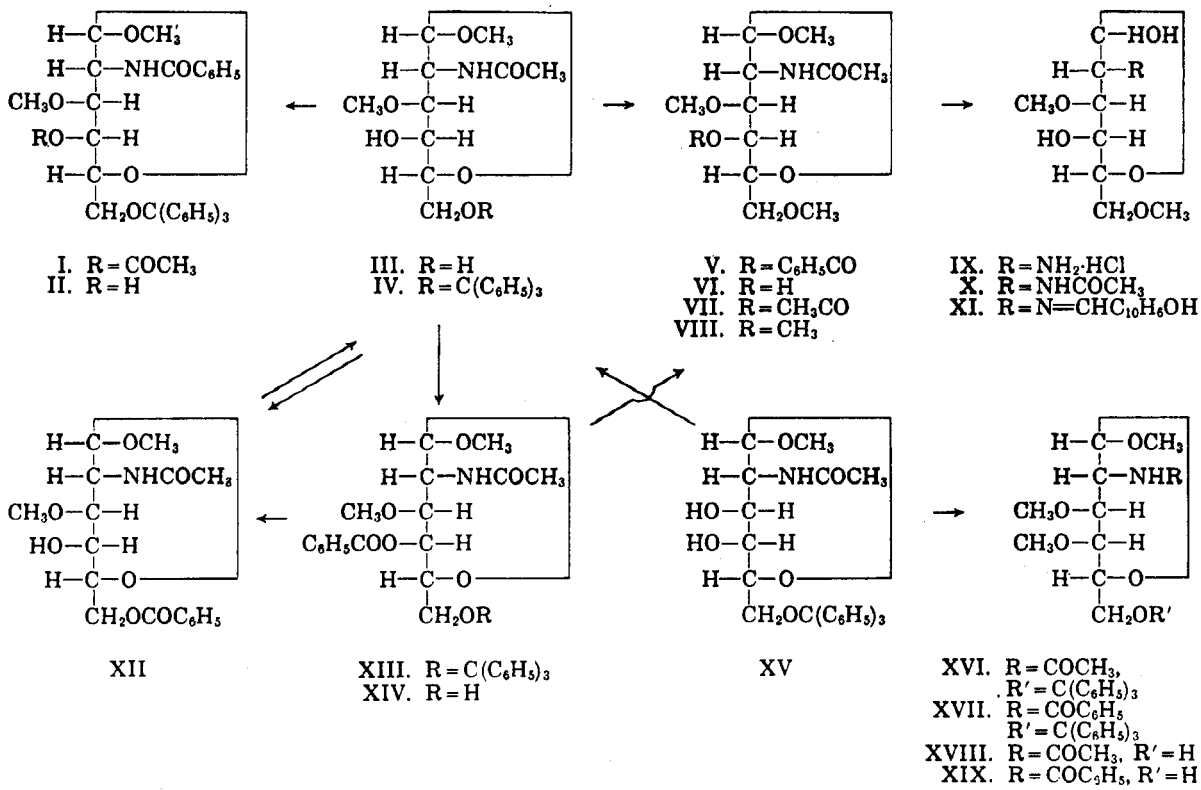
methyl - 6 - *O* - triphenylmethyl - α - D - galactopyranoside (XIII), any benzamido derivative formed remaining in the mother liquor. Removal of the trityl group of XIII with 60% acetic acid proceeded in a straightforward manner and crystalline methyl 2-acetamido-4-*O*-benzoyl-2-deoxy-3-*O*-methyl-α-D-galactopyranoside (XIV) was isolated in a 76% yield.

The alkaline conditions required for the methylation of XIV were too drastic for the stability of the axial 4-benzoate and about two thirds of the product showed a migration of the benzoyl group to the equatorial primary hydroxyl group. The structure of the product obtained in the largest amount during the methylation was shown to be



methyl 2-acetamido-6-*O*-benzoyl-2-deoxy-3-*O*-methyl-α-D-galactopyranoside (XII) by alkaline hydrolysis into the known methyl 2-acetamido-2-deoxy-3-*O*-methyl-α-D-galactopyranoside (III)[3] and by monobenzoylation of the latter compound to give back XII. The desired product, methyl 2-acetamido-4-*O*-benzoyl-2-deoxy-3,6-di-*O*-methyl-α-D-galactopyranoside (V) was isolated in a 30% crude yield, and subsequently hydrolyzed into methyl 2-acetamido-2-deoxy-3,6-di-*O*-methyl-α-D-galactopyranoside (VI).

Since the conformation which favors the migration of the benzoyl group from the axial hydroxyl group at C_4 to the primary equatorial hydroxyl group would also inhibit the methylation of the hydroxyl at C_4 and favor the methylation of the primary hydroxyl group, methyl 2-acetamido-2-deoxy-3-*O*-methyl-α-D-galactopyranoside (III) was directly treated with methyl iodide and silver oxide. The product VI obtained in a good yield was shown to be identical with the product obtained by protecting position 4 by benzoylation. Further methylation of VI gave the known methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-galactopyranoside (VIII),[8] a proof that the ring had not shifted during the partial methylation. The acid hydrolysis of VI gave a crystalline hydrochloride IX which was designated as the α-anomer on the basis of mutarotation. *N*-acetylation of the free base resulted also in a crystalline product X and condensation with 2-hydroxynaphthaldehyde[11] gave the crystalline Schiff's base XI.

EXPERIMENTAL

Melting points were taken on a hot stage, equipped with a microscope, and correspond to "corrected melting point." Rotations were determined in semimicro or micro (for amounts smaller than 3 mg.) tubes with lengths 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. Chromatograms were made with the flowing method using either silicic acid or alumina. The latter, "Alcoa Activated Alumina," grade F-20, 80–200 mesh, a product of the Aluminum Ore Co. of America, East St. Louis, Ill., was washed with acetic acid, then with distilled water to a *p*H above 5.5, dried and activated at 200° *in vacuo* for 24 hr. The silicic acid used for chromatograms was "Silica Gel Davison," from the Davison Co., Baltimore 3, Md. (grade 950; 60–200 mesh) without pretreatment. When deactiva-

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

tion by contact with moist air occurred, reactivation was obtained by heating to 170–200° (Manufacturer's instructions). 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. The proportion of weight of substance to be adsorbed to weight of adsorbent was 1 to 20–30 for alumina, and 1 to 50–100 for silicic acid. The proportion of weight of substance in g. to volume of fraction of eluant in ml. was 1 to 100. The ratio of diameter to length of the column was 1 to 5 for alumina and 1 to 20 for silicic acid. Evaporations were carried out *in vacuo*, with an outside bath temperature kept below 45°. Amounts of volatile solvent smaller than 20 ml. were evaporated by blowing dry nitrogen. The microanalyses were done by Dr. K. Ritter, Basel, and Dr. M. Manser, Zurich, Switzerland.

Methylation of methyl 2-acetamido-2-deoxy-6-O-triphenylmethyl-α-D-galactopyranoside (XV). To a solution of 2.03 g. of XV[5] in 20 ml. of methyl iodide was added 2 g. of silver oxide. After 24 hr. agitation at room temperature, 20 ml. of methyl iodide and 2 g. of silver oxide were added, followed 12 hr. later by 2 g. of silver oxide. After an additional 24 hr. of agitation, the mixture was filtered, the residue was washed well with hot acetone and the filtrate was evaporated to give 2.14 g. of sirup. It was chromatographed on alumina, mixtures of benzene and ether in proportions 5:1, 3:1, and 1:1 eluting 0.76 g. of crystalline fractions. Recrystallization from a mixture of acetone and ether afforded 0.69 g. (32%) of methyl-2-acetamido-2-deoxy-3,4-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (XVI), melting after a second recrystallization at 223–224°, $[\alpha]_D^{26}$ + 70 ± 2° (in chloroform, *c* 0.64).

Anal. Calcd. for $C_{30}H_{35}O_6N$: C, 71.26; H, 6.98; OCH_3, 18.41. Found: C, 71.28; H, 6.98; OCH_3, 18.32. In admixture with the product previously described,[6] the melting point was not depressed.

A mixture of ether and methanol in proportion 5:1 eluted 1.37 g. of crystalline fractions. Recrystallization from a mixture of acetone, ether and pentane gave 1.10 g. (53%) of *methyl 2-acetamido-2-deoxy-3-O-methyl-6-O-triphenylmethyl-α-D-galactopyranoside* (IV), m.p. 234–235°, $[\alpha]_D^{26}$ + 65 ± 2° (in chloroform, *c* 0.95).

Anal. Calcd. for $C_{29}H_{33}O_6N$: C, 70.85; H, 6.77; OCH_3, 12.63. Found: C, 70.78; H, 6.84; OCH_3, 12.69. In admixture with the product described below, the melting point was not depressed.

Detritylation of 168 mg. of XVI with 60% acetic acid (see below the preparation of XIV) afforded, after chromatography, 66 mg. of crystalline fractions eluted with a mixture of ethyl acetate and acetone 2:1 and pure acetone. Recrystallization from a mixture of methanol and ether yielded 54 mg. (63%) of crystals, m.p. 216–217°, $[\alpha]_D^{28}$ +150 ± 2° (in methanol, *c* 0.68).

Anal. Calcd. for $C_{11}H_{21}O_6N$: C, 50.18; H, 8.04; OCH_3, 35.36. Found: C, 50.31; H, 8.06; OCH_3, 35.23.

There was no depression of melting point in admixture with methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranoside (XVIII).[6]

Methylation of XV followed by benzoylation. To a solution of 2.75 g. of methyl 2-acetamido-2-deoxy-6-*O*-triphenylmethyl-α-D-galactopyranoside (XV) in 50 ml. of methyl iodide was added 3.5 g. of silver oxide. After 24 hr. of mechanical agitation at room temperature, the silver oxide was removed by filtration, and the filtrate and acetone washings were evaporated to dryness. Remethylation with 3.5 g. of silver oxide and 50 ml. of methyl iodide was continued for 24 hr. when 3.5 g. of fresh silver oxide was added. Stirring was continued for 8 hr., the residue after filtration was extracted with hot acetone and the filtrate and washings evaporated to dryness to yield 2.80 g. of sirup, which was purified by silicic acid chromatography. The crystalline fractions weighed 2.72 g. and were benzoylated with 1.4 ml. of benzoyl chloride in 11 ml. of pyridine for 5 days at 0°. After addition of ice and chloroform the solution was washed successively with dilute sulfuric acid, sodium hydrogen carbonate, and water. After drying over sodium sulfate and evaporation of the solution to dryness the crude product was chromatographed on alumina. Elution with benzene and mixtures of benzene and ether gave 2.79 g. of sirup and 69 mg. of methyl 2-acetamido-4-*O*-benzoyl-2-deoxy-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (XIII), m.p. 278–280°.

The above sirup was purified by chromatography on silicic acid. A mixture of benzene and ether 9:1 eluted 2.78 g. of material. One of the fractions was analyzed and showed $[\alpha]_D^{26}$ + 93 ± 2° (in chloroform, *c* 0.32). The elementary analyses corresponded to methyl 2-acetamido(or benzamido)-2-deoxy-4-*O*-benzoyl(or acetyl)-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside.

Anal. Calcd. for $C_{36}H_{37}O_7N$: C, 72.58; H, 6.26. Found: C, 72.55; H, 6.26.

A mixture of ether and ethyl acetate 2:1 eluted the remaining material, 135 mg. of sirup, from which 45 mg. of XIII was obtained in crystalline form.

Removal of the triphenylmethyl group of 1.75 g. of the sirup eluted with the mixture of benzene and ether 9:1 was done with 60% acetic acid in the usual manner, and the hydrolysis mixture was separated by chromatography on silicic acid. Elution with ethyl acetate gave 190 mg. of sirup that yielded on crystallization from a mixture of acetone, ether and pentane 95 mg. with m.p. 189–191°, $[\alpha]_D^{25}$ + 118 ± 2° (in chloroform, *c* 0.58).

Anal. Calcd. for $C_{16}H_{23}O_6N$: C, 59.06; H, 7.13. Found: C, 58.60; H, 7.05.

On the basis of elementary analysis and the results of attempted debenzoylation (see below), this product is assigned the formula *methyl 2-benzamido-2-deoxy-3,4-di-O-methyl-α-D-galactopyranoside* (XIX). A mixture of ethyl acetate and acetone 3:1 eluted 130 mg. of sirup, and crystallization of it from a mixture of acetone, ether, and pentane afforded 36 mg. of methyl 2-acetamido-4-*O*-benzoyl-2-deoxy-3-*O*-methyl-α-D-galactopyranoside (XIV). The largest amount of material was eluted with acetone (305 mg.); crystallization of it from acetone, ether, and pentane gave 200 mg. (11%) of methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranoside (XVIII). The last two crystalline products showed no depression of melting point when mixed with authentic material. No work was done with the sirup (160 mg.) obtained by elution with ether and various mixtures of ether and ethyl acetate.

The remaining 0.64 g. of the sirup eluted with the mixture of benzene and ether 9:1 was debenzoylated with 0.3 ml. of 1*N* barium methoxide in 6 ml. of methanol for 20 hr. at 4°. After addition of 40 ml. of chloroform, it was extracted with 2*N* sodium carbonate, then with water, and dried over sodium sulfate. The residue of 425 mg. after removal of the chloroform by evaporation was separated into two products by silicic acid chromatography. With a mixture of benzene and ether 3:1, 145 mg. of crystalline material was eluted which after recrystallization from a mixture of acetone, ether, and pentane gave needles with m.p. 215–217°, $[\alpha]_D^{25}$ + 60 ± 2° (in chloroform, *c* 0.32).

Anal. Calcd. for $C_{17}H_{22}O_7N$: C, 73.76; H, 6.37. Found: C, 73.70; H, 6.35.

This compound corresponds to *methyl 2-benzamido-2-deoxy-3-O-methyl-6-O-triphenylmethyl-α-D-galactopyranoside* (II). With a mixture of ether and ethyl acetate 1:1, 190 mg. of sirup was eluted which on crystallization from a mixture of chloroform, ether, and pentane yielded 130 mg. of prisms with m.p. 234–236°, showing no depression in melting point when mixed with IV. The material eluted with a mixture of benzene and ether 9:1, therefore, was a mixture of XIII and methyl 4-*O*-acetyl-2-benzamido-2-deoxy-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (I).

To a solution of 113 mg. of methyl 2-benzamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranoside (XIX) in 5 ml. of methanol, 0.2 ml. of 1*N* barium methoxide was added. After 24 hr. at 0° half of the solvent was removed by evapora-

tion and an equal amount of water added before removal of barium ions with Dowex 50. Concentration of the eluant yielded 106 mg. of material with m.p. 189–191°, showing no depression of the melting point when mixed with the starting material.

Methyl 2-acetamido-2-deoxy-3-O-methyl-6-O-triphenylmethyl-α-D-galactopyranoside (IV). A mixture of 2.12 g. of methyl 2-acetamido-2-deoxy-3-*O*-methyl-α-D-galactopyranoside (III),[3] 3.55 g. of triphenylchloromethane, and 26.5 ml. of anhydrous pyridine was kept at 55° for 3 days. The crystalline product after removal of pyridine by distillation was chromatographed on silicic acid. Mixtures of ether and methanol (49:1 and 19:1) eluted 3.60 g. of IV, and 0.40 g. of III was recovered with increased concentrations of methanol. Recrystallization from a mixture of acetone, ether, and pentane yielded 3.30 g. of prisms (97% after correction for the recovered starting material), m.p. 235–236°, $[\alpha]_D^{26}$ + 63 ± 2° (in chloroform, *c* 0.96).

Anal. Calcd. for $C_{29}H_{33}O_6N$: C, 70.85 H, 6.77; OCH_3, 12.63. Found: C, 70.78; H, 6.84; OCH_3, 12.69.

Fifty milligrams of methyl 2-acetamido-2-deoxy-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (IV) was acetylated with 0.18 ml. of acetic anhydride in 0.3 ml. of pyridine for 3 days at room temperature. After addition of ice and chloroform, the solution was washed successively with cold 2*N* sulfuric acid, saturated sodium hydrogen carbonate, and water. Evaporation of the chloroform extract after drying over anhydrous sodium sulfate yielded 71 mg. of sirup. Crystallization from a mixture of acetone, ether, and pentane afforded 41 mg. (59%) of the *4-O-acetyl* derivative, m.p. 238–239°; $[\alpha]_D^{26}$ + 60 ± 2° (in chloroform, *c* 0.35).

Anal. Calcd. for $C_{31}H_{35}O_7N$: C, 69.77; H, 6.61. Found: C, 69.62; H, 6.57.

Methyl 2-acetamido-4-O-benzoyl-2-deoxy-3-O-methyl-6-O-triphenylmethyl-α-D-galactopyranoside (XIII). A mixture of 825 mg. of IV, 3 ml. of anhydrous pyridine, and 0.6 ml. of benzoyl chloride was kept overnight at 0°, then at room temperature for 2 hr. before addition of ice and water. The crude crystalline material (1.05 g. with m.p. 263–274°) obtained by filtration was recrystallized from a mixture of chloroform and ether after decolorization through a double layer of Darco G-60 and Celite to yield 850 mg. (77%) of XIII as needles, m.p. 273–276°, $[\alpha]_D^{27}$ + 93 ± 2° (in chloroform, *c* 0.55).

Anal. Calcd. for $C_{36}H_{37}O_7N$: C, 72.58; H, 6.26. Found: C, 72.45; H, 6.25.

Methyl 2-acetamido-4-O-benzoyl-2-deoxy-3-O-methyl-α-D-galactopyranoside (XIV). To a solution of 600 mg. of methyl 2-acetamido-4-*O*-benzoyl-2-deoxy-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (XIII) in 12 ml. of glacial acetic acid, 7 ml. of water was added dropwise, and the mixture was heated for 45 min. on a steam bath. The mixture was cooled and evaporated, and traces of acetic acid and water were removed by codistillation with absolute ethanol and toluene. The product was purified by silicic acid chromatography. A mixture of benzene and ether 39:1 eluted 251 mg. (96%) of triphenyl carbinol, while ethyl acetate and a mixture of ethyl acetate and acetone 39:1 eluted 365 mg. of sirupy XIV. Crystallization of XIV from a mixture of acetone, ether, and pentane gave 270 mg. (76%) of prisms, m.p. 182–184°, $[\alpha]_D^{32}$ + 217 ± 2° (in chloroform, *c* 0.29). When recrystallized from a mixture containing a minimum amount of acetone, needles were obtained, m.p. 171–176°; 212–222°.

Anal. Calcd. for $C_{17}H_{22}O_7N$: C, 57.78; H, 6.56. Found: C, 57.84; H, 6.50.

Methylation of methyl 2-acetamido-4-O-benzoyl-2-deoxy-3-O-methyl-α-D-galactopyranoside (XIV). To 200 mg. of XIV in 2 ml. of acetone, 10 ml. of methyl iodide and 500 mg. of silver oxide were added and after refluxing for 24 hr., the reaction mixture was filtered through a double layer of Darco G-60 and Celite and washed well with acetone. After evaporation of the filtrate to dryness, 10 ml. of methyl iodide and 500 mg. of silver oxide were added, and refluxing was continued for 22 hr. The mixture was worked up as described above and chromatographed on silicic acid. With a mixture of ether and ethyl acetate (3:1) 61 mg. (30%) of sirup with $[\alpha]_D^{32}$ + 158 ± 2° (in methanol, *c* 0.69) was eluted, which from the results of its debenzoylation described below is *methyl 2-acetamido-4-O-benzoyl-2-deoxy-3,6-di-O-methyl-α-D-galactopyranoside* (V). With ethyl acetate and a mixture of ethyl acetate and acetone 39:1, 129 mg. (65%) was eluted. Crystallization from methanol, ether, and pentane yielded 92 mg. of clusters of needles with m.p. 225–227°, $[\alpha]_D^{24}$ +124 ± 2° (in chloroform, *c* 0.27).

Anal. Calcd. for $C_{17}O_7H_{23}N$: C, 57.78; H, 6.56. Found: C, 57.78; H, 6.56. On the basis of elementary analysis and of debenzoylation (see below) this compound is *methyl 2-acetamido-6-O-benzoyl-2-deoxy-3-O-methyl-α-D-galactopyranoside* (XII).

To a solution of 50 mg. of XII in 2.5 ml. of methanol was added 0.1 ml. of 1*N* barium methoxide. After refrigerating for 22 hr., most of the methanol was removed, 2 ml. of water was added, and barium ions were removed with Dowex 50. The resulting sirup (42 mg.) was purified by silicic acid chromatography after evaporation to dryness of the water solution with additions of absolute ethanol to remove the last traces of water. With a mixture of ethyl acetate and acetone 1:3 and pure acetone 38 mg. of crystalline material was eluted. Recrystallization from methanol, acetone and ether yielded 24 mg. of III, m.p. 196–198°, $[\alpha]_D^{29}$ + 186 ± 2° (in methanol, *c* 0.25). There was no depression of melting point when mixed with authentic III.[3]

Methyl 2-acetamido-6-O-benzoyl-2-deoxy-3-O-methyl-α-D-galactopyranoside (XII). Fifty milligrams of III[3] was cooled to −20° before addition of 0.5 ml. of pyridine and 0.024 ml. of benzoyl chloride previously cooled to −20°. After 20 hr. at 0°, 10 ml. of chloroform was added and the solution washed successively with cold water, 2*N* sulfuric acid, saturated sodium hydrogen carbonate, and water. Concentration of the solution after drying over sodium sulfate yielded 32 mg. (45%) of sirup. Crystallization was effected from a mixture of methanol, ether and pentane, m.p. 224–227°, $[\alpha]_D^{28}$ +118 ± 2° (in chloroform, *c* 0.54). No depression of melting point occurred when mixed with the product (XII) obtained during methylation of XIV.

Methyl 2-acetamido-2-deoxy-3,6-di-O-methyl-α-D-galactopyranoside VI. (*a*) *From* V. Debenzoylation of 59 mg. of sirupy V was carried out as described above. The product (39 mg.) was purified by silicic acid chromatography. With a mixture of ethyl acetate and acetone 7:1, 31 mg. (73%) of needles of VI was obtained, m.p. 170–171° with previous sublimation at about 150°, $[\alpha]_D^{24}$ + 149 ± 2° (in chloroform, *c* 0.69).

Anal. Calcd. for $C_{11}H_{21}O_6N$: C, 50.18; H, 8.04; OCH_3, 35.36. Found: C, 50.11; H, 8.13; OCH_3, 35.38.

(*b*) *From* III. Five hundred milligrams of III, 1.5 g. of silver oxide, 8 ml. of acetone, and 75 ml. of methyl iodide were stirred for 18 hr. An additional 1.3 g. silver oxide was added and stirring continued for 24 hr. after which the reaction mixture was filtered through a double layer of Darco G-60 and Celite. The filtrate was evaporated to dryness and the residue crystallized from a mixture of acetone and ether to yield 390 mg. of VI (74%) with m.p. 163–172°. Recrystallization gave 326 mg. of pure VI, showing no depression of melting point when mixed with VI prepared from method (*a*) above.

Further methylation for 96 hr. of VI with methyl iodide and silver oxide added in four portions at 24-hr. intervals yielded methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-galactopyranoside (VIII) m.p. 190–191°. A mixed melting point with authentic material[3] showed no depression.

Acetylation of 50 mg. of VI with acetic anhydride and pyridine in the usual manner gave, after crystallization from a mixture of acetone, ether, and pentane, 14 mg. (24%) of the *4-O-acetyl* derivative (VII) as prisms, m.p. 155–158°, $[\alpha]_D^{25}$ + 152 ± 2° (in chloroform, *c* 0.29).

Anal. Calcd. for $C_{15}H_{23}O_7N$: C, 51.14; H, 7.59. Found: C, 51.16; H, 7.60.

3,6-Di-O-methyl-α-D-galactosamine hydrochloride (2-amino-2-deoxy-3,6-di-O-methyl-α-D-galactose) (IX). A solution of 95 mg. of VI in 3 ml. of 2*N* hydrochloric acid was heated in a sealed tube on a steam bath for 3 hr. After cooling, the reaction mixture was evaporated to dryness with additions of absolute ethanol and toluene to remove the last traces of acids and water. The quantitative yield of sirup was decolorized through a double layer of Darco G-60 and Celite and crystallized on standing (49 mg., 56%). Recrystallization from a mixture of methanol, acetone, and ether afforded clusters of small prisms, which darken at 157° and decompose above 170°; $[\alpha]_D^{24}$ + 132 (after 15 min.) to $[\alpha]_D^{25}$ + 121 ± 2° after 3 and 22 hr. (in water, *c* 0.5).

Anal. Calcd. for $C_8H_{18}O_5NCl$: C, 39.43; H, 7.44; Cl, 14.55. Found: C, 39.46; H, 7.58; Cl, 14.61.

2-Acetamido-2-deoxy-3,6-di-O-methyl-α-D-galactose (X). Acetylation of 98 mg. of 3,6-di-*O*-methyl-α-D-galactosamine hydrochloride (IX) was done at room temperature for 19 hr. in the presence of 1 ml. of methanol, 0.1 ml. of acetic anhydride, and 95 mg. of silver acetate. After the reaction mixture was filtered through a layer of Celite and the residue washed with 2 ml. of hot water, the filtrate and washings were treated with 2 drops of 2*N* hydrochloric acid. Filtration after 2 hr. and evaporation to dryness gave a quantitative yield of sirup. The sirup was chromatographed on silicic acid, and a fraction of 82 mg. of sirup was eluted with acetone. This was re-chromatographed and from a mixture of ethyl acetate and acetone 1:1 and pure acetone partially crystalline fractions were obtained (75 mg.). From 42 mg. of the above product, 7 mg. of 2-acetamido-2-deoxy-3,6-di-*O*-methyl-α-D-galactose was obtained as needles; m.p. 162–164°; $[\alpha]_D^{24}$ + 120 ± 2° (after 15 min.) to $[\alpha]_D^{24}$ + 97 ± 2° (after 21 hr., in water, *c* 0.39).

Anal. Calcd. for $C_{10}H_{19}O_6N$: C, 48.18; H, 7.68. Found: C, 48.12; H, 7.75.

2-Deoxy-2-(2'-hydroxynaphthylidenamino)-3,6-di-O-methyl-β-D-galactose (XI). A solution of 62 mg. of IX and 84 mg. of sodium acetate trihydrate in 1 ml. of water was treated as previously described[11,12] with 125 mg. of 2-hydroxynaphthaldehyde in 8 ml. of methanol. Purification was effected by silicic acid chromatography; the substance (66 mg., 72%) was eluted by ethyl acetate and a mixture of ethyl acetate and acetone. Crystallization from Methyl Cellosolve and ether yielded 40 mg. of prisms, m.p. 191–194°. A slow mutarotation was observed from $[\alpha]_{5461}^{25}$ + 96 ± 2° (after 1 hr.) to $[\alpha]_{5461}^{25}$ + 243 ± 3° after 140 and 145 hr. (in Methyl Cellosolve, *c* 0.19).

Anal. Calcd. for $C_{19}H_{23}O_6N$: C, 63.15; H, 6.41. Found: C, 63.07; H, 6.46.

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[CONTRIBUTION FROM THE DEPARTMENT OF MEDICINE, HARVARD MEDICAL SCHOOL, AND THE MASSACHUSETTS GENERAL HOSPITAL]

3,6-Di-*O*-methyl-D-glucosamine Hydrochloride (2-Amino-2-deoxy-3,6-di-*O*-methyl-D-glucose Hydrochloride)[1]

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3,6-Di-*O*-methyl-D-glucosamine hydrochloride (2-amino-2-deoxy-3,6-di-*O*-methyl-D-glucose hydrochloride) has been synthesized from the known methyl 2-acetamido-2-deoxy-3-*O*-methyl-α-D-glucopyranoside and its free base was characterized by the crystalline *N*-acetyl and *N*-(2'-hydroxynaphthylidene) derivatives.

The synthesis of 3,6-di-*O*-methyl-D-glucosamine hydrochloride (XV) was undertaken in order to complete the series of the *O*-methyl ethers of 2-amino-2-deoxy-D-glucopyranose used as reference compounds in the determination of the structure of D-glucosamine containing natural products.[3–8]

Although this synthesis was completed seven years ago,[1] publication has been delayed until the final identification of side products was made. In addition, a derivative of 3,6-di-*O*-methyl-D-glucosamine has been recently isolated from the hydrolyzate of methylated α_1-acid glycoprotein of human serum.[9]

The route followed began with the previously described methyl 2-acetamido-2-deoxy-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (I)[6] by blocking position 4 with a benzoyl group to give II. The removal of the trityl group afforded III and subsequent methylation of the liberated primary

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