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3,4-Di-*O*-methyl-D-galactosamine Hydrochloride (2-Amino-2-deoxy-3,4-di-*O*-methyl-D-galactose Hydrochloride)[1,2]

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The synthesis of 3,4-di-*O*-methyl-D-galactosamine hydrochloride (2-amino-2-deoxy-3,4-di-*O*-methyl-D-galactose hydrochloride), a reference substance for structural studies of galactosamine-containing substances, is described. It was prepared from 1,6:2,3-dianhydro-β-D-talopyranose, and was transformed into the crystalline *N*-acetyl and *N*-(2'-hydroxynaphthylidene) derivatives and into methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranoside. The latter compound was found identical to a similar product synthesized from the known methyl 2-acetamido-2-deoxy-α-D-galactopyranoside, prepared from D-galactosamine, obtained from a natural source.

Dimethyl derivatives of D-galactosamine are of special importance in the elucidation of the structure of derivatives of galactosamine isolated from natural sources, such as chondrosine,[3] and uridine diphosphate–acetylgalactosamine sulfate.[4] The synthesis of 4,6-di-*O*-methyl-D-galactosamine hydrochloride has been reported previously.[5,6] In this paper, the synthesis of a second dimethylgalactosamine, 3,4-di-*O*-methyl-D-galactosamine hydrochloride (XV), is described. Although the synthesis of 3,4-di-*O*-methyl-D-glucosamine hydrochloride successfully has been reported,[7] starting from D-glucosamine and using a 6-*O*-trityl derivative as an intermediate, an analogous synthesis in the galactosamine series was at first not considered, because of the unavailability of large amounts of D-galactosamine as starting material. Instead, the synthesis was started with a material obtained from lactose, which had been used for the preparation of 4-*O*-methyl-D-galactosamine hydrochloride, namely, 1,6:2,3-dianhydro-β-D-talose (II).[8]

The synthesis of the key compound, 2-acetamido-1,6-anhydro-2-deoxy-3,4-di-*O*-methyl-β-D-galactopyranose (VII), was investigated, using various intermediates and methylation procedures. In a first pathway, catalytic deacetylation of 2-acetamido-3,4-di-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-galactopyranose[9] (VI) with barium methoxide gave 2-acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose (V). The same compound was obtained in acetylating 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose (I), with acetic anhydride in methanol. Consideration of the spatial structure of 2-acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose shows that the hydroxyl in position 3 is in axial position and is considerably shielded by the 1,6-anhydro ring. Consequently, its reactivity is expected to be much lower than the reactivity of the vicinal equatorial group in position 4. This was indeed the case and methylation of the hydroxyl in position 3 was very slow.[10] From the treatment of V with methyl iodide and silver oxide, only the starting material could be recovered in crystalline form. Methylation in dimethylformamide solution[11] was not successful, no crystalline product being isolated. Methylation with methyl sulfate and sodium hydroxide afforded the best way to obtain, in a 35% yield, the dimethyl derivative VII, whereas the 4-*O*-methyl derivative VIII was isolated in a 40% yield. Direct methylation of the 3,4-di-*O*-acetyl derivative VI with methyl sulfate and sodium hydroxide did not proceed successfully and only 11% of the dimethyl derivative was obtained.

In the second pathway, methylation of 2-acetamido-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactose (VIII) and its 3-*O*-acetyl derivative IX[8] was studied. The starting material VIII was obtained either by catalytic deacetylation of IX or by acetylation of 2-amino-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactopyranose (III)[8] with acetic anhydride in methanol. Methylation of VIII with methyl iodide and silver oxide afforded the crystalline dimethyl derivative in a low yield of 15%, whereas reaction with methyl iodide after treatment with potassium in absolute ether or liquid ammonia did not lead to crystalline compounds. Methylation with methyl sulfate and sodium hydroxide was again the best method and dimethyl derivative VII and starting material VIII were isolated in yields of 35 and 45%, respectively.

The lack of reactivity of the hydroxyl in position 3 was also reflected in its very small contribution to the polarity of the molecule. Whereas in adsorption chromatography on silicic acid mono- and dimethyl ethers are generally eluted into two very distinct peaks, VIII and VII were eluted in a continuous peak, in which the middle fractions always contained a mixture of both.

Hydrolysis of VII with 2 *N* hydrochloric acid for 24 hours was carried out as described for the 4-*O*-methyl compounds.[3] From the resulting mixture, the crystalline 2-amino-1,6-anhydro-2-deoxy-3,4-di-*O*-methyl-β-D-galactose hydrochloride (XIV) was

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(2) Presented before the Division of Carbohydrate Chemistry at the 129th Meeting of the American Chemical Society, Dallas, Texas, April, 1956.

(3) J. Hebting, *Biochem. Z.*, **63**, 353 (1914).

(4) J. L. Strominger, *Biochim. Biophys. Acta*, **17**, 283 (1955).

(5) P. J. Stoffyn and R. W. Jeanloz, THIS JOURNAL, **76**, 563 (1954).

(6) For an addendum, see Experimental part.

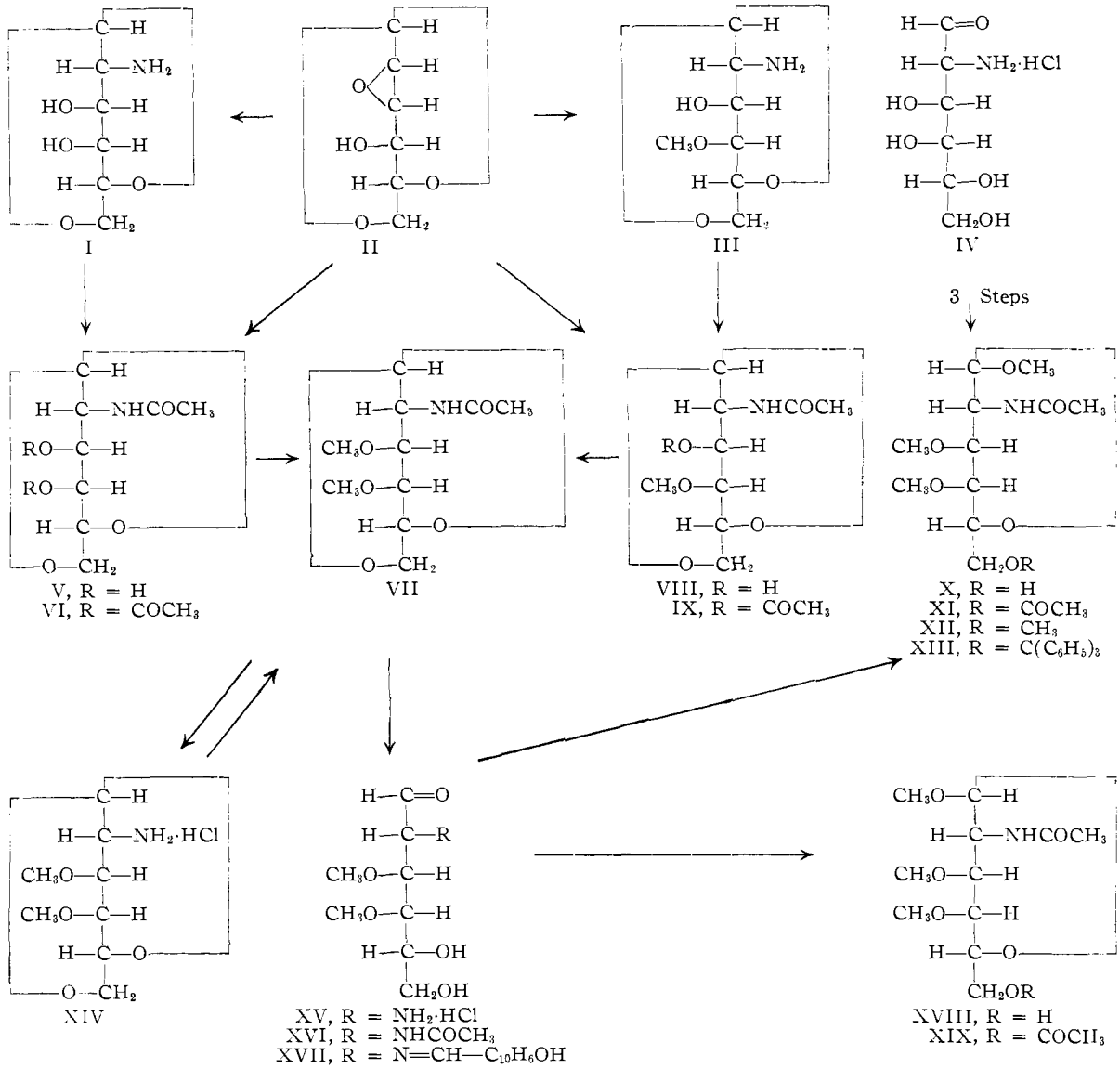
(7) R. W. Jeanloz, THIS JOURNAL, **74**, 4597 (1952).

(8) R. W. Jeanloz and P. J. Stoffyn, *ibid.*, **76**, 5682 (1954).

(9) S. P. James, F. Smith, M. Stacey and L. F. Wiggins, *J. Chem. Soc.*, 625 (1946).

(10) A similar observation has been made in the methylation of 1,6-anhydro-β-D-galactopyranose, which afforded mostly the 2,4-di-*O*-methyl derivative (private communication of Dr. J. Fellig, Massachusetts Institute of Technology).

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



isolated in an 8% yield. The remaining mother liquors were *N*-acetylated and after chromatography 22% of starting material was recovered, whereas the 3,4-di-*O*-methyl-D-galactosamine (XV) was isolated as its crystalline *N*-acetyl derivative XVI in a 23% yield. When XV was isolated as the crystalline *N*-(2′-hydroxynaphthylidenamino) derivative XVII, yields up to 41% were obtained. When the hydrolysis was followed by two methanolyses, a yield of up to 59% of crystalline α- and β-methyl glycosides X and XVIII was obtained, whereas only 9% of starting material was recovered.

The relatively low yields of free amino sugar hydrochloride XV obtained and the large amount of starting material recovered, compared to the nearly quantitative yield obtained in hydrolysis of methyl *N*-acetylglycoside derivatives, are easily explained on the basis of the relative speed of scission of the *N*-acetyl groups, and of the internal (1,6-anhydro) and external (methyl) glycosidic bonds. In the cases of 2-acetamido-1,6-anhydro compounds and methyl 2-acetamidoglycosides, hydrolysis of the acetyl radical linked to the amino group proceeds concurrently with the hydrolysis of the glycosidic linkages. Studies in the glucose, galactose and mannose series have shown, however, the 1,6-anhydro internal glycosidic bond to be more resistant to hydrolysis than the glycosidically linked methoxyl. Consequently, the amount of free amino groups produced during hydrolysis of the internal glycosidic bond is much greater than that produced during the hydrolysis of the methoxyl glycosidic linkage. It has also been demonstrated a number of times that the presence of a vicinal free amino group inhibits completely the hydrolysis of a methoxyl bond by dilute acid and it is probable that a similar inhibition takes place in 1,6-internal glycosidic bond. The formation of free amino groups will thus control the degree of opening of the ring. The influence of the substitution at position 3 or 4 on the splitting of the acetyl group and consequently on the formation of substituted galactosamine with free aldehyde groups could not be

clearly established, as the results depended greatly on the isolation of the final products. When *N*-acetylated derivatives were prepared, a maximum yield of 23% of 3,4-di-*O*-methyl-D-galactosamine could be isolated and 30% of starting material recovered in the 3,4-dimethyl series, whereas a yield of 53% of 4-*O*-methyl-D-galactosamine (as crystalline hydrochloride) was obtained and 17% of starting material recovered in the 4-monomethyl series (ref. 8 and Experimental part). Concurrent inhibition of the opening of the anhydro ring by formation of the free amino group is quite large also in the non-methylated series. In a repetition of the work of James, *et al.*,[9] by one of us (P.J.S.) at the University of Brussels, it was observed during the hydrolysis of 2-acetamido-3,4-di-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-galactopyranose (VI) with 2 *N* hydrochloric acid that the first product to crystallize from the mixture was 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose hydrochloride, characterized by its transformation into V.[12]

The pure sirupy 3,4-di-*O*-methyl-D-galactosamine hydrochloride (2-amino-2-deoxy-3,4-di-*O*-methyl-D-galactose hydrochloride) (XV) was obtained by hydrolysis of the *N*-acetyl derivative XVI.

In order to correlate the dimethylgalactosamine XV prepared in such a way with a compound prepared from a natural source, the crude product of the hydrolysis of 2-acetamido-1,6-anhydro-2-deoxy-3,4-di-*O*-methyl-β-D-galactopyranose (VII) was fully acetylated and then glycosidified. After isolating some unreacted starting material, two crystalline compounds were obtained, to which the structures of α- and β-glycosides X and XVIII were attributed on the basis of their rotation. The residual mother liquors were subjected to a second glycosidification, and the total yields in crystalline material were 9% for the starting material, 53% for the α-glycoside X and 6% for the β-glycoside XVIII. These two compounds gave crystalline monoacetates XI and XIX.

The α-glycoside X and its 6-*O*-acetyl derivative XI did not show any depression in their melting points in admixture with identical products obtained by methylation of methyl 2-acetamido-2-deoxy-6-*O*-triphenylmethyl-α-D-galactopyranoside. This compound had been synthesized from methyl 2-acetamido-2-deoxy-α-D-galactopyranoside prepared from D-galactosamine (IV) which was isolated from a natural source.[13] In addition, the trityl derivative XIII was prepared from the α-glycoside X obtained *via* the route of the 1,6-anhydro derivatives and found to be identical with the same derivative synthesized from natural D-galactosamine. Such identity is not only evidence that galactosamine prepared from lactose and natural galactosamine are identical, but it also proves that X is really the α-anomer and possesses the pyranose configuration.

James, *et al.*, have proved in their work[9] the precise configuration of chondrosamine to be that of 2-amino-2-deoxy-D-galactose. The establishment of identity of the synthetic and the natural product was achieved by comparison of the X-ray powder diagrams and observation of the mutarotations. The β-pentaacetate derivative of the synthetic product was obtained in a yield not reported and found identical with the one from the natural product.

The present work presents further evidence for the identity of the two products, as three derivatives possessing definite melting point and rotation were compared and their mixed m.p.'s determined.

Preparation of the known 3,4,6-tri-*O*-methyl ether XII from X was additional proof of the identity of synthetic and natural product and of the α-anomerism and pyranose configuration of X.

Experimental[14]

2-Acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose (V) from I.—To a solution of 1.3 g. of 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose[9] (I) in 40 ml. of methanol cooled at 0° was added 1.75 ml. of acetic anhydride. After 10 minutes, the solution was allowed to stand at room temperature for 3 hours, then evaporated under a stream of nitrogen and the residue dried in a desiccator overnight. Crystallization from a mixture of methanol and ether gave 1.48 g. (91%) of prisms, m.p. 207–208°, $[\alpha]^{25}D$ −5 ± 1° (in methanol, *c* 1.02). *Anal.* Calcd. for $C_8H_{13}O_5N$: C, 47.29; H, 6.45. Found: C, 47.20; H, 6.49.

2-Acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose (V) from VI.—To a solution of 2.90 g. of 2-acetamido-3,4-di-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-galactopyranose[9] (VI) in 100 ml. of methanol was added 10 ml. of a 1.6 *N* barium methoxide solution. After refluxing for 10 minutes, the solution was cooled, diluted with a small amount of water and neutralized with a stream of CO_2. After filtration through Celite, it was evaporated *in vacuo*. The filtered material and the dry residue were extracted exhaustively in a Soxhlet apparatus with acetone. The combined extracts gave 1.92 g. of crystalline material, which after recrystallization from a mixture of methanol and ether afforded 1.89 g. (92%), melting at 204–207°. In admixture with the material previously described, the m.p. was not depressed.

2-Acetamido-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactopyranose (VIII) from III.—A solution of 95 mg. of 2-amino-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactopyranose[8] (III) in methanol was treated with acetic anhydride as described above for I. Crystallization from a mixture of acetone and ether gave 103 mg. (87%) of prismatic needles, m.p. 122–123°. When the melt was seeded with the material described below, crystallization in stout prisms occurred and a m.p. of 152–153° was observed, $[\alpha]^{24}D$ −53 ± 2° (in chloroform, *c* 0.98). *Anal.* Calcd. for $C_9H_{15}O_5N$: C, 49.76; H, 6.96. Found: C, 49.78; H, 6.84.

2-Acetamido-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactopyranose (VIII) from IX.—To a solution of 1.53 g. of 2-acetamido-3-*O*-acetyl-1,6-anhydro-4-*O*-methyl-β-D-galactopyranose[8] (IX) in 50 ml. of methanol was added 5 ml. of a 1.6 *N* barium methoxide solution. After refluxing for 10 minutes, the cooled solution was diluted with water, neutralized with a stream of CO_2 and filtered through Celite and charcoal. The filter was washed with water, the combined filtrates evaporated *in vacuo*, and the residue was extracted with boiling acetone. After evaporation, 1.30 g. of crude product was obtained; crystallization from a mixture of acetone and ether gave 1.16 g. (90%) of VIII, m.p. 120–122°. In admixture with the material described above, the m.p. was not depressed.

Methylation of V with Methyl Sulfate and Sodium Hydroxide.—To a solution of 2.21 g. of V in a minimum amount of water was added, with vigorous stirring and at room temperature, 33.3 ml. of methyl sulfate and 102.4 ml. of a 30% sodium hydroxide solution, in 20 portions each

(12) Using concentrated hydrochloric acid for 30 hours (2.2 *N* in the text of the Experimental part!) James, *et al.*,[9] were able to split the 1,6-anhydro ring in presence of a free amino group and obtain a yield of D-galactosamine hydrochloride greater than 50%. So great a concentration of acid was avoided in the treatment of methylated sugars in order to avoid demethylation.

(13) R. W. Jeanloz and R. G. Naves, unpublished.

(14) R. W. Jeanloz, THIS JOURNAL, **76**, 555 (1954); R. W. Jeanloz and D. A. Jeanloz, *ibid.*, **79**, 2579 (1957).

at 15-minute intervals. The *p*H was checked frequently and always kept on the alkaline side. After the last addition, the mixture was stirred for a half-hour at room temperature, and then neutralized with CO_2. The precipitate was filtered off, and the filtrate was extracted several times with chloroform. The combined chloroform extracts were dried over sodium sulfate and evaporated *in vacuo*, giving 1.6 g. of crystalline residue. The water layer was evaporated *in vacuo* at 40°, and the residue dried in a desiccator. Combined with the filtered material, it was extracted with chloroform, in a Soxhlet apparatus. After drying over sodium sulfate, the chloroform was evaporated *in vacuo*, and the sirupy residue combined with the first residue gave 2.5 g. of crude product, which was chromatographed on silicic acid. Mixtures of ethyl acetate and acetone 4:1 eluted 940 mg. of crystalline fractions of **2-acetamido-1,6-anhydro-2-deoxy-3,4-di-*O*-methyl-β-D-galactopyranose (VII)**. After recrystallization from a mixture of acetone, ether and pentane, 880 mg. (35%) of stout prisms was obtained, m.p. 109–111°, $[\alpha]^{27}D$ −87 ± 2° (in chloroform, *c* 1.14). *Anal.* Calcd. for $C_{10}H_{17}O_5N$: C, 51.94; H, 7.41; N, 6.06; OCH_3, 26.84. Found: C, 52.04, 51.83; H. 7.56, 7.50; N, 6.18; OCH_3, 26.82.

The same mixture of ethyl acetate and acetone 4:1 eluted 300 mg., which could not be crystallized, and then 1.49 g. of partially crystalline fractions, which after recrystallization from a mixture of acetone and ether gave 935 mg. (40%) of VIII, melting at 119–121°. In admixture with the material described above, the m.p. was not depressed.

Methylation of VI with Methyl Sulfate and Sodium Hydroxide.—The methylation was carried out on 350 mg. of VI at 55° and 2.4 ml. of methyl sulfate and 7.1 ml. of a 30% solution of sodium hydroxide were introduced in 10 portions for two hours. After purification as described above, 32 mg. (11%) of VII was obtained, m.p. 108–110°, showing no depression in admixture with the compound described above; $[\alpha]^{26}D$ −82 ± 4° (in chloroform, *c* 0.60).

Methylation of VIII with Methyl Sulfate and Sodium Hydroxide.—A solution of 200 mg. of VIII in the minimum amount of water was methylated at room temperature with 1.3 ml. of methyl sulfate and 4.0 ml. of a 30% solution of sodium hydroxide, as described for V. After chromatography, 72 mg. (34%) of VII was obtained, melting at 108–110°, and showing no depression in admixture with the compound obtained above. In addition, 64 mg. (32%) of starting material, m.p. 120–121°, was obtained. In other experiments on a larger scale, the yield of VII varied from 25 to 37% and the yield in starting material was such as to give a total yield of crystalline products of 65 to 70%. The recovered starting material added to the non-crystallizable mother liquors gave again, after methylation, the same yield in VII.

Methylation of VIII with Methyl Iodide and Silver Oxide.—Five hundred mg. of VIII was methylated under reflux with 20 ml. of methyl iodide and four times 500 mg. of silver oxide, added over a 36-hour period. After 48 hours, the silver salts were filtered off and washed with acetone. The solution was evaporated *in vacuo*, and the residue chromatographed on silicic acid to give VII in a 15% yield, m.p. 103–105°, showing no depression with the material described above. No crystalline starting material could be recovered.

Methylation of IX with Methyl Sulfate and Sodium Hydroxide.—Two hundred mg. of IX was methylated at 55° with 1.4 ml. of methyl sulfate and 4.1 ml. of a 30% solution of sodium hydroxide as described for VI; 26 mg. (12%) of VII was obtained, m.p. 108–110°, showing no depression with the material described above.

3,4-Di-*O*-methyl-D-galactosamine Hydrochloride (2-Amino-2-deoxy-3,4-di-*O*-methyl-D-galactose Hydrochloride (XV) and 2-Acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranose (XVI).—A solution of 0.70 g. of VII in 50 ml. of 2 *N* hydrochloric acid in a sealed tube was heated for 24 hours in a boiling water-bath. After filtration through a layer of Darco G-60, the solution was evaporated *in vacuo* at 50° and the last traces of water and hydrochloric acid were removed by co-distillation with absolute ethanol. After a few weeks, the colorless sirup crystallized spontaneously, and was filtered after dilution with a mixture of methanol and acetone. Recrystallization from a mixture of methanol and acetone gave 55 mg. (8%) of **2-amino-1,6-anhydro-2-deoxy-3,4-di-*O*-methyl-β-D-galactose hydrochloride (XIV)**, as needles, subliming above 230° and decomposing above 250°, $[\alpha]^{27}D$ −26 ± 2° (in water, *c* 0.85). *Anal.* Calcd. for $C_8H_{16}O_4NCl$: C, 42.56; H, 7.15; Cl, 15.71; OCH_3, 27.50. Found: C, 42.48; H, 7.07; Cl, 15.68; OCH_3, 27.55. To a solution of 18 mg. of XIV in 1 ml. of methanol was added 14 mg. of silver acetate and 0.2 ml. of acetic anhydride. After standing a few hours at room temperature in the dark, the solution was filtered and one drop of 0.01 *N* hydrochloric acid was added to the filtrate. After one hour, the solution was filtered and evaporated *in vacuo* to dryness. The residue was dissolved in acetone, and filtered through a double layer of Celite and Darco G-60. Evaporation and crystallization of the residue in a mixture of acetone, ether and pentane gave 18 mg. (95%) of VII, m.p. 110–111°, $[\alpha]^{24}D$ −88 ± 2° (in chloroform, *c* 0.97); the m.p. showed no depression in admixture with the material described above.

The mother liquors of XIV (dry weight 0.72 g.) were subjected to a new hydrolysis by refluxing with 20 ml. of 3 *N* hydrochloric acid for 24 hours. After evaporation *in vacuo*, dissolution of the residue in water, filtration through a double layer of Celite and Darco G-60, and evaporation to dryness, 0.72 g. of a colorless sirup was obtained. Elementary analysis and rotation showed that it was composed approximately of 60% of **XV** and 40% of XIV, $[\alpha]^{27}D$ +62 ± 2° (in water, *c* 3.93). *Anal.* Found: C, 41.14; H, 8.18; O, 31.89. In order to separate those two components, 0.60 g. of the above sirup was dissolved in 10 ml. of methanol and 0.46 g. of silver acetate and 0.5 ml. of acetic anhydride were added. After standing for 2 days at room temperature in the dark, the solution was filtered, one drop of 0.1 *N* hydrochloric acid was added, and after a few hours the solution was filtered through a double layer of Celite and Darco G-60. After concentration *in vacuo*, 0.59 g. of a colorless sirup was obtained. Dissolved in chloroform, it was chromatographed on silicic acid. Elution with various mixtures of ethyl acetate and acetone gave 152 mg. (26%) of crude VII; recrystallization from a mixture of acetone, ether and pentane gave 134 mg. (22%), m.p. 110–112°, $[\alpha]^{25}D$ −86 ± 1° (in chloroform, *c* 1.18); the m.p. was not depressed in admixture with the compound described above.

Elution with mixtures of acetone and methanol gave 235 mg. (38%) of crude **2-acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranose (XVI)**; recrystallization from a mixture of methanol, ether and pentane gave 150 mg. (23%) of prisms, m.p. 199–200° (with slight decomposition). The product showed mutarotation from $[\alpha]^{27}D$ +114° (after 4 minutes) to $[\alpha]^{26}D$ +92 ± 2° (after 24 hours, in water, *c* 1.07). *Anal.* Calcd. for $C_{10}H_{19}O_6N$: C, 48.18; H, 7.68. Found: C, 48.07; H, 7.64.

The yields in crystalline materials showed that 30% of the starting material VII was recovered after *N*-acetylation, whereas 23% had its 1,6-anhydro ring opened and was transformed into the crystalline derivative XVI.

A solution of 110 mg. of XVI in 2 ml. of 2 *N* hydrochloric acid was heated on the steam-bath for 2 hours. After distillation *in vacuo* and co-distillation with absolute ethanol, the sirupy residue was left overnight in a desiccator over soda lime. It was dissolved in methanol, filtered through a double layer of Celite and Darco G-60 and evaporated to give 127 mg. (100%) of a colorless sirup, **3,4-di-*O*-methyl-D-galactosamine hydrochloride (XV)**, $[\alpha]^{24}D$ +108 ± 2° (in water, *c* 1.77). *Anal.* Calcd. for $C_9H_{18}O_5NCl$: C, 39.43; H, 7.44; Cl, 14.55; OCH_3, 25.47. Found: C, 39.27; H, 7.59; Cl, 14.51; OCH_3, 25.67.

2-Deoxy-2-(2′-hydroxynaphthylidenamino)-3,4-di-*O*-methyl-β-D-galactopyranose (XVII).—Hydrolysis of 200 mg. of VII gave 200 mg. of crude sirup. Dissolved in 2 ml. of water, it was treated as previously described[7] with 290 mg. of sodium acetate trihydrate and 440 mg. of 2-hydroxynaphthaldehyde dissolved in 20 ml. of methanol. On purification by chromatography, mixtures of ethyl acetate and acetone 4:1, 2:1, 1:1 and pure acetone eluted crystalline fractions. Crystallization from methanol and ether gave 130 mg. (41%) of yellow crystals, m.p. 203–204° (with slight decomposition). The product showed mutarotation from $[\alpha]^{26}_{5461}$ +107° (after 8 minutes) to $[\alpha]^{27}_{5461}$ +332 ± 5° (after 5 days, in methanol, *c* 0.15). *Anal.* Calcd. for $C_{19}H_{23}O_6N$: C, 63.15; H, 6.41. Found: 63.08; H, 6.52.

Methyl 2-Acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranoside (X) and Methyl 2-Acetamido-2-deoxy-3,4-di-*O*-methyl-β-D-galactopyranoside (XVIII) from VII.—The crude product of hydrolysis (534 mg.) of 475 mg. of VII was shaken for 60 hours with 15 ml. of acetic anhydride and

15 ml. of dry pyridine. After evaporation *in vacuo*, the last traces of reagents were removed by co-distillation with dry toluene. The amorphous residue was refluxed for two hours with 40 ml. of 2% hydrochloric acid in methanol. After cooling, the chloride ion was removed with silver carbonate, and the last traces of silver with hydrogen sulfide. After filtration through a double layer of Darco G-60 and Celite, the solvent was evaporated *in vacuo* and the crude crystalline residue, dissolved in chloroform, was chromatographed on silicic acid. Elution with ethyl acetate gave after recrystallization 37 mg. of starting material VII, m.p. 108–110°. Elution with a mixture of ethyl acetate and acetone 2:1 gave crystalline fractions, which after recrystallization from a mixture of methanol and ether afforded 185 mg. of **methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-α-D-galactopyranoside (X)**, as prismatic needles, m.p. 219–220°, $[\alpha]^{25}D$ +146 ± 1° (in methanol, *c* 1.50). *Anal.* Calcd. for $C_{11}H_{21}O_6N$: C, 50.18; H, 8.04; OCH_3, 35.36. Found: C, 50.35; H, 8.17; OCH_3, 35.18. In admixture with material obtained by hydrolysis of methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside, synthesized from natural D-galactosamine,[13] the m.p. was not depressed. Acetylation of 51 mg. of X with acetic anhydride and pyridine in the usual manner gave, after recrystallization from a mixture of acetone and ether, 51 mg. (90%) of the **6-*O*-acetyl derivative XI**, as fine needles, m.p. 203–204°, $[\alpha]^{27}D$ +123 ± 2° (in chloroform, *c* 0.70). *Anal.* Calcd. for $C_{13}H_{23}O_7N$: C, 51.14; H, 7.59. Found: C, 51.10; H, 7.71. In admixture with material prepared from natural D-galactosamine,[13] the m.p. was not depressed.

Elution with a mixture of ethyl acetate and acetone 1:1 gave a crystalline fraction. After recrystallization from a mixture of methanol and ether, 30 mg. (6%) of **methyl 2-acetamido-2-deoxy-3,4-di-*O*-methyl-β-D-galactopyranoside (XVIII)** was obtained as needles, m.p. 247–249°, $[\alpha]^{26}D$ −18 ± 3° (in methanol, *c* 0.76). *Anal.* Calcd. for $C_{11}H_{21}O_6N$: C, 50.18; H, 8.04. Found: C, 50.05; H, 8.09. Acetylation of 16 mg. of XVIII with acetic anhydride and pyridine in the usual manner gave, after recrystallization from a mixture of methanol and ether, 16 mg. (85%) of the **6-*O*-acetyl derivative (XIX)**, as prismatic needles, m.p. 247–248°, $[\alpha]^{26}D$ 0 ± 4° (in chloroform, *c* 0.63). In admixture with the starting material, the m.p. was depressed at 215–235°. *Anal.* Calcd. for $C_{13}H_{23}O_7N$: C, 51.14; H, 7.59. Found: C, 51.21; H, 7.73.

The residual mother liquors and non-crystalline fractions were refluxed with 25 ml. of 2% hydrochloric acid in methanol for 2 hours and the solution was treated as described above, but using lead carbonate instead of silver carbonate to remove the chloride ion. After chromatography, 40 mg. of crude starting material VII was recovered, from which only 6 mg. of crystalline product was obtained, giving a total yield of 43 mg. (9%). An additional yield of 84 mg. of crude crystalline α-glycoside X was isolated from which 50 mg. of pure compound was crystallized, to give a total yield of 285 mg. (53%).

In another experiment, in which a smaller amount of starting material was subjected to only one hydrolysis and one methanolysis, the yield in crystalline starting material VII recovered was 20%, whereas 24% of pure crystalline α-glycoside X and 3% of pure crystalline β-glycoside XVIII were isolated.

Fifty mg. of X was methylated under reflux for 48 hours with 10 ml. of methyl iodide and two additions of 100 mg. of silver oxide. After filtration of the silver salts and evaporation, the crystalline residue was crystallized from a mixture of acetone and ether to give 47 mg. (90%) of methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-galactopyranoside (XII), m.p. 189–192°, after a second recrystallization. In admixture with authentic material,[15] the m.p. was not depressed; $[\alpha]^{27}D$ +143 ± 2° (in methanol, *c* 0.79).

Methyl 2-Acetamido-2-deoxy-3,4-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (XIII).—A solution of 36 mg. of X and 56 mg. (1.5 moles) of triphenylchloromethane in 0.5 ml. of anhydrous pyridine was heated at 55° for three days. After dilution with 10 ml. of ice-cold water, the precipitate was filtered off, dried in a desiccator and dissolved in a mixture of benzene and hexane 1:1. Chromatography on alumina afforded a large amount of triphenylcarbinol, eluted with pure benzene. A mixture of ether and methanol 9:1 eluted 40 mg. of crystalline XIII. Recrystallization from a mixture of acetone, ether and pentane gave 30 mg. (43%) of prismatic needles, m.p. 222–224°, $[\alpha]^{27}D$ +66 ± 4° (in chloroform, *c* 0.52). *Anal.* Calcd. for $C_{30}H_{35}O_6N$: C, 71.26; H, 6.98. Found: C, 71.29; H, 7.09. In admixture with material obtained by methylation of methyl 2-acetamido-2-deoxy-6-*O*-triphenylmethyl-α-D-galactopyranoside, synthesized from natural D-galactosamine (IV),[13] the m.p. was not depressed.

Hydrolysis of 2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-4-*O*-methyl-α-D-galactopyranose (IX).—In a preceding paper,[8] the hydrolysis of 300 mg. of IX with 2.5 *N* hydrochloric acid has been reported and 140 mg. of 4-*O*-methyl-α-D-galactosamine hydrochloride was isolated. The residual mother liquors were dissolved in 5 ml. of methanol and 165 mg. of silver acetate and 0.2 ml. of acetic anhydride were added. After standing at room temperature for 48 hours, in the dark, the solution was filtered and one drop of 0.1 *N* hydrochloric acid was added. After a few hours, the solution was filtered through Darco G-60 and Celite, evaporated *in vacuo* and the residue, dissolved in chloroform, was chromatographed on silicic acid. Mixtures of ethyl acetate and acetone eluted 50 mg. of crystalline fractions, 2-acetamido-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactopyranose (VIII). Recrystallization from a mixture of acetone and ether gave 43 mg. (17%) of stout prisms, m.p. 153–154°, $[\alpha]^{25}D$ −51 ± 2° (in chloroform, *c* 0.95). In admixture with the material described above (m.p. 122–123°) the m.p. was not depressed.

Elution with a mixture of acetone and methanol 49:1 gave 24 mg. of crystalline fractions, behaving like authentic 2-acetamido-2-deoxy-4-*O*-methyl-D-galactose.[16] However, recrystallization from a mixture of methanol and acetone afforded only 4 mg. of impure crystals. The remaining mother liquors were not further investigated.

Methyl 2-Acetamido-2-deoxy-4,6-di-*O*-methyl-3-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside.—This compound had been previously obtained only in sirupy form.[5] After standing one year, it crystallized spontaneously. It was recrystallized from a mixture of ether and pentane to give prisms melting at 106–108°, $[\alpha]^{21}D$ +94 ± 2° (in chloroform, *c* 1.17). *Anal.* Calcd. for $C_{18}H_{27}O_8NS$: C, 51.78; H, 6.52. Found: C, 51.82; H, 6.53.

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