CARBOHYDRATES CONTAINING NITROGEN IN A FIVE-MEMBERED RING AND AN ATTEMPTED SYNTHESIS OF A CARBOHYDRATE WITH NITROGEN IN A SEVEN-MEMBERED RING¹

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ABSTRACT

Lead tetraacetate oxidation of 6-acetamido-6-deoxy-D-galactose (IX) yielded a syrup which was converted to a compound formulated as 4-acetamido-4-deoxy-1,2-O-isopropylidene-Dthreofuranose (XII). The same syrup was obtained by alkaline degradation of the product of oxidation of 5-acetamido-5-deoxy-D-xylose diethyl dithioacetal (XVII) with peroxypropionic acid. Treatment of compound XII with p-toluenesulfonyl chloride yielded crystalline 4-acetamido-4-deoxy-1,2-O-isopropylidene-3-O-p-tolylsufonyl-D-threofuranose (XIII).

Demercaptalation of 6-acetamido-2,3,4,5-tetra-O-acetyl-6-deoxy-D-galactose diethyl dithioacetal (XX) with mercuric chloride and cadmium carbonate in aqueous acetone did not yield a nitrogen-containing septanose ring but an acyclic derivative.

CARBOHYDRATES CONTAINING NITROGEN IN A FIVE-MEMBERED RING

In a previous paper (1) from this laboratory the synthesis of methyl 4-acetamido-4deoxy-L-erythrofuranoside (I), the first example of a sugar with nitrogen in a fivemembered ring, was described. Very shortly after this announcement, Hanessian and Haskell (2) reported that they had obtained syrupy 4-acetamido-4-deoxy-L-erythrofuranose by the alkaline degradation of 5-acetamido-5-deoxy-L-arabinose diethylsulfonal. In the same paper Hanessian and Haskell reported the preparation of a novel sugar derivative, 4-amino-4-deoxy-D-erythronolactam (II). In the present publication we describe the synthesis by two different routes of derivatives of 4-acetamido-4-deoxy-Dthreofuranose (XI).



1,2;3,4-Di-O-isopropylidene- α -D-galactopyranose (IV) (3) was prepared from D-galactose (III) and treated with p-toluenesulfonyl chloride in pyridine to give 1,2;3,4-di-O-isopropylidene-6-O-p-tolylsulfonyl- α -D-galactopyranose (V) (4). Compound V reacted with sodium azide in N,N-dimethylformamide to afford a homogeneous pale yellow oil, the infrared spectrum of which showed the highly characteristic azide group absorption at 2 100 cm⁻¹ but no aromatic ring and sulfonate group absorptions. The new substance is therefore 6-azido-6-deoxy-1,2;3,4-di-O-isopropylidene- α -D-galactopyranose (VI). This derivative could be reduced to 6-amino-6-deoxy-1,2;3,4-di-O-isopropylidene- α -D-galactopyranose (VII) (5) by merely stirring it with an excess of Raney nickel, a procedure described by Wolfrom *et al.* (6). Treatment of compound VII with acetic anhydride in pyridine afforded a glass which gave a negative ninhydrin reaction. The glassy product

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showed amide I and amide II bands in the infrared, and thus is 6-acetamido-6-deoxy-1,2;3,4-di-O-isopropylidene- α -D-galactopyranose (VIII). Hydrolysis of VIII with Amberlite IR-120 (H form) resin yielded glassy 6-acetamido-6-deoxy-D-galactose (IX), which was characterized by its conversion to crystalline 6-acetamido-6-deoxy-D-galactitol (X) on sodium borohydride reduction.



It has been known for some time that aldohexoses, when treated with lead tetraacetate, rapidly consume 2 moles of oxidant, after which the reaction becomes very slow (7, 8). Thus, Perlin and Brice (8) were able to degrade D-glucose selectively to di-O-formyl-D-erythrose by oxidation with 2 moles of lead tetraacetate. The ester groups were easily hydrolyzed, giving D-erythrose in an overall yield of at least 80% of theory. D-Galactose showed similar behavior, but the product formed was D-threose esterified with 1.8 formate groups per molecule (9). Significantly, substitution of the C-6 hydroxyl group in D-glucose did not alter the rate of uptake of lead tetraacetate (10). This result implies that the primary carbinol group is not involved in the oxidation of D-glucose itself.

The results cited above suggested that oxidation of 6-acetamido-6-deoxy-D-galactose (IX) with 2 moles of lead tetraacetate would yield a 4-acetamido-4-deoxy-D-threose derivative in which there existed the possibility of formation of a nitrogen-containing furanose ring. Oxidation of compound IX with 2 moles of lead tetraacetate followed by hydrolysis of the ester groups by heating of the product in water afforded a syrup which was reducing towards Fehling's solution and whose infrared spectrum showed absorption

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attributable to OH and a very broad amide I band, but no significant amide II band. The infrared data suggested that the new substance exists primarily in the furanose form (XI). The results of periodate oxidation in unbuffered aqueous solution were consistent also with the proposed structure. The n.m.r. spectrum in deuterium oxide (Fig. 1) could



FIG. 1. Nuclear magnetic resonance spectrum of "4-acetamido-4-deoxy-D-threofuranose" at room temperature.

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not be satisfactorily interpreted, however, on the basis of this formulation. In the region 1.96-2.15 p.p.m., characteristic of the protons of an *N*-acetyl group (11), there are five peaks. The portion of the spectrum from 5.24 p.p.m. to 5.43 p.p.m., which can be attributed to anomeric protons (12), is also unusually complex. An attractive suggestion is that the new substance is a mixture of α - and β -anomers, and that each anomer displays restricted rotation about the *CO*—*N* bond. Such hindered internal rotation has been demonstrated in methyl 4-acetamido-4-deoxy-L-erythrofuranoside and in two nitrogen-containing pyranose sugars (13). In addition there may be present a small amount of the acyclic form of the compound.

The new substance appeared on both paper and thin-layer chromatograms as two spots which moved very close to one another. A separation of the two components by preparative paper chromatography was attempted. The zones were located and extracted with methanol. Examination of the two extracts on paper chromatograms still showed in each case, however, the presence of the two original components. This observation indicated that a transformation of one component into the other occurred during the extraction or chromatography process.

Treatment of the oxidation product with dry acetone in the presence of anhydrous copper (II) sulfate and concentrated sulfuric acid afforded a pale yellow syrup. In contrast to the starting material, the product migrated as a homogeneous spot on a thin-layer chromatogram. The infrared spectrum of this material showed a doublet of approximately equal intensity attributable to a $C(CH_3)_2$ grouping, absorption attributable to OH,

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and an amide I band but no amide II band. This evidence is consistent with structure XII for the new compound, which is named 4-acetamido-4-deoxy-1,2-O-isopropylidene-D-threofuranose. The n.m.r. spectrum in deuterium oxide at room temperature (Fig. 3) shows two peaks at 1.36 and 1.41 p.p.m. which may be assigned to the protons of an isopropylidene group, and two peaks at 2.08 and 2.16 p.p.m. in the region characteristic of the protons of N-acetyl groups. Since there is no possibility of anomers in 4-acetamido-4-deoxy-1,2-O-isopropylidene-D-threofuranose, the two signals in the N-acetyl region may



FIG. 2. Nuclear magnetic resonance spectrum of "4-acetamido-4-deoxy-L-erythrofuranose" at room temperature.



FIG. 3. Nuclear magnetic resonance spectrum of 4-acetamido-4-deoxy-1,2-O-isopropylidene-p-threo-furanose (LXXXVI) at room temperature.

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arise from restricted rotation about the CO-N bond. At 80°, however, there was no measurable merging of the two signals. Treatment of compound XII with *p*-toluenesulfonyl chloride in pyridine yielded crystalline 4-acetamido-4-deoxy-1,2-O-isopropylidene-3-O-*p*-tolylsulfonyl-D-threofuranose (XIII). The five-membered ring structure of XIII was indicated by the absence of the amide II band in its infrared spectrum. The n.m.r. spectrum of 4-acetamido-4-deoxy-1,2-O-isopropylidene-3-O-*p*-tolylsulfonyl-D-threofuranose in deuterochloroform at room temperature is presented in Fig. 4. The group of peaks centered at 7.60 p.p.m. with an intensity corresponding to four protons may be assigned to tosyl ring protons. The peak at 2.47 p.p.m., corresponding to three protons, is assigned to the tosyl methyl group. The n.m.r. spectrum shows also two peaks at 1.35 and 1.39 p.p.m. attributable to the protons of an isopropylidene group. Evidence in favor of restricted rotation about the CO-N bond was obtained by the appearance of two peaks at 2.00 and 2.17 p.p.m. which may be assigned to the protons of the *N*-acetyl group, and two doublets at 5.90 and 6.20 p.p.m. in the general region characteristic of anomeric protons.

In the present work the preparation of the syrupy product obtained by lead tetraacetate oxidation of 6-acetamido-6-deoxy-D-galactose was accomplished also by a different approach. 1,2-O-Isopropylidene-5-O-p-tolylsulfonyl-D-xylose (XIV) was prepared from p-xylose by the method of Levene and Raymond (14). Treatment with sodium azide in N,N-dimethylformamide gave crystalline 5-azido-5-deoxy-1,2-O-isopropylidene-D-xylose (XV). This compound was readily reduced with Raney nickel at room temperature to give a crystalline product which, when treated with aqueous acetic anhydride, gave 5-acetamido-5-deoxy-1,2-O-isopropylidene-D-xylose (XVI) (15). The furanose ring of XVI could be opened by treatment with ethanethiol and hydrochloric acid to give crystalline 5-acetamido-5-deoxy-D-xylose diethyl dithioacetal (XVII). Oxidation of compound XVII with peroxypropionic acid afforded a glass, probably 5-acetamido-5-deoxy-D-xylose diethylsulfonal. Treatment of this material with aqueous ammonia afforded crystalline bis (ethylsulfonyl) methane and a syrup. The infrared and proton magnetic resonance spectra and chromatographic properties of this material were the same as those of the syrup obtained from the lead tetraacetate oxidation.

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It is of interest to note that hydrolysis with Amberlite IR-120 (H form) resin of methyl 4-acetamido-4-deoxy-L-erythrofuranoside (I) (1) afforded a reducing syrup which exhibited behavior entirely analogous to that shown by the product derived from the two degradation procedures described above. The infrared spectrum of the syrup showed absorption attributable to OH and a broad amide I band, but no significant absorption in the region characteristic of an amide II band. On the basis of the infrared data and the structure of the precursor I, a reasonable formulation of the new syrup would be that shown by XVIII.



The results of periodate oxidation in unbuffered aqueous solution could be accommodated also by this structure. The n.m.r. spectrum in deuterium oxide (Fig. 2), however, is very complex but resembles closely the spectrum shown in Fig. 1. Two spots were detected again by both paper and thin-layer chromatography, and an attempted separation of the components by preparative paper chromatography indicated that they are interconvertible.

ATTEMPTED SYNTHESIS OF A CARBOHYDRATE CONTAINING NITROGEN IN A SEVEN-MEMBERED RING

The synthesis of derivatives of seven-membered ring sugars or septanoses has been achieved by Micheel *et al.* (16–18). By a series of reactions α - and β -1,2,3,4,5-penta-Oacetyl-D-galactoseptanose were prepared. The septanose structure was confirmed by conversion of the pentaacetate to a methyl tetra-O-methyl-D-galactoseptanoside which, upon oxidation with nitric acid, gave tetra-O-methylmucic acid (17). In the present work the synthesis of a sugar derivative with nitrogen as the hetero atom in a seven-membered ring was attempted by a method analogous to that described by Micheel and Suckfüll (16).

Treatment of 6-acetamido-6-deoxy-1,2;3,4-di-O-isopropylidene- α -D-galactopyranose (VIII) (vide supra) with ethanethiol and hydrochloric acid gave crystalline 6-acetamido-6-deoxy-D-galactose diethyl dithioacetal (XIX). Acetylation of XIX with acetic anhydride in pyridine then afforded crystalline 6-acetamido-2,3,4,5-tetra-O-acetyl-6-deoxy-Dgalactose diethyl dithioacetal (XX). Demercaptalation of compound XX with mercuric chloride and cadmium carbonate in aqueous acetone, by the method employed by Wolfrom (19) to prepare the monoethyl alcoholate of 2,3,4,5,6-penta-O-acetyl-aldehydo-galactose, gave a crystalline product XXI which, on heating, reduced Fehling's solution. The infrared spectrum of this material showed strong absorption attributable to OH, absorption owing to O-acetyl groups, an amide I band, and an amide II band. Thus compound XXI is presumably the aldehydrol of 6-acetamido-2,3,4,5-tetra-O-acetyl-6-deoxy-aldehydo-Dgalactose. Accordingly, compound XXI was allowed to stand in dry pyridine for 24 h and then treated with acetic anhydride. The presence of an amide II band in the infrared spectrum of the product indicated, however, that the desired cyclization to form a nitrogen-containing septanose ring had not occurred.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus. Optical rotations were measured with a Hilger standard polarimeter. Infrared spectra were measured with a Perkin-Elmer model 21 spectrophotometer. The n.m.r. spectra were determined at 60 Mc/s with a Varian A-60 n.m.r. spectrometer

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Can. J. Chem. Downloaded from www.nrcresearchpress.com by 111.68.111.42 on 11/20/14 For personal use only. using approximately 10% by weight solutions; chemical shifts were determined as p.p.m. downfield from tetramethylsilane as an external standard for the deuterium oxide solutions and as an internal standard for the deutero chloroform solutions. Paper chromatography was carried out by the descending method at room temperature on Whatman No. 1 filter paper for qualitative purposes or on Whatman 3 MM filter paper for preparative purposes in the following solvent systems (v/v): (A) butan-1-ol:ethanol:water, 3:1:1; (B) ethyl acetate:acetic acid:formic acid:water, 18:3:1:4. Sugars were detected on paper chromatograms by the following spray reagents: (i) alkaline silver nitrate (20); (ii) *p*-anisidine hydrochloride (21); (iii) sodium metaperiodate – potassium permanganate (22). Rates of movement of the sugars on paper chromatograms are given relative to that of rhamnose (R_{rh}). Thin-layer chromatography was carried out on Silica Gel G supplied by Research Specialties Company, Richmond, California. The developed plates were dried in air, sprayed with concentrated sulfuric acid, and then heated in an oven at about 150°. Raney nickel catalyst in water was supplied by Aldrich Chemical Co., Inc., Milwaukee, Wisconsin.

1,2;3,4-Di-O-isopropylidene-6-O-p-tolylsulfonyl- α -D-galactopyranose (V)

1,2;3,4-Di-O-isopropylidene- α -D-galactopyranose (IV) was prepared from D-galactose (36 g) according to Tipson (3). The crude product (33 g) was dissolved in dry pyridine (65 ml) and p-toluenesulfonyl chloride (36.8 g, 1.5 moles) was added at room temperature. After 3 h the mixture was poured into 400 ml of ice-water and the precipitated product (44.1 g, 84%) was isolated in the usual way. After two recrystallizations from methanol the compound had m.p. 101.5-102.5° and $[\alpha]_D^{25} = -62°$ (c, 4.33 in chloroform containing 0.75% ethanol). Foster et al. (4) report m.p. 89-91° and $[\alpha]_D = -63.4°$ (chloroform); Freudenberg and Raschig (23) report m.p. 102-103°.

6-Azido-6-deoxy-1,2;3,4-di-O-isopropylidene-α-D-galactopyranose (VI)

To a solution of 1,2;3,4-di-O-isopropylidene-6-O-p-tolylsulfonyl- α -D-galactopyranose (V) (27.0 g) in N,N-dimethylformamide (230 ml) was added water (12 ml), sodium azide (6.38 g, 1.5 moles), and urea (0.8 g). The mixture was heated for 19 h at 120° under a stream of nitrogen. The cooled solution was poured into 600 ml of ice water and extracted several times with chloroform. The combined extracts were washed with aqueous sodium hydrogen carbonate, then with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to leave a pale yellow oil (15.6 g, 84%), $[\alpha]_D^{21} = -92.1^\circ$ (c, 1.48 in chloroform containing 0.75% ethanol). Thin-layer chromatography in methanol:benzene, 1:9 (v/v), showed only one component. The infrared spectrum of this material in chloroform showed azide absorption at 2 100 cm⁻¹, but no aromatic ring and sulfonate group absorptions, and no hydroxyl group absorption.

6-Amino-6-deoxy-1,2;3,4-di-O-isopropylidene- α -D-galactopyranose (VII)

A solution of 6-azido-6-deoxy-1,2;3,4-di-O-isopropylidene- α -D-galactopyranose (VI) (14.4 g) in methanol (300 ml) was treated with Raney nickel (80 g) for 44 h, filtered, and concentrated to give a pale yellow syrup (13.7 g). The infrared spectrum of this material in chloroform showed N-H deformation vibration at 1 587 cm⁻¹ and N-H stretching vibration in the 3 300 cm⁻¹ region, but no absorption attributable to an azide grouping. The product was distilled to yield a mobile colorless syrup which had $[\alpha]_D^{28} = -44.0^{\circ}$ (c, 1.31 in methanol). Veksler *et al.* (5) report $[\alpha]_D^{21} = -40.1^{\circ}$ (in methanol) for syrupy 6-amino-6-deoxy-1,2;3,4-di-O-isopropylidene- α -D-galactopyranose.

6-Acetamido-6-deoxy-1,2;3,4-di-O-isopropylidene-a-D-galactopyranose (VIII)

To a solution of 6-amino-6-deoxy-1,2;3,4-di-*O*-isopropylidene- α -D-galactopyranose (VII) (12.2 g) in reagent pyridine (45 ml) was added acetic anhydride (17 ml) portionwise with ice-cooling. After 20 h at room temperature the solution was poured into 400 ml of ice water, and the mixture was extracted several times with chloroform. The combined chloroform extracts were washed with water, then shaken with an aqueous solution of cadmium chloride (to remove pyridine). The pyridine – cadmium chloride complex was filtered, the chloroform solution washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to leave an almost colorless glass (15.5 g). This material gave a negative ninhydrin reaction and had $[\alpha]_D^{23} = -8.3^{\circ}$ (c, 1.81 in chloroform containing 0.75% ethanol). The infrared spectrum in chloroform showed *N*—*H* stretching vibration absorption at 3 440 cm⁻¹, an amide I band at 1 663 cm⁻¹, and a doublet at 1 387 cm⁻¹ and 1 376 cm⁻¹ attributable to *C*—*H* deformation vibrations of a C(CH₃)₂ grouping.

6-Acetamido-6-deoxy-D-galactose (IX)

A suspension of 6-acetamido-6-deoxy-1,2;3,4-di-O-isopropylidene- α -D-galactopyranose (VIII) (1.5 g) in water (225 ml) was stirred with 7.5 g of Amberlite IR-120 (H form) resin at 60° for $3\frac{1}{2}$ h. The resin was then removed by filtration, and the filtrate was shaken briefly with a small amount of Duolite A-4 (OH form) resin to remove any trace of acid. The resin was removed, and the clear colorless solution was concentrated under reduced pressure to leave a colorless glass (1.2 g). This material was reducing towards Fehling's solution, and had $[\alpha]_D^{22} = +81^\circ$ (constant, during 24 h) (c, 1.24 in water). Thin-layer chromatography in 2-propanol:benzene, 1:2 (v/v), showed only one component; paper chromatography also showed only one component with $R_{\rm rh} 0.50$ (solvent A, sprays i and ii).

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6-Acetamido-6-deoxy-D-galactitol (X)

Can. J. Chem. Downloaded from www.nrcresearchpress.com by 111.68.111.42 on 11/20/14 For personal use only. To a cold solution of 6-acetamido-6-deoxy-D-galactose (IX) (0.26 g) in water (10 ml) 0.26 g of sodium borohydride was added, with shaking. The solution was allowed to stand in a refrigerator for 3 h and then 30 min at room temperature. Excess sodium borohydride was destroyed by the addition of acetone, and the solution was then passed through Amberlite IR-120 (H form) exchange resin. The eluate and washings were concentrated to dryness under reduced pressure. Boric acid was removed by repeated distillation with methanol. A white crystalline material was obtained which was recrystallized from methanol to give crystals (0.12 g) which had $[\alpha]_D^{21} = +20.4^{\circ}$ (c, 1.38 in water), $R_{\rm rh}$ 0.6 (solvent A, spray i), and m.p. 183–183.5°. The infrared spectrum in Nujol mull showed strong absorption at 3 280 cm⁻¹ attributable to *OH* and *NH*, an amide I band at 1 645 cm⁻¹, and an amide II band at 1 557 cm⁻¹.

Anal. Calcd. for C₈H₁₇O₆N: C, 43.04; H, 7.68; N, 6.28. Found: C, 42.78; H, 7.58; N, 6.48.

Lead Tetraacetate Oxidation of 6-Acetamido-6-deoxy-D-galactose (IX)

To a rapidly stirred solution of 6-acetamido-6-deoxy-D-galactose (0.53 g, 0.00238 mole) in 2 ml of water and 50 ml of acetic acid was added lead tetraacetate (2.2 g, 0.00497 mole), prepared according to the procedure of Vogel (24), over a period of 3 to 4 min. After 18 min oxalic acid dihydrate (ca. 0.7 g), dissolved in glacial acetic acid, was added, and the suspension was stirred for an additional 30 min; a negative potassium iodide – starch test was then obtained. The precipitate was filtered off and washed with acetic acid, and the filtrate was concentrated under reduced pressure at 35° to a volume of a few milliliters. Ethyl acetate was added and the precipitate which formed was triturated with several portions of ethyl acetate. The extracts were combined, filtered, and concentrated to a syrup which was further purified by extraction with ethyl acetate. The product was a pale yellow syrup (0.40 g).

The yellow syrup was taken up in water (25 ml) and heated on a stream bath for 3 h. The solution was then concentrated under reduced pressure to yield a light brown syrup (0.26 g) which was examined on paper chromatograms. Sprays i and ii showed the presence of 6-acetamido-6-deoxy-D-galactose at $R_{\rm rh}$ 0.5 and two closely moving components at $R_{\rm rh}$ 1.05 and 1.32 (solvent A). The two components having $R_{\rm rh}$ 1.05 and 1.32 were separated as one fraction from the 6-acetamido-6-deoxy-D-galactose by preparative paper chromatography in solvent A. The syrupy fraction was purified by dissolving it in water and washing the solution with chloroform. Concentration of the aqueous phase under reduced pressure gave an almost colorless syrup (ca. 0.14 g) which reduced Fehling's solution in a few minutes on heating, and had $[\alpha]_D^{24} = -15.5^\circ$ (c, 1.68 in methanol). In solvent B the syrup was revealed as two spots at $R_{\rm rh}$ 1.06 and 1.13 (sprays i and ii). Two spots were detected also by thin-layer chromatography in 2-propanol:benzene, 1:2 (v/v). The infrared spectrum of this material (smear between "IRTRAN-2" plates) showed strong absorption at 3 380 cm⁻¹ attributable to OH, and a very broad band at 1 627 cm⁻¹ attributable to N-Ac.

A separation of the two components was attempted by preparative paper chromatography using solvent A. The zones were located (spray i), cut, and extracted with methanol. Examination of the two extracts on paper chromatograms still showed in each case the presence of the two original components.

4-Acetamido-4-deoxy-1,2-O-isopropylidene-D-threofuranose (XII)

To a portion (0.096 g) of the lead tetraacetate oxidation product were added dry acetone (20 ml), anhydrous copper sulfate (2 g), and concentrated sulfuric acid (1 drop). The mixture was shaken mechanically for 24 h and filtered, and the filtrate was then poured into a rapidly stirred saturated aqueous solution (ca. 24 ml) of sodium hydrogen carbonate. Most of the acetone was removed by evaporation under reduced pressure and the solution was then continuously extracted with chloroform overnight. The chloroform extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to leave a pale yellow syrup (0.058 g). This material was distilled under vacuum to yield a syrup which had $[\alpha]_D^{25} = +162^{\circ}$ (c, 1.64 in methanol). Thin-layer chromatography in methanol:benzene, 1:9 (v/v), showed only one component. The infrared spectrum of this material in chloroform showed absorption at 3 420 cm⁻¹ attributable to OH, a doublet of approximately equal intensity at 1 382 and 1 391 cm⁻¹ caused by an isopropylidene grouping, and an amide I band at 1 645 cm⁻¹ but no amide II band.

Anal. Calcd. for C₉H₁₅O₄N · ¹/₂H₂O: C, 51.5; H, 7.62; N, 6.68. Found: C, 51.9; H, 7.28; N, 6.15.

4-Acetamido-4-deoxy-1,2-O-isopropylidene-3-O-p-tolylsulfonyl-D-threofuranose (XIII)

Syrupy 4-acetamido-4-deoxy-1,2-O-isopropylidene-D-threofuranose (0.51 g) was dissolved in dry pyridine (10 ml) and p-toluenesulfonyl chloride (0.57 g, 1.2 moles) was added at room temperature. After 24 h the solution was poured into ice water; a crystalline material separated after a few min. The product (0.61 g) was recrystallized from ether to give crystals which had m.p. 129–129.5° and $[\alpha]_D = +84°$ (c, 1.73 in chloroform containing 0.75% ethanol). The infrared spectrum in (KBr) showed absorption at 1 600 cm⁻¹ attributable to an aromatic ring, and an amide I band at 1 653 cm⁻¹, but no absorption attributable to OH, nor an amide II band.

Anal. Calcd. for C₁₆H₂₁O₆NS: C, 54.07; H, 5.96; N, 3.94. Found: C, 53.86; H, 5.76; N, 4.05.

1,2-O-Isopropylidene-5-O-p-tolylsulfonyl-D-xylose (XIV)

This compound was prepared from D-xylose (33 g) by the method of Levene and Raymond (14). The

crystalline product (44 g, 58)% was recrystallized from ethyl acetate and it then melted at 133–134° and had $[\alpha]_D = -12.4^\circ$ (c, 2.9 in chloroform containing 0.75% ethanol). Levene and Raymond report m.p. 133–134° and $[\alpha]_{D^{20}} = -13.0^\circ$ (c, 2.0 in chloroform).

5-Azido-5-deoxy-1,2-O-isopropylidene-D-xylose (XV)

To a solution of 1,2-O-isopropylidene-5-O-p-tolylsulfonyl-D-xylose (14.0 g) in N,N-dimethylformamide (125 ml) was added water (6.5 ml), sodium azide (3.4 g), and urea (0.25 g). The mixture was heated overnight at 110° under a stream of nitrogen. The cooled solution was poured into 150 ml of ice water and extracted with chloroform. The combined extracts were washed with aqueous sodium hydrogen carbonate, then with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to leave a yellow syrup (9.2 g) which appeared as one spot on a thin-layer chromatogram run in methanol:benzene, 1:9 (v/v). This syrup was crystallized from chloroform:n-hexane, ca. 1:15 (v/v), as long needles. A further recrystallization gave material of m.p. 58.5-60° and $[\alpha]_D^{21} = 44^\circ$ (c, 1.55 in methanol). The infrared spectrum in chloroform showed absorption at 3 480 cm⁻¹ attributable to OH, a doublet of approximately equal intensity at 1 382 and 1 391 cm⁻¹ caused by an azide grouping, and strong absorption at 2 115 cm⁻¹ caused by an azide group, but no aromatic absorptions.

Anal. Calcd. for C₈H₁₃O₄N₃: C, 44.64; H, 6.09; N, 19.53. Found: C, 44.66; H, 6.07; N, 19.62.

5-Acetamido-5-deoxy-1,2-O-isopropylidene-D-xylose (XVI)

To a solution of 5-azido-5-deoxy-1,2-O-isopropylidene-D-xylose (2.0 g) in methanol (60 ml) was added Raney nickel (35 g). The mixture was shaken mechanically overnight, fresh catalyst (10 g) was added, and, after it was shaken for an additional 4 h, the solution was filtered and concentrated under reduced pressure to give a crystalline product (1.1 g). This material could be readily recrystallized from ether. A sharp melting point was not obtained, however, but rather the crystals started to soften at 104° and finally melted at 107.5-109°. The substance is hygroscopic, and satisfactory analytical results were not obtained. The infrared spectrum in chloroform showed absorption at 3 350 cm⁻¹ attributable to OH and NH and absorption at 1 382 and 1 392 cm⁻¹ caused by an isopropylidene grouping, but was devoid of azide absorption.

A portion (0.95 g) of the crystalline compound obtained above was dissolved in water (7.7 ml) and treated with acetic anhydride (1.1 ml). The solution was allowed to stand for 20 min with occasional shaking, then was concentrated under reduced pressure to leave a light brown syrup (0.98 g) which crystallized on standing. Recrystallization from chloroform-hexane-ether gave rectangular plates with the same melting point and infrared spectrum as those of the previously reported (15) 5-acetamido-5-deoxy-1,2-*O*-isopropyl-idene-D-xylose.

5-Acetamido-5-deoxy-D-xylose Diethyl Dithioacetal (XVII)

5-Acetamido-5-deoxy-1,2-O-isopropylidene-D-xylose (0.4 g) was suspended in ice-cold concentrated hydrochloric acid (2.8 ml). Cold ethanethiol (2.8 ml) was then added, and the mixture was stirred in an ice-water bath for 7 h and finally left to stand in a refrigerator overnight. The mixture was then diluted with cold methanol and neutralized with lead carbonate and filtered, and the filtrate concentrated under reduced pressure to leave a clear colorless syrup which crystallized immediately (0.4 g, 78%). This material was recrystallized from methanol-ether to give white glistening crystals which had m.p. $106-107^{\circ}$, $[\alpha]_D^{23} = 0^{\circ}$ (c, 2.50 in methanol), and $R_{\rm rh} 2.3$ (solvent A, spray iii and iodine vapor). The infrared spectrum in chloroform showed absorption at 3 460 cm⁻¹ attributable to OH and NH, an amide I band at 1 662 cm⁻¹ and an amide II band at 1 525 cm⁻¹.

Anal. Calcd. for C11H23O4NS2: C, 44.4; H, 7.80; N, 4.71. Found: C 44.33; H, 7.85; N, 4.73.

Sulfone Degradation

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To a solution of 5-acetamido-5-deoxy-D-xylose diethyl dithioacetal (0.30 g) in dioxane (5 ml) was added, dropwise with shaking, peroxypropionic acid (25) (15% excess over the required 4 molar equivalents) over a period of 10 min. The solution was allowed to stand for 10 min and then cooled in ice for 1 h. The clear solution was then concentrated under reduced pressure to a syrup which was repeatedly dissolved in methanol and reconcentrated until only traces of peroxypropionic acid remained. The syrup was dried over potassium hydroxide in a desiccator to yield a colorless glass (0.38 g), the infrared spectrum (chloroform) of which showed amide bands at 1 653 and 1 545 cm⁻¹. Spray iii showed the presence of only one component at $R_{\rm rh}$ 2.02 (solvent A).

The preceding product (0.33 g) was dissolved in dilute aqueous ammonia (5 ml, pH 8–9). After 5 min the pH fell to 5 and was restored with more ammonia solution. Paper chromatography indicated that degradation was nearly complete in 5 h. The solution was allowed to stand at room temperature overnight. A small amount of a fine precipitate appeared which was removed by filtration. The pH of the filtrate was adjusted to 3–4 with dilute acetic acid, and the solution was then passed through Amberlite IR-120 (H form) and Duolite A-4 (OH form) ion exchange resins. The eluate was extracted three times with chloroform, and the combined extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield a white solid (0.087 g). After recrystallization from water this material melted at 101–102°, and showed no depression on the melting point on admixture with an authentic sample of bis-(ethylsulfonyl)-methane. The aqueous phase was concentrated under reduced pressure to leave a syrup (0.10 g) whose infrared and

n.m.r. spectra and chromatographic properties were the same as those of the product from the lead tetraacetate oxidation.

Hydrolysis of Methyl 4-Acetamido-4-deoxy-L-erythrofuranoside (I)

An aqueous solution (25 ml) of methyl 4-acetamido-4-deoxy-L-erythrofuranoside (I) (0.094 g), purified through the di-O-acetyl derivative (1), was stirred with 1 g of Amberlite IR-120 (H form) resin at 60° for 1 h. The resin was then removed by filtration, and the filtrate was shaken briefly with a small amount of Duolite A-4 (OH) form) resin to remove any trace of acid. The resin was removed, and the solution was concentrated under reduced pressure to leave an almost colorless syrup (0.075 g) which was examined on paper chromatograms. Sprays i, ii, and iii showed the presence of components at $R_{\rm rh}$ 1.00 and 1.18 (solvent A). In solvent B an elongated spot at $R_{\rm rh}$ 1.12 (possibly two spots) was detected. Two spots were detected also by thin-layer chromatography in 2-propanol:benzene, 1:2 (v/v). The syrup was reducing towards Fehling's solution and had $[\alpha]_{\rm D}^{24} = -6.6^{\circ}$ (c, 1.54 in methanol). The infrared spectrum of this material (smear between "IRTRAN-2" plates) showed strong absorption at 3 360 cm⁻¹ (OH) and a very broad band at 1 617 cm⁻¹ (N-Ac). Attempts were made to separate the two components by preparative paper chromatography using solvents A and B. The zones were located (spray i), cut, and extracted with methanol. Examination of the extracts on paper chromatograms still showed in every case the presence of the two original components.

Periodate Oxidations

The compound under examination (10-15 mg) was dissolved in water containing 0.3 M sodium metaperiodate solution (1 ml). The total volume was made up to 25 ml with additional water. A blank experiment was carried out at the same time. The oxidation was carried out in the dark and at room temperature. Formic acid yield and periodate uptake were determined in the usual fashion (26). The results are summarized in Table I.

TABLE I

Periodate oxidations

	(a) ''4-Acet	tamido-4-deox	y-D-threofura	nose''		
Time (h) Periodate (moles/mole) Formic acid (moles/mole)	$\begin{array}{c} 0.35\\ 1.08\end{array}$	$\substack{1.35\\1.24\\0.79}$	$4.92 \\ 1.39 \\ 0.93$	$9.94 \\ 1.75 \\ 1.13$	$25.1 \\ 1.74 \\ 1.51$	$76.1 \\ 1.77 \\ 2.04$
	(b) ''4-Aceta	imido-4-deoxy	-L-erythrofur	anose''		
Time (h) Periodate (moles/mole) Formic acid (moles/mole)	$0.35 \\ 1.42 \\ 0.72$	$1.28 \\ 1.60 \\ 0.97$	$5.85 \\ 1.77 \\ 1.10$	$10.8 \\ 1.70 \\ 1.25$	$\begin{smallmatrix}25.6\\1.75\\1.29\end{smallmatrix}$	74.7 1.84 1.35

6-Acetamido-6-deoxy-D-galactose Diethyl Dithioacetal (XIX)

A solution of 6-acetamido-6-deoxy-1,2;3,4-di-O-isopropylidene- α -D-galactopyranose (VIII) (7.7 g) in concentrated hydrochloric acid (45 ml) at 0 °C was stirred with ethanethiol (45 ml) for 12 h at 0 °C. The mixture was then diluted with cold methanol and neutralized with an excess of lead carbonate. The solution was filtered and concentrated under reduced pressure to a volume of about 100 ml, whereupon a white crystalline material separated from solution (5.0 g). This solid was recrystallized from methanol-ether to give crystalwhich had m.p. 182.5–184°, $[\alpha]_D = +16.6°$ (c, 1.00 in methanol), and R_{rh} 2.18 (solvent A, spray iii, and iodine vapor). The infrared spectrum (Nujol mull) showed strong absorption at 3 270 cm⁻¹ attributable to OH and NH, and amide I band at 1 645 cm⁻¹ and an amide II band at 1 564 cm⁻¹.

Anal. Calcd. for C₁₂H₂₅O₅NS₂: C, 44.0; H, 7.64; N, 4.28. Found: C, 44.2; H, 7.82; N, 4.68.

6-Acetamido-2,3,4,5-tetra-O-acetyl-6-deoxy-D-galactose Diethyl Dithioacetal (XX)

A solution of 6-acetamido-6-deoxy-D-galactose diethyl dithioacetal (4.7 g) in dry pyridine (100 ml) was cooled in an ice-water bath and treated with acetic anhydride (28 ml). The clear colorless solution was left to stand in a refrigerator for 22 h, then at room temperature for 1 h and poured into ice water (800 ml), and the mixture extracted several times with chloroform. The combined extracts were washed with water, then shaken with an aqueous solution of cadmium chloride. The pyridine – cadmium chloride complex was filtered, and the chloroform solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to leave a white crystalline material (6.9 g, 97%). Two recrystallizations from methanol-water gave crystals which melted at 131°, and had $[\alpha]_D = 84°$ (c, 1.73 in chloroform containing 0.75% ethanol). The infrared spectrum in chloroform showed *NH* stretching vibration at 3 430 cm⁻¹, absorption at 1 743 cm⁻¹ caused by *O*-acetyl groups, an amide I band at 1 675 cm⁻¹, and an amide II band at 1 520 cm⁻¹.

Anal. Calcd. for C₂₀H₃₃O₉NS₂: C, 48.48; H, 6.71. Found: C, 48.36; H, 6.53.

Demercaptalation of 6-A cetamido-2,3,4,5-tetra-O-acetyl-6-deoxy-D-galactose Diethyl Dithioacetal

6-Acetamido-2,3,4,5-tetra-0-acetyl-6-deoxy-D-galactose diethyl dithioacetal (1 g) was dissolved in acetone (14 ml). Water (6 ml) and an excess (2 g) of cadmium carbonate were added, and under rapid stirring a

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solution of mercuric chloride (1.96 g, 3.6 moles) in acetone (8 ml) was gradually added. Stirring was maintained at room temperature for 24 h with occasional additions of cadmium carbonate. The solution was then filtered, an excess of fresh cadmium carbonate being placed in the suction flask, and the precipitate was washed with acetone. The filtrate and washings were then concentrated under reduced pressure (water bath temperature 35°) and in the presence of excess cadmium carbonate. The residue was extracted several times with warm chloroform; the combined extracts were then cooled and filtered. The chloroform filtrate was washed with water, with aqueous solution of potassium iodide and again with water. The chloroform solution was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to leave a thick syrup (0.35 g). Thin-layer chromatography of this material in 2-propanol: benzene, 1:2 (v/v), showed an elongated spot (possibly two spots) which moved at a slower rate than the starting material. The syrupy product crystallized on contact with ether. The ether was evaporated and the crude product was dissolved in acetone: ether, 2:1 (v/v); hexane was then added to opalescence. The crystals (XXI) which separated (0.10 g) reduced Fehling's solution on heating and migrated as a single spot with slight tailing on a thin-layer chromatogram. The mother liquors had trace quantities of two faster moving components. The crystals did not melt sharply, but rather started to soften at 90° and finally melted at 116°. The infrared spectrum (Nujol mull) showed strong absorption at 3 400 cm⁻¹ attributable to OH, absorption at 1 753 cm⁻¹ caused by O-acetyl groups, an amide I band at 1 663 cm⁻¹, and an amide II band at 1 553 cm⁻¹.

Attempted Cyclization of XXI

The preceding product XXI (0.072 g) was allowed to stand in dry pyridine (5 ml) for 24 h at room temperature. In a few hours the solution assumed a yellow color and finally darkened to orange. The solution was then cooled in an ice bath and treated with acetic anhydride (0.75 ml). After 1 h at 0° and at room temperature overnight, the solution was poured into ice water, and the product extracted with chloroform. The extract was washed with water, then shaken with an aqueous solution of cadmium chloride. The pyridine - cadmium chloride complex was filtered off, the chloroform filtrate washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to leave a slight brown syrup (0.026 g). This material was distilled under vacuum to yield a yellow syrup. Thin-layer chromatography in 2-propanol:benzene, 1:2 (v/v), showed the presence of only one component which migrated faster than XXI. The infrared spectrum in chloroform showed weak absorption at 3525 cm⁻¹ attributable to NH stretching vibrations, strong absorption at 1 757 cm⁻¹ caused by O-acetyl groups, an amide I band at 1 685 cm⁻¹, and an amide II band at 1 528 cm⁻¹.

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