Synthesis of 2-amino-2-deoxy-D-talose and 2-amino-2-deoxy-D-galactose[1]

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Treatment of D-lyxose with nitromethane in the presence of sodium methoxide gave 1-deoxy-1-nitro-D-galactitol which, after conversion to 2,3,4,5,6-penta-*O*-acetyl-1-deoxy-1-nitro-D-galactitol, reacted with saturated methanolic ammonia solution to yield 2-acetamido-1,2-dideoxy-1-nitro-D-talitol and 2-acetamido-1,2-dideoxy-1-nitro-D-galactitol. 2-Acetamido-1,2-dideoxy-1-nitro-D-talitol and 2-acetamido-1,2-dideoxy-1-nitro-D-galactitol were converted by a modified Nef reaction to 2-acetamido-2-deoxy-D-talose and 2-acetamido-2-deoxy-D-galactose which on hydrolysis with hydrochloric acid afforded 2-amino-2-deoxy-D-talose hydrochloride and 2-amino-2-deoxy-D-galactose hydrochloride. The properties and derivatives of the aminoglycoses are described.

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The increasing importance of aminoglycoses as components of biological systems and the frequent occurrence of new compounds in microbial products have, in connection with the work of this laboratory, made it desirable to have available many aminoglycoses and their derivatives for use as reference standards and as biological substrates. We have prepared six 2-amino-2-deoxy-D-aldohexoses from D-ribose, D-xylose, and D-lyxose by treatment of the aldopentoses with nitromethane to yield 1-deoxy-1-nitrohexitols (1). This was followed by treatment of the derived penta-*O*-acetyl-1-deoxy-1-nitrohexitols or corresponding 3,4,5,6-tetraacetoxy-1-nitro-1-hexenes with ammonia to yield epimeric pairs of 2-acetamido-1,2-dideoxy-1-nitrohexitols which were converted to 2-acetamido-2-deoxyhexoses *via* the Nef (2) reaction. The method has been previously applied to two aldopentoses; 2-amino-2-deoxyglucose and 2-amino-2-deoxymannose were obtained from arabinose (3–6) and 2-amino-2-deoxy-D-gulose was obtained from D-xylose (7). This paper records the successful application of the synthetic method to D-lyxose to prepare 2-amino-2-deoxy-D-talose and 2-amino-2-deoxy-D-galactose.

2-Amino-2-deoxy-D-galactose may be obtained from chondroitin sulfate (8–11). It may be synthesized from D-lyxose by reduction of 2-amino-2-deoxy-D-galactononitrile prepared by the addition of hydrogen cyanide to 1-amino-1-deoxy-D-lyxose (D-lyxosylamine) (12), and by a method involving addition of ammonia to 2,3:1,6-dianhydro-β-D-talopyranose (13). 2-Amino-2-deoxy-D-talose has been synthesized from D-lyxose by the action of aniline (14), or 9-aminofluorene (15) and hydrogen cyanide, followed by reduction of the product having the D-talo configuration, and from 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-idopyranoside by Walden inversion of its 3-*O*-(methylsulfonyl) derivative and subsequent hydrolysis (16). Recently, Lemieux and coworkers (17, 18) have synthesized 2-amino-2-deoxy-D-galactose and 2-amino-2-deoxy-D-talose from tri-*O*-acetyl-D-galactal by reactions involving the addition of nitrosyl chloride, followed by conversion of the adduct to the acetylated 2-oximinohexose and reduction of the oxime to amine.

In the present work D-lyxose was condensed with nitromethane in the presence of sodium methoxide and the resulting precipitated sodium salts of 1-deoxy-1-nitro-D-galactitol (96%) and 1-deoxy-1-nitro-D-talitol (4%) were deionized with hydrogen form ion-exchange resin to remove sodium, and the product afforded pure 1-deoxy-1-nitro-D-galactitol. The 1-deoxy-1-nitro-D-galactitol gave only D-galactose with sulfuric acid (2). The optical rotary dispersion (o.r.d.) curve for the 1-deoxy-1-nitro-D-galactitol showed a positive Cotton effect centered at 310 mμ in agreement with the rules proposed by Satoh, Kiyomoto, and Okuda (19, 20) for *C*-nitro glycitols which stated that derivatives having groups at C-2 in the S-configuration show positive Cotton effects in the 310 mμ region.

The 2,3,4,5-penta-*O*-acetyl-1-deoxy-1-nitro-D-galactitol obtained on acetylation of the 1-deoxy-1-nitro-D-galactitol with saturated methanolic ammonia (6) afforded a mixture of

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2-acetamido-1,2-dideoxy-1-nitro-D-talitol and 2-acetamido-1,2-dideoxy-1-nitro-D-galactitol which were separated in pure form by fractional crystallization from ethanol solution. The o.r.d. curves for the compounds showed a positive Cotton effect for the 2-acetamido-1,2-dideoxy-1-nitro-D-galactitol and a negative Cotton effect for the 2-acetamido-1,2-dideoxy-1-nitro-D-talitol, both centered about 310 mμ, in agreement with the proposed rules of Satoh *et al.* (19, 20).

The 2-acetamido-1,2-dideoxy-1-nitrohexitols were treated separately with barium hydroxide solution and on treatment with 5 *N* sulfuric acid (6) gave the corresponding derivatives 2-acetamido-2-deoxy-D-talose and 2-acetamido-2-deoxy-D-galactose. Under the mild conditions used to effect the Nef reaction (2) it was observed that the D-talose derivative was hydrolyzed in part to the free aminoglycose and the product was therefore treated with aqueous acetic anhydride in the presence of basic ion-exchange resin to reconvert it to the *N*-acetyl derivative.

The 2-acetamido-2-deoxy-D-talose and 2-acetamido-2-deoxy-D-galactose obtained in the above synthesis had chemical and physical properties identical with those of authentic glycoses. The 2-acetamido-2-deoxyglycoses were each hydrolyzed with hot dilute hydrochloric acid to yield 2-amino-2-deoxy-D-talose hydrochloride and 2-amino-2-deoxy-D-galactose hydrochloride. Reduction of the 2-acetamido-2-deoxyglycoses with aqueous sodium borohydride afforded crystalline 2-acetamido-2-deoxy-D-talitol and 2-acetamido-2-deoxy-D-galactitol in good yield, and the glycitols appear to be convenient derivatives for the characterization of the aminoglycoses.

The synthesis of the aminoglycoses from 2,3,4,5,6-penta-*O*-acetyl-1-deoxy-1-nitro-D-galactitol as described above, but without the isolation of intermediates, afforded a mixture of the 2-acetamido-2-deoxyglycoses which were separated by cellulose column chromatography to yield pure 2-acetamido-2-deoxy-D-talose and 2-acetamido-2-deoxy-D-galactose in 41% and 28% yield respectively from D-lyxose. The preparative method provides a convenient three-step procedure for the synthesis of 2-acetamido-2-deoxy-D-talose and 2-acetamido-2-deoxy-D-galactose in good yield and provides a method for the synthesis of the 1-^{14}C aminoglycoses by condensation of D-lyxose with $^{14}CH_3NO_2$.

Experimental

Paper chromatography was performed by the descending method (21) on Whatman No. 1 filter paper using pyridine – ethyl acetate – water (2:5:5 v/v, top layer) as the mobile phase. Glycose derivatives were detected with either 1% silver nitrate in acetone, followed by 2% sodium hydroxide in ethanol (22), or by 2% *p*-anisidine hydrochloride in butan-1-ol (23). The rates of movement of the glycoses on the paper chromatograms are quoted relative to D-galactose (R_{Gal}).

Gas–liquid partition chromatography was carried out at 200 °C using a Hewlett–Packard model 402 chromatograph with a hydrogen flame detector and fitted with glass U tubes (4 ft × 6 mm × 3 mm internal diameter) packed with 10% neopentylglycol sebacate polyester on 80–100 mesh acid-washed Chromosorb W. Retention times of the compounds are quoted relative to 2-acetamido-2-deoxy-1,3,4,5,6-penta-*O*-(trimethylsilyl)-D-glucitol (T_{GN}) (24).

Melting points were determined on a Fisher–Johns apparatus and are corrected. Solutions were concentrated under reduced pressure, below 40 °C.

Optical rotations were determined at 20 °C using a Perkin–Elmer 141 polarimeter. Optical rotary dispersion (o.r.d.) measurements were made using a JASCO model ORD/UV-5 automatically recording spectropolarimeter.

2-Amino-2-deoxy-D-talose and 2-Amino-2-deoxy-D-galactose

1-Deoxy-1-nitro-D-galactitol

To a suspension of D-lyxose (10 g) in absolute methanol (50 ml) and nitromethane (50 ml), contained in a 500 ml flask, was added a solution of sodium (2.2 g) in absolute methanol (75 ml), and the mixture was shaken at room temperature for 24 h. Following the addition of ether (60 ml), the precipitated product was collected by filtration, washed with cold methanol, ether, and light petroleum (b.p. 30–60 °C) and dried under vacuum. The product was dissolved in cold water (200 ml) and passed down a column of Rexyn 101 (H^+) ion-exchange resin (200 ml) and the eluate and water washings were concentrated to a syrup. This was dissolved in hot methanol (50 ml) and on keeping at 5 °C successive crops of crystalline 1-deoxy-1-nitro-D-galactitol (12.2 g), m.p. 141 °C were collected. After three recrystallizations from methanol pure 1-deoxy-1-nitro-D-galactitol had m.p. 143 °C; $[\alpha]_D$ +1.7 ° (*c*, 0.8 in water); o.r.d. (*c*, 0.3 in water) $[\phi]_{342-344}$ + 833 °.[2]

Anal. Calcd. for $C_6H_{13}O_7N$: C, 34.13; H, 6.21; N, 6.63. Found: C, 33.9; H, 5.94; N, 6.6.

A portion of the 1-deoxy-1-nitro-D-galactitol (0.2 g) was dissolved in 2 *N* sodium hydroxide (2 ml) and the solution was added dropwise to 6 *N* sulfuric acid (2.5 ml) at 0 °C. After 2 h at room temperature the mixture was diluted with water (10 ml) and neutralized ($BaCO_3$). The filtered solution was passed down Rexyn 101 (H^+)

[2]The molecular rotation $[\phi]$ is defined by $[\phi] = \frac{[\alpha]M}{100} = \frac{M\alpha_r Sc}{cl}$ where α_r is the reading of the rotation in degrees, M is the molecular weight, *c* is the concentration in g per 100 ml of solution, *l* is the path length in dm, and Sc is the scale setting.

(4 ml) and Rexyn RG6 (OH^-) (4 ml) ion-exchange resins and the eluate and washings were concentrated to a syrup (150 mg). Paper chromatographic examination of the product showed a single spot corresponding to galactose and from ethanol solution crystalline D-galactose (90 mg) having m.p. and mixture m.p. 170 °C and $[\alpha]_D$ +80 ° (*c*, 0.5 in water) was obtained.

2,3,4,5,6-Penta-O-acetyl-1-deoxy-1-nitro-D-galactitol

1-Deoxy-1-nitro-D-galactitol (10 g) in acetic anhydride (90 ml) was treated with two drops of concentrated sulfuric acid and the mixture was heated for 40 min on a boiling water bath. The cooled reaction mixture was poured into an ice and water mixture (500 ml), and the product was extracted with chloroform in the usual way. After removal of the solvent the residual syrup was dissolved in hot methanol (50 ml) and on cooling crystalline 2,3,4,5,6-penta-*O*-acetyl-1-deoxy-1-nitro-D-galactitol (15.8 g) having m.p. 130 °C was obtained. After three recrystallizations from methanol the product had m.p. 130 °C and $[\alpha]_D$ +6° (*c*, 1.5 in chloroform).

Anal. Calcd. for $C_{16}H_{23}O_{12}N$: C, 45.62; H, 5.50; N, 3.32. Found: C, 45.43; H, 5.3; N, 3.3.

2-Acetamido-1,2-dideoxy-1-nitro-D-talitol and 2-Acetamido-1,2-dideoxy-1-nitro-D-galactitol

2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-nitro-D-galactitol (12 g) dissolved in absolute methanol (140 ml), was cooled to 0 °C, and anhydrous ammonia gas was passed into the solution for 1 h. The saturated solution was then allowed to stand for 18 h at room temperature. The reaction mixture was concentrated to a syrup which was triturated with hot chloroform (3 × 100 ml) to remove acetamide. The light-brown syrup remaining was dissolved in hot ethanol, treated with charcoal, filtered, and after concentration to about 60 ml, was kept at 5 °C. Successive crops of 2-acetamido-1,2-dideoxy-1-nitro-D-talitol (3.9 g) were first obtained. After two recrystallizations from ethanol these gave a product (3.2 g), m.p. 158 °C; $[\alpha]_D$ +20 ° (*c*, 1.8 in water); o.r.d. (*c*, 0.3 in water) $[\phi]_{344-348}$ −288 °.

Anal. Calcd. for $C_8H_{16}O_7N_2$: C, 38.10, 6.39; N, 11.11. Found: C, 38.3; H, 6.5; N, 11.1.

Following the removal of the 2-acetamido-1,2-dideoxy-1-nitro-D-talitol, concentration of the mother liquors and cooling to 2 °C yielded 2-acetamido-1,2-dideoxy-1-nitro-D-galactitol (2.0 g), which after two recrystallizations from ethanol gave the pure compound (1.7 g), m.p. 168 °C; $[\alpha]_D$ −25.7 ° (*c*, 1 in water); o.r.d. (*c*, 0.3 in water) $[\phi]_{348-350}$ +277 °.

Anal. Calcd. for $C_8H_{16}O_7N_2$: C, 38.10; H, 6.39; N, 11.11. Found: C, 37.6; H, 6.5; N, 11.0.

2-Acetamido-2-deoxy-D-talose

2-Acetamido-1,2-dideoxy-1-nitro-D-talitol (3 g) was dissolved in a solution of $Ba(OH)_2 \cdot 8H_2O$ (3.7 g) in water (60 ml) and the solution was added dropwise to a cooled, stirred solution of concentrated sulfuric acid (3.4 ml) in water (35 ml). The mixture was stirred for 4 h at 20 °C and was then left at 24 °C for 18 h. The reaction mixture was neutralized with barium carbonate, the filtered solution was concentrated to about 50 ml, and following the addition of Dowex-1 ($CO_3^=$) ion-exchange resin (30 ml), methanol (10 ml), and acetic anhydride (0.4 ml), the mixture was shaken for 20 min. The filtered solution, after passage down columns of Rexyn 101 (H^+) (10 ml) and Rexyn RG6 (OH^-) (10 ml) ion-exchange resins, was concentrated to a syrup (2.1 g) which on paper chromatographic analysis, showed a single spot (R_{Gal} 1.92), having the same mobility as authentic 2-acetamido-2-deoxy-D-talose. The syrup, which could not be induced to crystallize had, $[\alpha]_D$ −8.8 ° (*c*, 2 in water) (lit. $[\alpha]_D$ −11 ° (16)).

Anal. Calcd. for $C_8H_{15}O_6N$: C, 43.44; H, 6.82; N, 6.33. Found: C, 43.22; H, 6.9; N, 6.3.

The fully trimethylsilylated (24) 2-acetamido-2-deoxy-D-talose on gas–liquid partition chromatography showed three peaks having T_{GN} 0.85, 1.04, and 1.66.

2-Amino-2-deoxy-D-talose Hydrochloride

2-Acetamido-2-deoxy-D-talose (0.5 g) in 2 *N* hydrochloric acid (15 ml) was heated on a boiling water bath for 2 h and then concentrated to dryness. The residue was co-distilled with ethanol and benzene to remove the last trace of water and acetic acid, and on keeping the product moistened with a little ethanol, it gave crystalline 2-amino-2-deoxy-D-talose hydrochloride (0.37 g) which had m.p. 150 °C (decomposed) and $[\alpha]_D$ −6 ° (*c*, 1.5 in water).

Anal. Calcd. for $C_6H_{14}O_5$ NCl; C, 33.26; H, 6.84; Cl, 16.44. Found: C, 33.0; H, 6.8; Cl, 16.5.

Paper chromatographic analysis of the 2-amino-2-deoxy-D-talose hydrochloride revealed a single spot having R_{Gal} 0.56.

2-Acetamido-2-deoxy-D-talitol

2-Acetamido-2-deoxy-D-talose (0.2 g) in water (5 ml) was reduced by the addition of sodium borohydride (80 mg), and after 2 h at room temperature, the excess borohydride was destroyed by the addition of acetic acid. The reaction mixture was passed down a column of Rexyn 101 (H^+) ion-exchange resin (5 ml) and the concentrated eluate and washings were repeatedly evaporated with absolute methanol to remove boric acid. The final residue was taken up in hot methanol (2–3 ml) and filtered. On cooling the methanol solution, crystalline 2-acetamido-2-deoxy-D-talitol (0.17 g) was obtained, which after two recrystallizations from methanol had m.p. 153 °C and $[\alpha]_D$ +33 ° (*c*, 0.8 in water).

Anal. Calcd. for $C_8H_{17}O_6N$: C, 43.05; H, 7.68; N, 6.27. Found: C, 42.9; H, 7.8; N, 6.2.

On paper chromatographic analysis the 2-acetamido-2-deoxy-D-talitol gave a single spot having R_{Gal} 1.30.

2-Acetamido-2-deoxy-D-galactose

2-Acetamido-1,2-dideoxy-1-nitro-D-galactitol (1.7 g) was converted to 2-acetamido-2-deoxy-D-galactose (1.2 g) using the conditions described above for the conversion of 2-acetamido-1,2-dideoxy-1-nitro-D-talitol to 2-acetamido-2-deoxy-D-talose. The 2-acetamido-2-deoxy-D-galactose, obtained crystalline from ethanol–water mixture, gave a single spot on paper chromatograms with R_{Gal} 1.43 and had m.p. and mixture m.p. 110 °C and $[\alpha]_D$ +84 ° (*c*, 2 in water). The trimethylsilylated (24) derivative on gas–liquid partition chromatography gave a single peak (T_{GN} 1.72) having the same retention time as an authentic sample of trimethylsilyl 2-acetamido-2-deoxy-3,4,5-tri-*O*-(trimethylsilyl)-α-D-galactopyranoside.

2-Amino-2-deoxy-D-galactose Hydrochloride

2-Acetamido-2-deoxy-D-galactose (0.3 g) after hydrolysis with 2 *N* hydrochloric acid for 2 h at 100 °C, afforded crystalline 2-amino-2-deoxy-D-galactose hydrochloride (0.21 g), having $[\alpha]_D$ +124° → +94° (*c*, 1.2 in water).

Anal. Calcd. for $C_6H_{14}O_5NCl$: C, 33.26; H, 6.84; Cl, 16.44. Found: C, 33.1; H, 6.7; Cl, 16.4.

On paper chromatography the 2-amino-2-deoxy-D-galactose hydrochloride gave a single spot having R_{Gal} 0.43.

2-Acetamido-2-deoxy-D-galactitol

2-Acetamido-2-deoxy-D-galactose (0.2 g) on borohydride reduction gave 2-acetamido-2-deoxy-D-galactitol (0.17 g), having m.p. and mixture m.p. 174 °C and $[\alpha]_D$ −44 ° (*c*, 0.5 in water) (25). On paper chromatography the derivative gave a single spot having R_{Gal} 1.96.

Anal. Calcd. for $C_8H_{17}O_6N$: C, 43.05; H, 7.68; N, 6.27. Found: C, 43.0; H, 7.6; N, 6.15.

Direct Synthesis of 2-Acetamido-2-deoxy-D-talose and 2-Acetamido-2-deoxy-D-galactose

2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-nitro-D-galactitol (10 g) was treated with methanolic ammonia as described above and the product was treated with sulfuric acid to convert the mixed resulting 2-acetamido-1,2-dideoxy-1-nitrohexitols to the corresponding 2-acetamido-2-deoxy-D-hexoses. These were separated on a cellulose column (4.5 × 40 cm) using butan-1-ol half-saturated with water as the mobile phase (26) and yielded chromatographically pure 2-acetamido-2-deoxy-D-galactose (1.9 g) and 2-acetamido-2-deoxy-D-talose (2.9 g).

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1. J. C. SOWDEN. Advan. Carbohydrate Chem. **6**, 315 (1951).
2. J. U. NEF. Ann. Chem. **280**, 263 (1894).
3. A. N. O'NEILL. Can. J. Chem. **37**, 1747 (1959).
4. J. C. SOWDEN and M. L. OFTEDAHL. J. Am. Chem. Soc. **82**, 2303 (1960).
5. S. D. GERO and J. DEFAYE. Compt. Rend. **261**, 1555 (1965).
6. C. SATOH and A. KIYOMOTO. Chem. Pharm. Bull. Tokyo, **12**, 615 (1964).
7. J. C. SOWDEN and M. L. OFTEDAHL. J. Org. Chem. **26**, 2153 (1961).
8. P. KARRER and J. MAYER. Helv. Chim Acta, **20**, 407 (1937).
9. M. STACEY. J. Chem. Soc. 272 (1944).
10. S. GARDELL. Acta Chem. Scand. **5**, 195 (1951).
11. M. L. WOLFROM and K. ONODERA. J. Am. Chem. Soc. **79**, 4737 (1957).
12. R. KUHN and W. KIRSCHENLOHR. Ann. Chem. **600**, 126 (1956).
13. S. P. JAMES, F. SMITH, M. STACEY, and L. F. WIGGINS. J. Chem. Soc. 625 (1946).
14. R. KUHN and H. FISCHER. Ann. Chem. **612**, 65 (1958).
15. R. KUHN and J. C. JOCHIMS. Ann. Chem. **641**, 143 (1961).
16. R. W. JEANLOZ, Z. T. GLAZER, and D. A. JEANLOZ. J. Org. Chem. **26**, 532 (1961).
17. R. U. LEMIEUX and T. L. NAGABHUSHAN. Tetrahedron Letters, **26**, 2143 (1965).
18. R. U. LEMIEUX and T. L. NAGABHUSHAN. Can. J. Chem. **46**, 401 (1968).
19. C. SATOH and A. KIYOMOTO. Carbohydrate Res. **3**, 248 (1966).
20. C. SATOH, A. KIYOMOTO, and T. OKUDA. Carbohydrate Res. **5**, 140 (1967).
21. S. M. PARTRIDGE. Biochem. J. **42**, 238 (1948).
22. W. E. TREVELYAN, D. D. PROCTER, and J. S. HARRISON. Nature, **166**, 444 (1950).
23. L. HOUGH, J. K. N. JONES, and W. H. WADMAN. J. Chem. Soc. 1702 (1950).
24. M. B. PERRY. Can. J. Biochem. **42**, 451 (1964).
25. W. R. C. CRIMMIN. J. Chem. Soc. 2838 (1957).
26. L. HOUGH, J. K. N. JONES, and W. H. WADMAN. J. Chem. Soc. 2511 (1949).