gen and carbon atoms of the pyranose ring, the CH_2OH group is somewhat less axial than in the pure 3 B conformation. This advantage is most clearly illustrated by the drawing of the skew form below that of conformation B 1 in Fig. 1.

In summary, it appears likely that the conformation of the non-reducing glucose unit is not one of the well known boat or chair forms. The skew conformation which is an intermediate in going from B 1 to 3 B meets all of the experimental and theoretical requirements discussed in this paper.

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[CONTRIBUTION FROM THE ROBERT W. LOVETT MEMORIAL UNIT, MEDICAL SERVICES OF THE MASSACHUSETTS GENERAL HOSPITAL, AND FROM THE DEPARTMENT OF MEDICINE, HARVARD MEDICAL SCHOOL]

The Synthesis of 2-Amino-1,6-anhydro-2-deoxy-β-D-gulopyranose Hydrochloride[1]

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2-Amino-1,6-anhydro-2-deoxy-β-D-gulopyranose hydrochloride was synthesized from 2-acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose, and was found identical to the product isolated from streptothricin and streptolin B. It was further transformed into methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-gulopyranoside. An identical product was obtained from both synthetic and natural D-gulosamine hydrochloride.

In the hydrolyzates of streptothricin and streptolin B, van Tamelen and associates[3] isolated a parent substance of D-gulosamine (XV).[4] Paper chromatographic evidence showed that this substance was produced by the action of hydrochloric acid on XV. On the basis of its elementary analysis and its degradation by the periodate ion into *cis*-1,3-dioxolane-2,4-carboxaldehyde, the formula of 2-amino-1,6-anhydro-2-deoxy-β-D-gulopyranose hydrochloride (XIV) was proposed for this substance.[3]

The synthesis of a compound possessing structure XIV was started as an alternate route to the preparation of D-gulosamine,[5] before the already described synthesis had been successfully completed. This second synthesis has the advantage of using a more readily available starting material, D-galactose or D-lactose. Another reason for undertaking it, was to study the limits of the type of Walden inversion introduced in the carbohydrate field by Baker, *et al.*,[7] and used for the synthesis of D-allosamine[8] and D-gulosamine.[5] This inversion is based on the solvolysis of a sulfonyl group *trans*-vicinal to an acetamido group.

The 1,6-anhydro derivatives of 2-acetamido-2-deoxy-D-galactose have been already prepared by James, *et al.*[9] A modification of their method allowed the preparation, from either D-galactose or D-lactose, of large amounts of 1,6:2,3-dianhydro-β-D-talopyranose, subsequently transformed into the recently described[10] 2-acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose (I). Consideration of the spatial structure of the molecule showed the hydroxyls at positions 3 and 4 to have, respectively, axial and equatorial conformations. Direct introduction of the methylsulfonyl group with one mole of reagent gave the 4-*O*-methylsulfonyl derivative VI, but in low yield, whereas no isomer at position 3 could be isolated. When, however, compound I was treated with one mole of benzoyl chloride in pyridine solution, the position 3 possessing an axial conformation reacted surprisingly faster than the equatorial position, and the 3-*O*-benzoyl II and 4-*O*-benzoyl III derivatives were isolated in the respective yields of 48 and 38%, besides 4% of the 3,4-dibenzoate IV. Use of benzoic anhydride as the reagent[11] did not change significantly the respective amounts of the products obtained. In order to identify the location of the benzoyl groups introduced, a monomethylsulfonyl derivative V was prepared from II. It was subsequently hydrolyzed into 2-acetamido-1,6-anhydro-2-deoxy-4-*O*-methylsulfonyl-β-D-galactopyranose (VI), identical with the product described above. Methylation of VI gave the 3-*O*-methyl ether VII different from 2-acetamido-1,6-anhydro-2-deoxy-4-*O*-methyl-3-*O*-methylsulfonyl-β-D-galactopyranose (X), which had been synthesized from the previously prepared 4-methyl ether XI.[10] The same sequence of reactions was carried out with the 4-*O*-benzoyl derivative III through the intermediate steps VIII and IX to give finally a 4-*O*-methyl ether X identical to the one prepared from XI.

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(2) Special Investigator of the Arthritis and Rheumatism Foundation.

(3) E. E. van Tamelen, J. R. Dyer, H. E. Carter, J. V. Pierce and E. E. Daniels, THIS JOURNAL, **78**, 4817 (1956).

(4) In the van Tamelen, *et al.*, communication[3] and in our publication,[8] the isolation of D-gulosamine has been referred to as the first isolation from natural sources of a sugar with the D-gulose configuration. Dr. T. Reichstein has kindly informed us of the previous isolation of 6-deoxy-D-gulose from α-antiarin.[6]

(5) Z. Tarasiejska and R. W. Jeanloz, THIS JOURNAL, **79**, 2660, 4215 (1957).

(6) K. Doebel, E. Schlittler and T. Reichstein, *Helv. Chim. Acta*, **31**, 688 (1948).

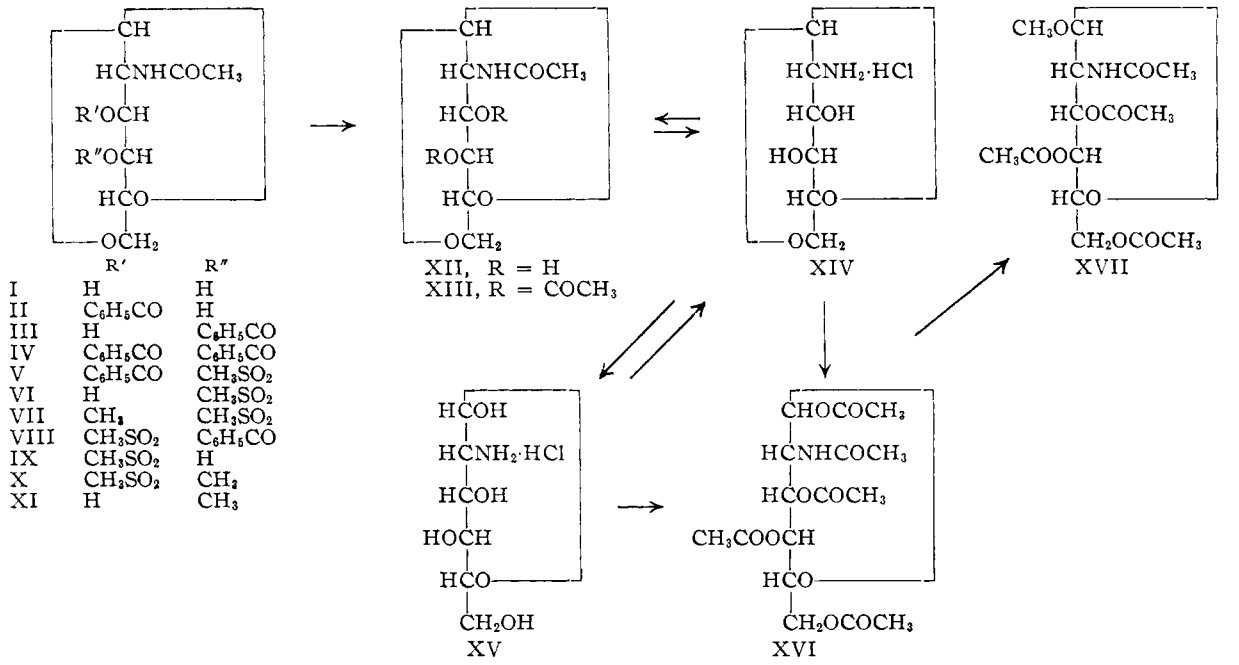
(7) B. R. Baker, R. E. Schaub, J. P. Joseph and J. H. Williams, THIS JOURNAL, **76**, 4044 (1954).

(8) R. W. Jeanloz, *ibid.*, **79**, 2591 (1957).

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

(10) R. W. Jeanloz, D. M. Schmid and P. J. Stoffyn, THIS JOURNAL, **79**, 2586 (1957).

(11) R. W. Jeanloz and D. A. Jeanloz, *ibid.*, **79**, 2579 (1957); **80**, 5692 (1958).



Solvolysis of 2-acetamido-1,6-anhydro-4-*O*-benzoyl-2-deoxy-3-*O*-methylsulfonyl-β-D-galactopyranose (VIII) in methyl Cellosolve in presence of sodium acetate,[7] gave 2-acetamido-1,6-anhydro-2-deoxy-β-D-gulopyranose (XII), isolated at its diacetate XIII in a 78% yield. In order to establish the identity of both natural and synthetic 1,6-anhydro derivatives of D-gulosamine, the hydrochloride XIV, isolated from the natural source, was *N*-acetylated to give a compound XII identical in every respect to the compound described above, thus conclusively demonstrating the correctness of the formula proposed by van Tamelen, *et al.*[3] Study by paper chromatography of the products of the action of aqueous hydrochloric acid on XII showed that dilute acid hydrolyzed the *N*-acetyl group with very little simultaneous hydrolysis of the 1,6-anhydro ring. Consequently, 2-amino-1,6-anhydro-2-deoxy-β-D-gulopyranose hydrochloride (XIV) was isolated in crystalline form directly from the hydrolyzate of XII. It showed similar properties to the ones exhibited by the natural product, but the analytical figures did not agree with the reported one mole of water of crystallization.[3] It had been previously reported that the *N*-acetyl group vicinal to a *cis*-hydroxyl group could be split off easily by the action of alkali.[12] Similar treatment of XII with barium hydroxide gave the sirupy free base of XIV, further transformed into the crystalline hydrochloride XIV. With both methods the yield of crystalline hydrochloride XIV was over 80%.

In the paper describing the synthesis of D-gulosamine,[5] it was stated that no 1,6-anhydro derivative XIV could be found, using paper chromatography, in the mother liquors of the D-gulosamine hydrochloride (XV) obtained by acid hydrolysis of methyl 2-acetamido-2-deoxy-α-D-gulopyranoside or after treatment of XV with 2 *N* hydrochloric acid at 100° for 7 hours. Since a paper chromatography study of 2-amino-1,6-anhydro-2-deoxy-β-D-gulopyranose (XIV) revealed this product to react very slowly with the silver reagent,[13] whereas its reaction with ninhydrin was immediate, the action of hydrochloric acid on XV was reinvestigated. It was possible to demonstrate that the action of 6 *N* hydrochloric acid on D-gulosamine hydrochloride (XV) at 100° for 20 hours definitely produces a large amount of the 1,6-anhydro derivative XIV, confirming the results previously published by van Tamelen, *et al.*[3] Since the relationship between D-gulosamine (XV) and its 1,6-anhydro derivative XIV had been established by paper chromatography only, it was of interest to correlate the synthetic and natural D-gulosamine hydrochloide XV and their 1,6-anhydro derivatives XIV, using a crystalline derivative with a definite melting point. Both natural and synthetic D-gulosamine hydrochlorides XV were acetylated (one was fully acetylated, the other *N*-acetylated), then glycosidified with methanol and hydrochloric acid, and finally acetylated to give an identical crystalline methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-gulopyranoside (XVII). Acetolysis in dilute solution of the synthetic 1,6-anhydro derivative XIV gave a sirupy pentaacetate derivative with a rotation almost identical to the one of the previously described pentaacetate of D-gulosamine.[5] When glycosidified and fully acetylated, a crystalline methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-gulopyranoside (XVII) was obtained, identical in every respect to the one described above. Since the identity of both natural and synthetic 1,6-anhydro derivatives has been established, the relationship between D-gulosamine and its 1,6-anhydro derivative, as well as the chemical structures proposed by van Tamelen, *et al.*,[3] for the natural products, are thus confirmed.

(12) B. R. Baker, J. P. Joseph and J. H. Williams, THIS JOURNAL, **77**, 1 (1955).

(13) W. E. Trevelyan, D. P. Procter and J. S. Harrison, *Nature*, **166**, 444 (1950).

Experimental[14]

2-Acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose (I) was prepared from D-galactose with the isolation of only 2 intermediates according to the methods of Fernez and Stoffyn[15] and James, *et al.*,[9] with a modification by Dr. S. Hakomori of this Laboratory. The over-all yield from D-galactose to 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactose[15] was about 55% without isolation of the intermediates α,β-D-galactose pentaacetates, 2,3,4,6-tetra-*o*-acetyl-α-D-galactopyranosyl bromide, phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside and 1,6-anhydro-β-D-galactopyranose.

The methanesulfonylation of 4.5 g. of 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose was carried out according to the method of James, *et al.*[9] To the resulting crude 1,6-anhydro-3,4-*O*-isopropylidene-2-*O*-methylsulfonyl-β-D-galactopyranose dissolved in 300 ml. of ethanol was added 150 ml. of 0.5 *N* sulfuric acid and the solution was refluxed for 1 hour. After diluting with 150 ml. of water, the ethanol was evaporated *in vacuo*, the sulfuric acid removed by passing through a column of Amberlite IR 400 and the filtrate was evaporated *in vacuo*. The crude crystalline residue of 1,6-anhydro-2-*O*-methylsulfonyl-β-D-galactopyranose was dissolved in 150 ml. of absolute methanol and 16 ml. of 1 *N* sodium methoxide were added. After standing four days at room temperature, the solution was diluted with 500 ml. of ice-water and passed through two columns of Dowex 50 and Amberlite IR 400. The filtrate was evaporated *in vacuo* and gave, after recrystallization from a mixture of acetone and ether, 2.9 g. (90%) of 2,3:1,6-dianhydro-β-D-talopyranose, m.p. 134–135°.

A solution of 1.86 g. of this compound in 100 ml. of concentrated aqueous ammonia was heated in a sealed tube at 100° for 24 hours. The solution was evaporated to dryness and the residue was dissolved in 50 ml. of methanol, cooled at 0° and 2 ml. of acetic anhydride was added. After standing overnight at room temperature, the solution was evaporated *in vacuo* and the residue recrystallized from a mixture of methanol and ether to give 1.57 g. (60%) of I, m.p. 206–208°. In order to separate some of the remaining I from the 3-acetamido-1,6-anhydro-3-deoxy-β-D-idopyranose also formed, it was necessary to acetylate the mother liquors and chromatograph on silicic acid.

2-Acetamido-1,6-anhydro-3,4-di-*O*-benzoyl-2-deoxy-β-D-galactopyranose (IV).—To a solution of 100 mg. of I in 1 ml. of anhydrous pyridine, cooled at 0°, was added 0.17 ml. (3 moles) of benzoyl chloride. After standing at 0° overnight, the solution was left at room temperature for a few hours, then the excess of benzoyl chloride was decomposed by ice, and the resulting mixture was extracted with chloroform. After numerous washings with 2 *N* sulfuric acid, saturated sodium bicarbonate and water, and drying over sodium sulfate, the solvent was evaporated *in vacuo*. Recrystallization of the crystalline residue from a mixture of acetone, ether and pentane gave, in a 90% yield, clusters of prismatic needles, m.p. 196–197°, $[\alpha]^{25}D$ −47 ± 2° (in chloroform, *c* 0.58). *Anal.* Calcd. for $C_{22}H_{21}O_7N$: C, 64.22; H, 5.15. Found: C, 64.28; H, 5.05.

2-Acetamido-1,6-anhydro-3-*O*-benzoyl-2-deoxy-β-D-galactopyranose (II) and 2-Acetamido-1,6-anhydro-4-*O*-benzoyl-2-deoxy-β-D-galactopyranose (III).—To a solution of 1.0 g. of I in 20 ml. of anhydrous pyridine, cooled at −5°, was added 0.62 ml. of benzoyl chloride. After standing three days at 0° and overnight at room temperature, the solution was treated as described above for the dibenzoate. The crystalline residue was purified by chromatography on silicic acid. Elution with mixtures of ether and ethyl acetate 19:1 gave 90 mg. of crystalline fractions. Recrystallization gave 83 mg. (4%) of the dibenzoate IV. Elution with mixtures of ether and ethyl acetate 9:1, 4:1 and 2:1 gave 675 mg. of crystalline fractions. Recrystallization from a mixture of ether and pentane afforded 575 mg. (38%) of **2-acetamido-1,6-anhydro-4-*O*-benzoyl-2-deoxy-β-D-galactopyranose (III)** as prismatic needles. The product melted with evolution of gas unsharply at 126–131°; after crystallizing on cooling, it melted again unsharply at 120–125°; $[\alpha]^{24}D$ −2 ± 1° (in chloroform, *c* 1.05). It gave a positive reaction for a methoxyl group and the analytical data corresponded to one-half molecule of methyl alcohol of crystallization. *Anal.* Calcd. for $C_{15}H_{17}O_6N \cdot \frac{1}{2}CH_3OH$): C, 56.87; H, 5.85; loss on drying, 4.89. Found: C, 56.81; H, 5.92; loss on drying, 5.46. Dried *in vacuo* in a fused state, it analyzed for $C_{15}H_{17}O_6N$. Calcd.: C, 58.63; H, 5.58. Found: C, 58.47; H, 5.44.

Elution with mixtures of ether and ether acetate 1:1 and pure ethyl acetate gave 760 mg. of crystalline fractions. Recrystallization from methanol or from a mixture of methanol, ether and pentane, afforded 730 mg. (48%) of **2-acetamido-1,6-anhydro-3-*O*-benzoyl-2-deoxy-β-D-galactopyranose (II)**, as rectangular prisms, m.p. 216–218°, $[\alpha]^{25}D$ −19 ± 1° (in chloroform, *c* 0.72). *Anal.* Calcd. for $C_{15}H_{17}O_6N$: C, 58.63; H, 5.58. Found: C, 58.55; H, 5.47.

The two first times II was prepared, it was isolated directly by crystallization of the resulting mixture of the benzoylation. However, after crystals of the monobenzoate III had been secured, all subsequent attempts at direct crystallization gave invariably a crystalline mixture of II and III.

When the benzoylation was carried out with benzoic anhydride, similar proportions of the 3-*O*-benzoyl II and 4-*O*-benzoyl III derivatives were isolated.

2-Acetamido-1,6-anhydro-3-*O*-benzoyl-2-deoxy-4-*O*-methylsulfonyl-β-D-galactopyranose (V).—To a solution of 540 mg. of II in 5 ml. of anhydrous pyridine, cooled at 0°, was added 0.25 ml. of methanesulfonyl chloride. After standing overnight at room temperature, ice was added and the reaction mixture was extracted with chloroform. After numerous washings with 2 *N* sulfuric acid, saturated sodium carbonate and water, the solution was dried over sodium sulfate and evaporated *in vacuo*. The crystalline residue was recrystallized from methanol and from a mixture of acetone, ether and pentane, to give 645 mg. (95%) of prismatic needles in clusters, m.p. 214–215° dec., $[\alpha]^{24}D$ −21 ±1° (in chloroform, *c* 2.74). *Anal.* Calcd. for $C_{16}H_{19}O_8NS$: C, 49.86; H, 4.97; S, 8.32. Found: C, 49.90; H, 5.01; S, 8.45.

2-Acetamido-1,6-anhydro-2-deoxy-4-*O*-methylsulfonyl-β-D-galactopyranose (VI). (a) From V.—To a solution of 195 mg. of V in 2 ml. of methanol was added 0.2 ml. of 1.5 *N* barium methoxide. After standing overnight at 0°, water was added, the solution was neutralized with CO_2, and filtered through a layer of Celite. The solvents were evaporated *in vacuo* and the sirupy residue was chromatographed on silicic acid. Elution with a mixture of ethyl acetate and acetone 9:1 gave crystalline fractions. After recrystallization from a mixture of acetone and ether, 133 mg. (91%) of stout prisms was obtained, m.p. 163–164°, $[\alpha]^{24}D$ −18 ±1° (in methanol, *c* 2.71). Recrystallization from mixtures, containing methanol, afforded a crystalline form with m.p. 90–91°. *Anal.* Calcd. for $C_9H_{15}O_7NS$: C, 38.43; H, 5.38. Found: C, 38.50; H, 5.37.

Acetylation of 19 mg. of VI with 0.05 ml. of acetic anhydride and 0.1 ml. of dry pyridine in the usual way afforded the crystalline **3-*O*-acetyl** derivative. Recrystallization from a mixture of acetone and ether gave 20 mg. (90%) of square plates, m.p. 208–210°, with slight decomposition; $[\alpha]^{24}D$ −23 ± 2° (in methanol, *c* 0.57). *Anal.* Calcd. for $C_{11}H_{17}O_8NS$: C, 40.86; H, 5.30. Found: C, 40.90; H, 5.37.

(b) From I.—To a solution of 300 mg. of I in 2 ml. of anhydrous pyridine, cooled at 0°, was added 0.125 ml. (1.1 moles) of methanesulfonyl chloride. After standing 3 hours at 0°, and overnight at room temperature, a few drops of water were added. The solvents were removed *in vacuo* by codistillation with absolute ethanol and toluene. The residue was dissolved in benzene and chromatographed on silicic acid. Elution with a mixture of ethyl acetate and acetone 19:1 afforded the crystalline 2-acetamido-1,6-anhydro-2-deoxy-4-*O*-methylsulfonyl-β-D-galactopyranose (VI), weighing, after recrystallization, 85 mg. (20%) and melting at 158–160°. In admixture with the compound described above, the m.p. was not depressed.

After elution with a mixture of ethyl acetate and acetone 9:1, 150 mg. (50%) of recrystallized starting material was obtained.

2-Acetamido-1,6-anhydro-2-deoxy-3-*O*-methyl-4-*O*-methylsulfonyl-β-D-galactopyranose (VII).—A mixture of 75 mg. of VI, 5 ml. of methyl iodide and 200 mg. of silver oxide was refluxed overnight under stirring. After addition of 200 mg. of silver oxide, stirring and heating were carried on for 8 hours. The solvent was evaporated, the residue extracted

(14) R. W. Jeanloz, THIS JOURNAL, **76**, 555 (1954); R. W. Jeanloz and D. A. Jeanloz, *ibid.*, **79**, 2579 (1957). Microanalysis by Dr. K. Ritter, Basel, Switzerland.

(15) A. Fernez and P. J. Stoffyn, *Tetrahedron* in press, (1959).

with acetone and the solution filtered through a double layer of Celite and Darco G-60. The solvent was then evaporated and the remaining solid was dissolved in benzene and chromatographed on silicic acid. Elution with a mixture of ethyl acetate and acetone 19:1 gave crystalline fractions, affording, after recrystallization from a mixture of acetone and ether, 8 mg. (10%) of prisms, m.p. 184–186°, $[\alpha]^{25}D$ −55 ± 2° (in chloroform, *c* 0.51). *Anal.* Calcd. for $C_{10}H_{17}O_7NS$: C, 40.67; H, 5.80. Found: C, 40.84; H, 5.92.

Elution with the same proportion of ethyl acetate and acetone gave, after recrystallization, 41 mg. (55%) of starting material.

2-Acetamido-1,6-anhydro-4-*O*-benzoyl-2-deoxy-3-*O*-methylsulfonyl-β-D-galactopyranose (VIII).—To a solution of 0.82 g. of crystalline III, corresponding to 0.77 g. of dry material, in 5 ml. of dry pyridine, cooled at −20°, was added 0.6 ml. (3 moles) of methanesulfonyl chloride. After standing 24 hours at 0° and 2 hours at room temperature, the excess chloride was decomposed by addition of ice, and the mixture was extracted with chloroform. The extract was washed many times each with 2 *N* sulfuric acid, saturated sodium bicarbonate, and water, and dried over sodium sulfate. Evaporation *in vacuo* gave 1.07 g. of sirupy residue. It was dissolved in benzene and chromatographed on silicic acid. A mixture of ether and ethyl acetate 19:1 eluted 0.87 g. of crystalline fractions. Recrystallization from a mixture of acetone and ether gave 0.80 g. (82%) of elongated prisms, m.p. 146–149°, $[\alpha]^{24}D$ +2 ± 1° (in chloroform, *c*, 2.53). *Anal.* Calcd. for $C_{16}H_{19}O_8NS$: C, 49.86; H, 4.97; S, 8.32. Found: C, 49.98; H, 5.04; S, 8.49.

2-Acetamido-1,6-anhydro-2-deoxy-3-*O*-methylsulfonyl-β-D-galactopyranose (IX).—To a solution of 200 mg. of VIII in 1 ml. of methanol, cooled at 0°, was added 0.1 ml. of 1 *N* barium methoxide. After standing 24 hours at 0°, water was added and the solution was passed through a column of Dowex 50 in the acidic form. The solvent was evaporated *in vacuo* and the crystalline residue was recrystallized from a mixture of methanol and ether to give 70 mg. (48%) of fine needles, m.p. 149–151°, $[\alpha]^{26}D$ −7 ±1° (in methanol, *c* 0.50). *Anal.* Calcd. for $C_9H_{15}O_7NS$: C, 38.43; H, 5.38. Found: C, 38.35; H, 5.37.

2-Acetamido-1,6-anhydro-2-deoxy-4-*O*-methyl-3-*O*-methylsulfonyl-β-D-galactopyranose (X). (a) **From XI.**—To a solution of 49 mg. of 2-acetamido-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-galactopyranose (XI)[10] in 0.5 ml. of anhydrous pyridine, cooled at 0°, was added 0.05 ml. (3 moles) of methanesulfonyl chloride. After standing overnight at room temperature, the excess chloride was decomposed by addition of ice and the mixture was evaporated to dryness *in vacuo* by codistillation with absolute ethanol. The residue was extracted with chloroform and chromatographed on silicic acid. Elution with a mixture of ethyl acetate and acetone 19:1 gave 37 mg. (55%) of crystalline fractions. Recrystallization from a mixture of acetone and ether gave 21 mg. of stout prisms, m.p. 140–142°. When the material was finely crushed, the m.p. was lowered to 131–135°, $[\alpha]^{24}D$ −41 ± 2° (in chloroform, *c* 0.66). *Anal.* Calcd. for $C_{10}H_{17}O_7NS$: C, 40.67; H, 5.80; S, 10.86. Found: C, 40.77; H, 5.82; S, 11.05.

(b) **From IX.**—To a solution of 48 mg. of IX in 2 ml. of acetone, were added 5 ml. of methyl iodide and 100 mg. of silver oxide. After heating under reflux with stirring overnight, 2 ml. of acetone, 5 ml. of methyl iodide and 200 mg. of silver oxide were added and the reaction was carried on for 24 hours. The mixture was evaporated to dryness, and the residue was extracted with hot methanol. The solution was filtered through a double layer of Celite and Darco G-60, and evaporated to give a sirupy residue. It was chromatographed on silicic acid, and elution with a mixture of ethyl acetate and acetone 19:1 and 9:1 gave sirupy fractions (total 21 mg.), crystallizing when seeded with the material described above. Recrystallization from a mixture of acetone and ether afforded 9 mg. (18%), m.p. 136–138°, showing no depression of the m.p. in admixture with the product described above.

2-Acetamido-3,4-di-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-gulopyranose (XIII).—To a solution of 665 mg. of VIII in 20 ml. of methyl Cellosolve, containing 5% of water, was added 600 mg. of sodium acetate trihydrate. After refluxing for 40 hours, the solution was evaporated *in vacuo* and the residue dried *in vacuo* at 65°. A mixture of 5 ml. of anhydrous pyridine and 3 ml. of acetic anhydride was added and after standing one day at room temperature, the excess anhydride was decomposed by addition of methanol. The solvents were evaporated *in vacuo*, the last traces being removed by codistillation with dry toluene, and the residue was suspended in benzene and chromatographed on silicic acid. Elution with mixtures of various concentrations of ether and ethyl acetate gave 440 mg. of crystalline fractions. Recrystallization from a mixture of acetone and ether gave 320 mg. (65%) of stout rectangular prisms, m.p. 144–145°, $[\alpha]^{27}D$ −19 ± 1° (in chloroform, *c* 0.86). *Anal.* Calcd. for $C_{12}H_{17}O_7N$: C, 50.17; H, 5.97. Found: C, 50.33; H, 5.93. Alkaline hydrolysis of the mother liquors gave an additional crop of 55 mg. of crystalline XII (see below) raising the yield to 78%.

2-Acetamido-1,6-anhydro-2-deoxy-β-D-gulopyranose (XII). (a) **From XIII.**—To a solution of 340 mg. of XIII in 2 ml. of methanol, cooled at 0°, was added 0.2 ml. of 1 *N* barium methoxide. After standing one day at 0°, the methanol was evaporated under a stream of nitrogen and the residue was dissolved in 5 ml. of water. The solution was passed through a column of Dowex 50 in the acid form and the eluate was evaporated to dryness *in vacuo*. Recrystallization from a mixture of methanol, acetone and ether gave 228 mg. (95%) of stout rectangular prisms, m.p. 182–183°, $[\alpha]^{27}D$ +45 ± 1° (in methanol, *c* 1.28). *Anal.* Calcd. for $C_8H_{13}O_5N$: C, 47.29; H, 6.45. Found: C, 47.15; H, 6.48.

(b) **From XIV.**—To a solution of 3.7 mg. of 2-amino-1,6-anhydro-2-deoxy-β-D-gulopyranose hydrochloride (XIV), isolated from natural sources,[3] in 0.2 ml. of methanol, was added 4.0 mg. of silver acetate and 0.02 ml. of acetic anhydride. After standing overnight, the mixture was diluted with 2 ml. of methanol and one drop of water and heated to boiling. The cooled solution was filtered through Celite, then through a small column of Dowex 50 in acidic form, finally through a double layer of Celite and Darco G-60 and evaporated. The crystalline residue was recrystallized from a mixture of methanol, acetone and ether to give 3.2 mg. (84%) of prisms, m.p. 180–181°, $[\alpha]^{26}D$ +46 ±2° (in methanol, *c* 0.86). In admixture with the product described above, the m.p. was not depressed.

2-Amino-1,6-anhydro-2-deoxy-β-D-gulopyranose hydrochloride (XIV).—A solution of 50 mg. of XII in 1 ml. of 0.5 *N* hydrochloric acid was heated for 2 hours at 100°. After addition of 20 ml. of absolute ethanol, the solvents were evaporated *in vacuo*. The addition of absolute ethanol, followed by distillation, was repeated, then the residue was dried over soda lime in a high vacuum. Recrystallization from a mixture of methanol and acetone, or from a mixture of water, ethanol and acetone, gave 39 mg. (80%) of shiny plates, becoming yellow at 240°, and partially melting with strong decomposition at 255–260°, $[\alpha]^{26}D$ +42 ± 1° (in water, *c* 0.85).[16] *Anal.* Calcd. for $C_6H_{12}O_4NCl$: C, 36.47; H, 6.12; Cl, 17.94. Found: C, 36.35; H, 6.27; Cl, 18.03, for a sample dried overnight at room temperature in a desiccator over P_2O_5.

A solution of 50 mg. of XII in 5 ml. of 0.5 *N* barium hydroxide was heated for one hour at 100°. After neutralization with solid carbon dioxide, the precipitate was filtered and the solution evaporated *in vacuo*. The sirupy residue, containing some crystalline material, was extracted with ethanol. After removal of the solvent, the resulting sirupy **2-amino-1,6-anhydro-2-deoxy-β-D-gulopyranose** was left in a desiccator for four months. Since it could not be induced to crystallize, it was transformed into the hydrochloride XIV by dissolution in 1 ml. of ethanol and addition of 0.25 ml. of a 10% hydrogen chloride solution in methanol. After removal of the solvent, the residue was dissolved in methanol and the solution was filtered through a double layer of Celite and Darco G-60. By addition of acetone and ether, 40 mg. (82%) of shiny plates crystallized. Recrystallized as described above, the crystals turned yellow at 240° and melted partially with strong decomposition at 250–260°, $[\alpha]^{26}D$ +41 ± 2° (in water, *c* 0.59). *Anal.* Calcd. for $C_6H_{12}O_4NCl$: C, 36.47; H, 6.12. Found: C, 36.42; H, 6.28 (same drying as above).

The compound could be detected on a paper chromatogram with ninhydrin and with $AgNO_3$. However, the $AgNO_3$ reaction was very much slower than the one with 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose. On a descending paper chromatogram, Whatman No. 1 and No.

(16) van Tamelen, *et al.*,[3] reported for the natural product m.p. 235–240° dec., $[\alpha]^{25}D$ +44.8° (anhydrous) (*c* 3.5, water).

54, developed with a mixture of 1-propanol and 1% ammonium hydroxide in proportions 7:3, it moved with an R_f 0.66. With the same mixture, the R_f of D-glucosamine was 0.50, D-galactosamine 0.46, synthetic and natural D-gulosamine 0.55 and 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose 0.57.[17] The natural and the synthetic XIV migrated at the same speed, either developed with the same mixture of solvents, or with the mixture *sec*-butyl alcohol–acetic acid–water in proportions 4:1:1.

Methyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-gulopyranoside (XVII). (a) **From Synthetic D-Gulosamine Hydrochloride (XV).**[18]—A solution of 215 mg. of crude synthetic sirupy D-gulosamine hydrochloride[5] (XV) was dissolved in 19 ml. of methanol. After addition of 0.5 g. of silver acetate and 1 ml. of acetic anhydride, the mixture was left overnight at room temperature. After heating to boiling, the silver salts were filtered off and the filtrate evaporated *in vacuo*. The residual sirup was dissolved in 20 ml. of a 2% solution of hydrogen chloride in absolute methanol and refluxed for 2 hours. After cooling, the solution was neutralized with lead carbonate, the filtrate then treated with hydrogen sulfide, filtered through a double layer of Darco G-60 and Celite, and evaporated *in vacuo*. The residual sirup was acetylated overnight with 2 ml. of absolute pyridine and 2 ml. of acetic anhydride. Both reagents were removed by codistillation with dry toluene, and the residue was dissolved in chloroform and chromatographed on silicic acid. Elution with mixtures of ether and ethyl acetate 1:1, and with pure ethyl acetate, gave 163 mg. of crystalline fractions. Recrystallization from a mixture of acetone and ether afforded 116 mg. (32%) of needles, with a double m.p. at 118–119° and 124–125°, $[\alpha]^{23}D$ −54 ±2° (in chloroform, *c* 0.66). *Anal.* Calcd. for $C_{15}H_{23}O_9N$: C, 49.86; H, 6.42. Found: C, 49.69; H, 6.58.

(b) **From Natural D-Gulosamine Hydrochloride (XV).**[18]—This experiment was carried out on 14 mg. of natural D-gulosamine hydrochloride[5] in an identical way as described above with the exception that the first step consisted in a total acetylation with 0.3 ml. of anhydrous pyridine and 0.2 ml. of acetic anhydride, instead of the *N*-acetylation. In the final chromatography, 13 mg. of crystalline fractions was isolated, giving, by recrystallization from a mixture of methanol and ether, 8 mg. (30%) of needles with a double m.p. at 118° and 124–125°, $[\alpha]^{23}D$ −53 ± 2° (in chloroform, *c* 0.56). The product showed no depression of the m.p. in admixture with the compound described under (a).

(c) **From XII.**—To a solution of 50 mg. of XII in 1.2 ml. of acetic anhydride and 0.8 ml. of glacial acetic acid was added 0.02 ml. of concentrated sulfuric acid.[19] After 15 minutes, the solution had $[\alpha]^{25}D$ +77°, after 3 hours +50°, after 24 hours +35°, after 48 hours +32°. The solution was then diluted with 50 ml. of chloroform, washed two times with saturated sodium bicarbonate, three times with water and dried over sodium sulfate. The residual sirup, weighing 92 mg., had $[\alpha]^{28}D$ +54 ± 2° (in chloroform, *c* 1.03). It was dissolved in 5 ml. of a 2% solution of hydrogen chloride in absolute methanol, refluxed, then acetylated as described above. From the chromatography, 78 mg. of crystalline fractions were isolated, giving after recrystallization, 38 mg. (43%) of needles, with double m.p. 117–118° and 124–126°; $[\alpha]^{27}D$ −51 ±2° (in chloroform, *c* 1.02); and showing no depression of the m.p. in admixture with the compound described under (a). When the same reaction was carried out with a higher concentration of XII (10%) for 24 hours, only the starting compound could be recovered as crystalline material.

Action of Hydrochloric Acid on Synthetic D-Gulosamine Hydrochloride (XV).—A solution of 0.5 mg. of XV in 0.1 ml. of 6 *N* HCl was heated in a sealed tube at 100° for 20 hours. After removal of the solvent, the product was chromatographed on Whatman No. 1 and No. 54 paper with a mixture 1-propanol and 1% ammonium hydroxide, in proportions 7:3. After revelation with ninhydrin and silver nitrate, a spot with R_f 0.67, corresponding to XIV, appeared in an amount estimated at one-fourth to one-half the amount of the original material. When XV was heated with 2 *N* hydrochloric acid for 7 hours,[5] no such spot appeared.

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(17) In the previous communication,[5] the $R_{glucosamine}$ of this compound has been erroneously reported at 1.45.

(18) This experiment was performed by Dr. Z. Tarasiejska.

(19) E. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 662 (1945).

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Synthesis of A-Norsteroids

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Ozonolysis of the 2-hydroxymethylene derivatives of testosterone and progesterone gave unsaturated 2,3-seco acids which were converted by pyrolysis to A-nortestosterone and A-norprogesterone. Catalytic reduction of the 3,4-double bond of A-nortestosterone gave only the A/B *cis* fused system whereas reduction with lithium in liquid ammonia yielded approximately equal amounts of A/B *cis* and A/B *trans* fused products. The structure of a by-product from the ozonolysis of hydroxymethylenetestosterone was elucidated and a number of A-nor-derivatives are described.

Although a number of A-norsteroids have been described in the literature,[1a] none having a 2-keto-Δ^3 system has been reported.[1b] The synthesis of the A-nor analogs of testosterone and progesterone appeared attractive in order to study the effect of this change in structure on physiological activity.

The unsaturated diacid IIa was reported[2] previously to be one of the products obtained from the ozonization of 2-hydroxymethylenetestosterone (I). This diacid was considered a convenient starting material since on distillation the compound should cyclize with loss of carbon dioxide to form A-nortestosterone, a reaction analogous to that used to prepare saturated A-norsteroids.[1a]

When 2-hydroxymethylenetestosterone (I) was treated with one equivalent of ozone followed by hydrogen peroxide and the acidic products esterified, there was isolated, in addition to the diester IIb, a monoester having the formula $C_{20}H_{30}O_5$, corresponding to a loss of one carbon atom from the parent hydroxymethylene compound. The substance showed no specific ultraviolet absorption and did not form a carbonyl derivative with either semicarbazide or 2,4-dinitrophenylhydrazine. The corresponding free acid ($C_{19}H_{28}O_5$) which could

(1) (a) For a summary see Elsevier's "Encyclopedia of Organic Chemistry," Supplement I, Vol. 14; (b) T. L. Jacobs and N. Takahashi (THIS JOURNAL **80**, 4865 (1958)) has recently reported the synthesis of A-norcholestenone.

(2) F. L. Weisenborn, D. C. Remy and T. L. Jacobs, *ibid.*, **76**, 552 (1954).