4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-D-talopyranose Hydrochloride[1,2]

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Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**1**) was converted into methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranosid-4-ulose (**2**) *via* a dimethyl sulfoxide–phosphorus pentoxide oxidation. Reaction of the 4-ketose derivative with hydroxylamine hydrochloride followed by lithium aluminum hydride reduction and *N*-acetylation afforded methyl 4-acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**9**) in high yield. The reduction was stereospecific since less than 2% of the C-4 epimer having the *manno* configuration could be isolated. The major isomer was converted into a number of *N*-substituted derivatives including the crystalline α and β isomers of the title compound, 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-D-talopyranose hydrochloride (**23** and **24**). Molecular rotations, nmr spectra, mixture melting point determinations, mass spectral data, X-ray crystallographic data, and degradation studies unambiguously confirm the assigned structures.

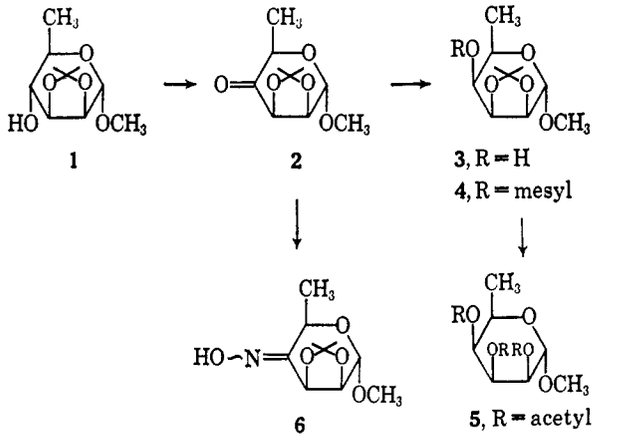
A rearrangement of 6-deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-mannopyranoside and related sulfonate esters recently was discovered in our laboratory. Under conditions expected to give normal displacement products with a variety of nucleophiles the sulfonate ester yielded ring-contracted products.[3-5] Accordingly, other routes to the D-*talo*, as well as the D-*manno* configurations were sought. One such reaction sequence involves the preparation of a suitably protected 4-oximino derivative of a hexos-4-ulose which could then be reduced to one or both of the 4-amino sugars having the D-*talo* and D-*manno* configurations depending on the stereochemistry of the reduction step. The synthesis of these potentially biologically interesting 4-amino-4,6-dideoxy sugar derivatives[6] forms the basis of this paper.[7]

Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**1**), readily available from our earlier work,[3] served as the starting material for the preparation of ketone **2**. The oxidation of the enantiomer of compound **1** had been reported earlier by Collins and Overend[8,9] using chromium trioxide–pyridine. Also, the crystalline triacetate **5** was described.[8,9] Recently, Jones, *et al.*,[10] have reported the same conversion using ruthenium tetroxide. In our hands, the chromium trioxide–pyridine reaction of Collins and Overend was time consuming, requiring five successive treatments to give a 30% yield of 91% pure 4-keto derivative **2**.

A modification of a recently reported phosphorus pentoxide–dimethyl sulfoxide procedure[11] was evaluated and gave good results. Thus compound **1** was oxidized smoothly with phosphorus pentoxide in a dimethyl sulfoxide–pyridine mixture to yield ketone **2** (96% purity by vpc analysis) in 81% yield (Scheme I), identical with the product obtained from the reported chromium trioxide oxidation. Compound **2** was reduced stereoselectively by sodium borohydride in methanol to yield **3**, the C-4 epimer of compound **1**, in 85% yield. The *talo* derivative **3** (90% purity) was contaminated with 2% of **1** and 8% of an unknown impurity. Compound **3** was converted into the crystalline triacetate **5** in 53% over-all yield by selective hydrolysis of the 2,3-*O*-isopropylidene bridge followed by acetylation with acetic anhydride in pyridine. The physical constants of triacetate **5** were in agreement with those reported for its enantiomer.[8,9] Compound **3** was also converted into its crystalline mesylate **4** in 73% yield by mesylation in pyridine. With these results in hand, ketone **2** was converted into its crystalline oxime derivative **6** in 64% yield. The nmr spectrum of the oxime (Figure 1) is in agreement with the proposed structure. The oxime **6** was reduced with

SCHEME I

PREPARATION OF DERIVATIVES OF METHYL 6-DEOXY-2,3-*O*-ISOPROPYLIDENE-α-D-*lyxo*-PYRANOSID-4-ULOSE (**2**)



(1) This research was supported by the National Institutes of Health, Grant GM 11520, and the Michigan Cancer Foundation.

(2) Preliminary results of this work have been presented earlier (C. L. Stevens, R. P. Glinski, and K. G. Taylor, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Abstract D16).

(3) C. L. Stevens, R. P. Glinski, K. G. Taylor, P. Blumbergs, and F. Sirokman, *J. Amer. Chem. Soc.*, **88**, 2073 (1966).

(4) C. L. Stevens, R. P. Glinski, G. Gutowski, and J. P. Dickerson, *Tetrahedron Lett.*, 649 (1967).

(5) S. Hannesian, *Chem. Commun.*, No. 21, 796 (1966).

(6) (a) C. L. Stevens, P. Blumbergs, F. A. Daniher, J. Strominger, M. Matsuhashi, D. Dietzler, S. Suzuki, T. Okazaki, K. Sugimoto, and R. Okazaki, *J. Amer. Chem. Soc.*, **86**, 2939 (1964); (b) C. L. Stevens, P. Blumbergs, and F. A. Daniher, *ibid.*, **85**, 1552 (1963); (c) R. W. Wheat, E. L. Rollins, and J. M. Leatherwood, *Biochem. Biophys. Res. Commun.*, **9**, 120 (1962); (d) C. L. Stevens, P. Blumbergs, D. Otterbach, J. Strominger, M. Matsuhashi, and D. Dietzler, *J. Amer. Chem. Soc.*, **86**, 2937 (1964); (e) C.-H. Lee and C. P. Schaffner, *Tetrahedron Lett.*, 5837 (1966); (f) C. L. Stevens, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstract D23. This reference described the importance of 4-amino-4,6-dideoxy sugars in biological systems as well as an improved method of degradation of 4-acetamido-4,6-dideoxy sugars to D- and L-threoninol and D- and L-allothreoninol oxalates. More detailed results will be published elsewhere.

(7) Dr. J. Jarý has indicated in a private communication and he and his co-workers have successfully prepared derivatives of methyl 4-amino-4,6-dideoxy-L-talopyranoside by a different route. NOTE ADDED IN PROOF.—This work has since appeared [J. Jarý, P. Novak, Z. Ksandr, and Z. Samek, *Chem. Ind.* (London), 1490 (1967)]; also *cf.* S. W. Gunner, W. G. Overend, and N. R. Williams, *Carbohyd. Res.*, **4**, 498 (1967).

(8) P. M. Collins and W. G. Overend, *Chem. Ind.* (London), 374 (1963).

(9) P. M. Collins and W. G. Overend, *J. Chem. Soc.*, 1912 (1965).

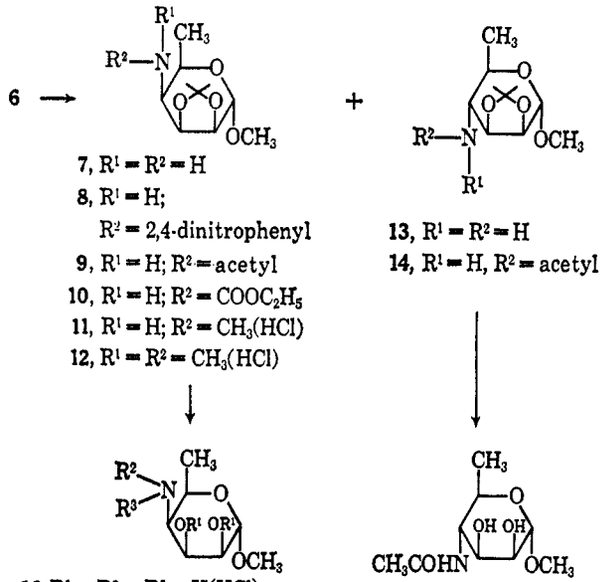
(10) U. M. Parikh and J. K. N. Jones, *Can. J. Chem.*, **43**, 3452 (1965).

(11) K. Onodera, S. Kirano, and N. Kashimura, *J. Amer. Chem. Soc.*, **87**, 4651 (1965).

excess lithium aluminum hydride in refluxing tetrahydrofuran to afford, in 95% yield, methyl 4-amino-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**) as an oil containing a small amount of the D-*manno* isomer **13** (Scheme II). The crude mixture was converted into

SCHEME II

METHYL 4-ACETAMIDO-4,6-DIDEOXY-α-D-MANNOPYRANOSIDE (14), METHYL 4-AMINO-4,6-DIDEOXY-α-D-TALOPYRANOSIDE HYDROCHLORIDE (16), AND DERIVATIVES



7, $R^1 = R^2 = H$
8, $R^1 = H$; R^2 = 2,4-dinitrophenyl
9, $R^1 = H$; R^2 = acetyl
10, $R^1 = H$; $R^2 = COOC_2H_5$
11, $R^1 = H$; $R^2 = CH_3(HCl)$
12, $R^1 = R^2 = CH_3(HCl)$
13, $R^1 = R^2 = H$
14, $R^1 = H$, R^2 = acetyl
15
16, $R^1 = R^2 = R^3 = H(HCl)$
17, $R^1 = R^2 = H$; R^3 = acetyl
18, $R^1 = R^2$ = acetyl; $R^3 = H$
19, $R^1 = H$; $R^2 = R^3 = CH_3$(picric acid)
20, $R^1 = H$; $R^2 = R^3 = CH_3(CH_3I)$
21, R^1 = acetyl; $R^2 = R^3 = CH_3$
22, R^1 = acetyl; $R^2 = R^3 = CH_3(HCl)$

the *N*-acetyl derivatives **9** and **14**. By crystallization, pure D-*talo*-4-acetamido derivative **9** was obtained in 66% yield. The mother liquor was subjected to preparative thin layer chromatography to yield an additional 5% of the D-*talo* compound **9**, as well as 1.3% of a new *N*-acetyl derivative **14** having an infrared spectrum (chloroform) very similar to that of compound **9**. The configuration of this component **14** was established as D-*manno;* selective hydrolysis of the 2,3-*O*-isopropylidene protecting group yielded methyl 4-acetamido-4,6-dideoxy-α-D-mannopyranoside (**15**). A mixture melting point of this product with compound **15** obtained by another route,[6f] similar to that reported by Jarý, Čapek, and Kovář,[12] was undepressed and the infrared spectra of both compounds were identical. Crude amine **7** was converted into the crystalline 4-(2,4-dinitroanilino) derivative **8** in 67% yield by the method of Lloyd and Stacey.[13]

Selective hydrolysis of the 2,3-*O*-isopropylidene group of crude **7** and the *N*-acetyl derivative **9** with dilute aqueous hydrochloric acid afforded methyl 4-amino-4,6-dideoxy-α-D-talopyranoside hydrochloride (**16**) in 63% yield and methyl 4-acetamido-4,6-dideoxy-α-D-talopyranoside (**17**) in 59% yield. A mixture melting point of compound **17** with methyl 4-acetamido-4,6-dideoxy-α-D-mannopyranoside (**15**) was

(12) J. Jarý, K. Čapek, and J. Kovář, *Collect. Czech. Chem. Commun.*, **28**, 2171 (1963).
(13) P. F. Lloyd and M. Stacey, *Tetrahedron*, **9**, 116 (1960).

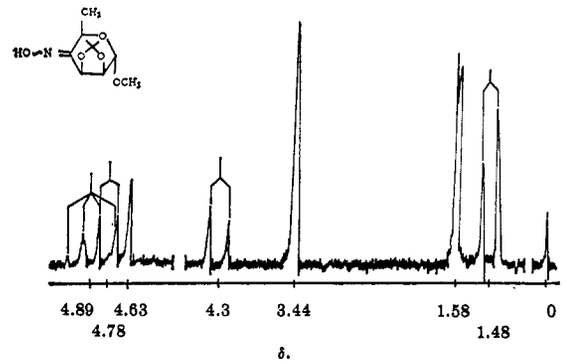


Figure 1—Nmr spectrum of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranosid-4-ulose oxime (**6**).

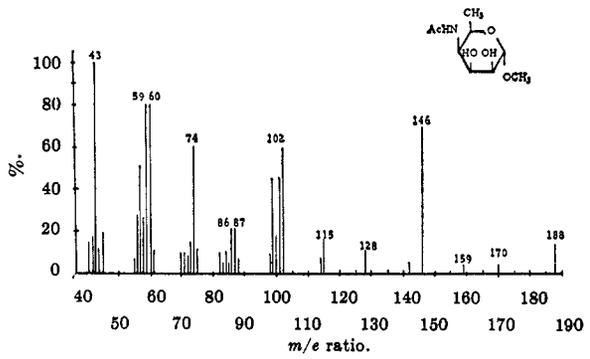


Figure 2—Mass spectrum of methyl 4-acetamido-4,6-dideoxy-α-D-talopyranoside (**17**).

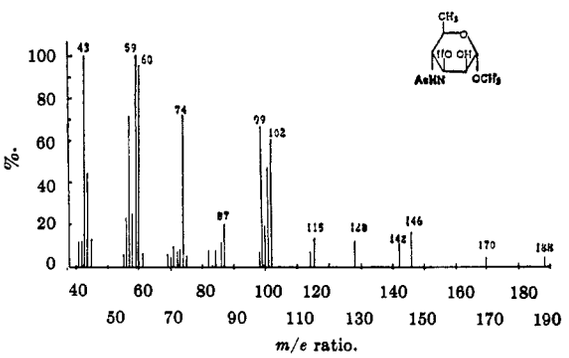


Figure. 3.—Mass spectrum of methyl 4-acetamido-4,6-dideoxy-α-D-mannopyranoside (**15**).

depressed 30°. The mass spectrum of compound **17** was identical with that of compound **15**[6f] (and certain other 4-acetamido sugars available in this laboratory) except for minor variations in peak intensity (Figures 2 and 3).

Acetylation of the free base of compound **16** in acetic anhydride and pyridine gave triacetate **18**. The same triacetate **18** was obtained from methyl 4-acetamido-4,6-dideoxy-α-D-talopyranoside (**17**), which in turn had been prepared from 2,3-*O*-isopropylidene protected *N*-acetyl derivative **9** by selective acid hydrolysis. The nmr spectrum of triacetate **18** is shown in Figure 4 and the mass spectral comparison with the triacetate obtained from *manno* derivative **15**[6f] is shown in Figures 5 and 6. Again the similarities of the mass spectra are striking. Assignments of the various protons in the nmr spectrum are given in the Experimental Section.

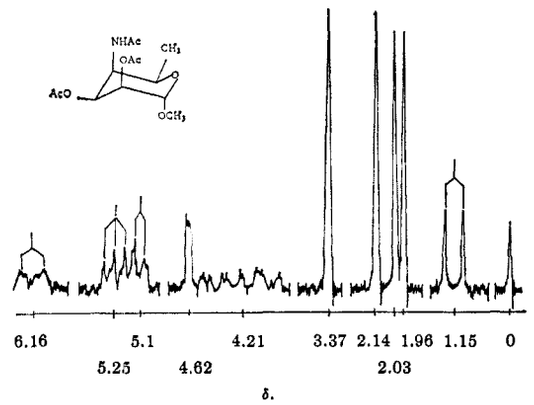


Figure 4.—Nmr spectrum of methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-talopyranoside (**18**).

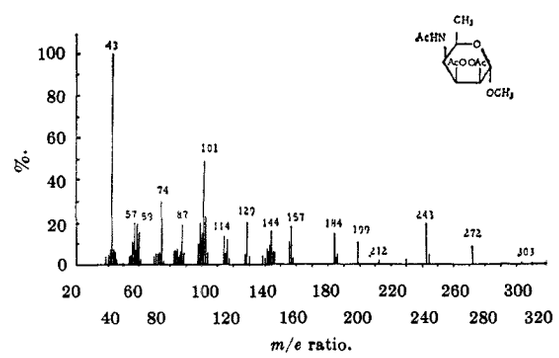


Figure 5.—Mass spectrum of methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-talopyranoside (**18**).

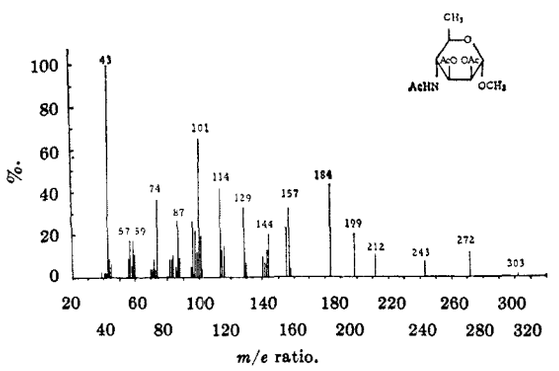


Figure 6.—Mass spectrum of methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-mannopyranoside.

Further support for the D-*talo* configuration of these amino sugar derivatives is given by a comparison of the molecular rotations of compounds **5**, **16**, **17**, **23**, and **24** with similar compounds of known D-*talo* configuration (Table I). In general, the molecular rotation of pyranose derivatives is not substantially affected by replacement of a hydroxyl by an amino group.[14-17] However, a correction factor of −3000° should be applied to the molecular rotation of an α- or β-D-hexose for comparison with the molecular rotation of a 6-deoxy-α- or β-hexose owing to the asymmetrical rotation of the 5,6-exocyclic bond, which does not contribute to the rotation of the 6-deoxyhexoses; a correction factor of +3000° should be applied also to L-hexoses.[18,19] This correction factor has been applied to the values quoted in Table I and in subsequent comparisons. The triacetates **5** and **18**, the glycoside

TABLE I

MOLECULAR ROTATION COMPARISONS OF VARIOUS AMINO SUGARS

	[α]D, deg	[M]D, deg
Methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-talopyranoside (**18**)	+82 (chloroform)	+24,800
	+67.8 (methanol)	+20,600
Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-talopyranoside (**5**)	+76 (methanol)	+23,100
Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-talopyranoside[c,d]	+73.3 (methanol)	+22,400[a]
	+75.9 (methanol)	+23,100[a]
Methyl 3-acetamido-2,4-di-*O*-acetyl-3,6-dideoxy-α-D-talopyranoside[e]	+72 (chloroform)	+21,800
Methyl 4-amino-4,6-dideoxy-α-D-talopyranoside hydrochoride (**16**)	+99.3 (water)	+21,200
Methyl 6-deoxy-α-D-talopyranoside[c,d]	+104 (water)	+18,600[a]
	+102 (water)	+18,200[a]
	+106 (water)	+18,900[a]
Methyl 3-amino-3-deoxy-α-D-talopyranoside hydrochloride[f]	+90 (water)	+20,600
		+17,600[b]
Methyl 2-amino-2,6-dideoxy-α-D-talopyranoside hydrochloride[c,g]	+84 (water)	+17,900[a]
Methyl 3-amino-3-deoxy-β-L-allopyranoside[h]	+54 (water)	+9,650
		+6,650[b]
Methyl β-L-allopyranoside[i,l]	... (water)	+10,900
		+7,900[b]
Methyl β-L-gulopyranoside[j,l]	+83.3 (water)	+16,200
		+13,200[b]
Methyl 4-acetamido-4,6-dideoxy-α-D-talopyranoside (**17**)	+139.5 (water)	+30,600
Methyl 3-acetamido-3,6-dideoxy-α-D-talopyranoside[e]	+104 (water)	+22,800
4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranose hydrochloride (**24**)	+35 (water)	+7,250
α-D-Talose[j,l]	+68 (water)	+12,200
		+9,200[b]
3-Amino-3,6-dideoxy-α-D-talose hydrochloride[e]	+41 (water)	+8,200
3-Amino-3-deoxy-α-D-talose hydrochloride[f]	+29.5 (water)	+9,300
		+6,300[b]
α-L-Gulose[j,l]	... (water)	−11,500
		−8,500[b]
4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-β-D-talopyranose hydrochloride (**23**)	+11.5 (water)	+2,600
β-D-Talose[j,l]	+13.2 (water)	+2,380
		−720[b]
6-Deoxy-β-L-allose[j,k]	... (water)	+2,000

[a] These values have been obtained from those quoted for the opposite (D or L) enantiomers. [b] A correction factor[14,18,19] of −3000° has been applied to the D sugars and +3000° to the L sugars. [c] See ref 8. [d] See ref 9. [e] See ref 14. [f] H. H. Baer, *J. Amer. Chem. Soc.*, **84**, 83 (1962). [g] P. M. Collins and W. G. Overend, *J. Chem. Soc.*, 3448 (1965). [h] B. Lindberg and O. Theander, *Acta Chem. Scand.*, **13**, 1226 (1959). [i] P. A. Levene and J. Compton, *J. Biol. Chem.*, **116**, 169 (1936). [j] F. J. Bates, "Polarimetry, Saccharimetry and the Sugars," U. S. Government Printing Office, Washington, D. C., 1942. [k] F. Micheel, *Chem. Ber.* **63**, 347 (1930). [l] See ref 18.

(14) A. C. Richardson and K. A. McLauchlan, *J. Chem. Soc.*, 2499 (1962).
(15) H. Ogawa, T. Ito, S. Kondo, and S. Inoue, *Bull. Agr. Chem. Soc. Japan*, **23**, 289 (1959).
(16) A. C. Richardson and H. O. L. Fisher, *J. Amer. Chem. Soc.*, **83**, 1132 (1961).
(17) E. E. van Tamelen, J. R. Dyer, H. E. Carter, J. V. Pierce, and E. E. Daniels, *ibid.*, **78**, 4817 (1956).
(18) D. H. Whiffen, *Chem. Ind.* (London), 964 (1956).
(19) J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5483 (1959).

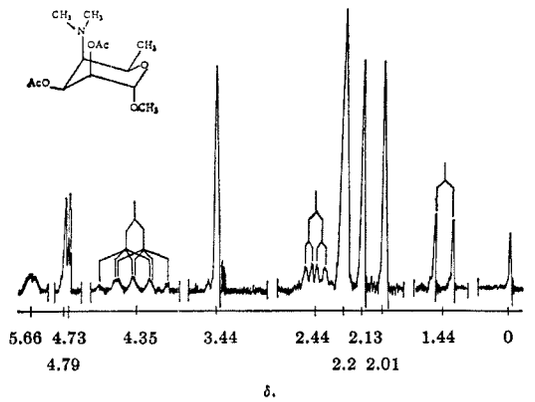


Figure 7.—Nmr spectrum of methyl 2,3-di-*O*-acetyl-4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside (**21**).

16, and the free sugars **23** and **24** compare very favorably with similar *talo* derivatives. There is a discrepancy in the comparison of *N*-acetyl derivative **17** with methyl 3-acetamido-3,6-dideoxy-α-D-talopyranoside. However, a similar difference in molecular rotation between various acetamido derivatives of glucose has been noted.[14] The molecular rotation of the β-D-free sugar **23** (+2600°), which compares favorably with β-D-talose (−720°), cannot be distinguished from 6-deoxy-β-L-allose (+2000°). However, the molecular rotation of the 4-aminoglycoside **16** (+21,200°) is very different from values for methyl β-L-allopyranoside derivatives (+6650, +7900°), but is in agreement with various methyl α-D-talopyranoside derivatives (+17,600 to +18,900°). Similarly the 4-aminoglycoside **16** (+21,200°) can be distinguished from β-L-gulopyranoside derivatives (+13,200°). Also, the molecular rotation of the α-D-free sugar **24** (+7250°) agrees with the values for α-D-talo derivatives (+6300 to +9200°) but not at all with α-L-gulose (−8500°). Derivatives of either or both of these L sugars could have resulted from epimerization of C-6 of ketone **2** during oxime formation, before reduction with lithium aluminum hydride. This possibility was eliminated by degradation of *N*-acetyl derivative **17** to L-threoninol oxalate,[6f] identical in all respects with an authentic sample prepared from L-threonine.[6f]

Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**) was converted into the *N*-methylamino hydrochloride derivative **11** by sequential *N*-carboethoxylation, lithium aluminum hydride reduction, and hydrochloride salt formation in an over-all yield of 76%. Furthermore, compound **7** also gave the *N*,*N*-dimethylamino derivative **12** in 75% yield by reductive methylation followed by conversion into the hydrochloride salt. The isopropylidene protecting group of compound **12** was selectively hydrolyzed to yield methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside. The latter compound was transformed into the crystalline picrate **19**, methiodide **20**, and diacetate **21**. The yields of picrate **19**, methiodide **20**, and diacetate **21** from starting material **12** were 94, 65, and 54%, respectively. Diacetate **21** also formed a crystalline hydrochloride **22**. The nmr spectrum of diacetate **21** is shown in Figure 7 and further details are given in the Experimental Section. *N*,*N*-Dimethylamino derivative **12** was treated with 1.0 *N* hydrochloride acid at 95° for 20 hr to give a 96% yield of crude free α- and β-D sugars **24** and **23**. The α anomer **24** was obtained as a residue by extraction of the mixture of α and β anomers with small portions of hot absolute ethanol which removed the more soluble β anomer. The β anomer **23** could be obtained relatively free of the α anomer by slow, careful crystallization from a methanol–ethyl ether mixture. The assignment of α and β configurations (Scheme III) is based on the

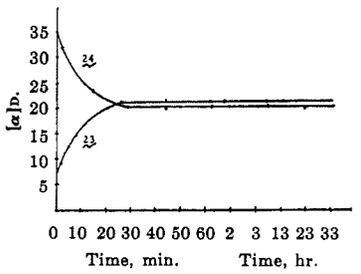
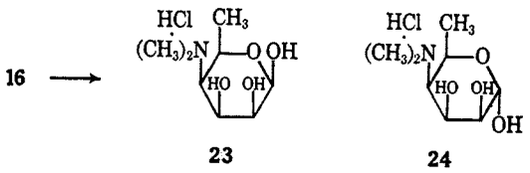


Figure 8.—Mutarotation curves of compounds **23** and **24**.

SCHEME III
4,6-DIDEOXY-4-(*N*,*N*-DIMETHYLAMINO)-α- AND -β-D-TALOPYRANOSE HYDROCHLORIDE.



mutarotation behavior of the two anomers which is represented in Figure 8. The pK_a of β anomer **23** (8.22) is quite high relative to that of the α anomer **24** (7.60). Attempts presently are being made in this laboratory to relate pK_a to conformation through various analytical tools (nmr, X-ray crystallography, etc.), an area that is currently little understood. As a preliminary step to this goal, the structure of methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside methiodide (**20**) was determined by X-ray crystallography and found to exist in the *1C* conformation.[20] The details of this X-ray analysis and those of other derivatives will form the subject matter of a future publication.

In summary, a new route to 4-amino-4,6-dideoxy sugars has been investigated and found to be successful. The fact that reduction of the oxime **6** affords almost exclusively the D-*talo* configuration may be ascribed to the steric accessibility of the lower side of the molecule as written; the approach of hydride to the upper side of the molecule is presumably hindered by both the C-6-methyl group and one of the methyl groups of the 2,3-*O*-isopropylidene bridge.

Experimental Section

All melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Thin layer chromatography was performed using silica gel H from Brinkman Instruments on 5 × 20 cm glass plates. Preparative thin layer chromatography was carried out on 20 × 40 cm glass plates coated with a 1-mm thickness of silica gel H. The following developing

(20) We are indebted to Dr. Milton Glick and coworkers of Wayne State University for the X-ray analysis.

solvents were used: (a) ethyl ether–*n*-pentane (1:1 v/v); (b) ethyl ether. Compounds were detected with a 6 *N* sulfuric acid spray followed by baking at 110° for 10–30 min. The bands on preparative plates were detected by spraying a 1-in. perpendicular band on both sides of the plates with sulfuric acid and baking. The bands were followed across the plates to the sprayed portions with ultraviolet light (Mineralight, U V S-11). pK_a data were determined in aqueous 50% methanol. Vpc analyses were performed on an F & M Scientific Corp. instrument (Model 810) fitted with a flame ionization detector. The following columns were used: (a) 10% Carbowax 20M on Chromosorb W, 2 ft × 0.25 in.; (b) 10% Carbowax 20M on Chromosorb W, 4 ft × 0.25 in. Nmr spectra were run in $CDCl_3$ using a Varian Associates A-60 spectrometer with tetramethylsilane as an internal standard. Pyridine was Merck Reagent Grade, dried over potassium hydroxide pellets. Microanalyses were performed by Midwest Microlab Inc., Indianapolis, Ind.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranosid-4-ulose (2).—Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**1**, 1.06 g) was dissolved in anhydrous dimethyl sulfoxide (4 ml) and dry pyridine (1 ml) and stirred under an atmosphere of dry nitrogen. Phosphorus pentoxide (1 g) was introduced quickly into the flask and the reaction mixture was heated at 60° for 1.5 hr. After it cooled to room temperature, dimethyl sulfoxide (2 ml), pyridine (0.5 ml), and phosphorus pentoxide (1 g) were added, and the heterogeneous mixture was heated at 60° for an additional 1.5 hr. This procedure was repeated (two to three times) until vpc analysis on column a (160°) showed little or no starting material. After the mixture cooled to room temperature, anhydrous K_2CO_3, equivalent to the P_2O_5 present, was added. Water was added dropwise until an evolution of gas occurred. Additional water was added cautiously until all gas evolution ceased. Then more water (10 ml) was added and the resulting homogeneous, dark reaction mixture was extracted with five 25-ml portions of *n*-pentane. The *n*-pentane extracts were dried (K_2CO_3) and concentrated *in vacuo* to give a crude oil. The oil was azeotroped several times with toluene to remove residual pyridine to yield compound **2**: 860 mg (81%); 96% pure by vpc analysis. A small portion was purified by preparative vpc on column a (130°). The physical constants are as follows: $n^{24}D$ 1.4478; $[\alpha]^{27}D$ +105° (*c* 0.71 in methanol). The literature[9,21] has reported $[\alpha]^{27}D$ −107° (ethanol) for the corresponding L isomer.

Compound **2** was prepared also by oxidizing compound **1** with chromium trioxide–pyridine according to Collins and Overend[8,9] in 30% yield. This method required five successive oxidations to obtain compound **2** in 91% purity by vpc analysis.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (3).—Sodium borohydride (100 mg) was added in portions over a 10-min period to a vigorously stirred solution of the ketone **2** (394 mg, 95% purity) dissolved in dry methanol (3 ml) at 0°. Hydrogen evolved, and the solution warmed slightly. The reaction mixture was stirred an additional 50 min at room temperature. Analysis by thin layer chromatography in system a showed complete reaction. The methanol was removed *in vacuo* and water (2 ml) was added. The mixture was heated at 95° for 1 hr. The aqueous solution was cooled and extracted with five 10-ml portions of *n*-pentane. The *n*-pentane extracts were combined, dried (K_2CO_3), and concentrated *in vacuo* to afford compound **3** as a colorless oil, 337 mg (85%). Vpc analysis using column a (180°) showed three peaks with retention times of 5.8 (90%), 8.2 (2%), and 10.9 min (8%). These retention times correspond to compound **3** (*talo*), compound **1** (*manno*), and an unknown impurity, respectively. Compound **3** was characterized as the mesylate **4** and triacetate **5**.

Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-α-D-talopyranoside (5).—Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**3**, 67.5 mg) was dissolved in methanol (1 ml) containing 2 drops of concentrated hydrochloric acid. Analysis by thin layer chromatography in system a after 15 min showed no starting material and one spot at the origin. The solution was neutralized with silver carbonate, and the silver salts were removed by filtration through Hyflo Supercel. The filtrate was concentrated *in vacuo* to afford a gum which did not reduce Benedict's solution. The gum was dissolved in pyridine (0.5 ml) and acetic anhydride (0.5 ml), and was allowed to stand at room temperature for 2 days. The solvents were removed *in vacuo* with repeated azeotroping (toluene) to yield an oil which crystallized to give 41.7 mg (53%) of compound **5**, mp 91–93°. Recrystallization from chloroform–*n*-hexane afforded analytical **5**: mp 91–91.5°; $[\alpha]^{26}D$ +76° (*c* 1.13 in methanol). The literature[8,9] has reported mp 91–92°, $[\alpha]^{20}D$ −75.9° (*c* 3.9 in methanol), for the corresponding L isomer.

Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.63. Found: C, 51.49; H, 6.65.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-talopyranoside (4).—Methyl 6-deoxy-2,3-*O*-isopropylidene-α,D-talopyranoside (**3**, 337 mg, 90% purity) was treated with mesyl chloride (0.23 ml) in pyridine (2 ml) at room temperature for 24 hr. The reaction mixture was poured onto an ice–water mixture (100 ml). The resulting precipitate was collected, washed well with water, and crystallized from aqueous ethanol to give compound **4**: yield, 330 mg (73%); mp 112–114° (needles). Three additional recrystallizations afforded needles with mp 116–117.5°, $[\alpha]^{27}D$ +20.2° (*c* 0.8 in methanol).

Anal. Calcd for $C_{11}H_{20}O_7S$: C, 44.58; H, 6.79; S, 10.81. Found: C, 44.53; H, 6.61; S, 10.65.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranosid-4-ulose Oxime (6).—Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranosid-4-ulose (**2**, 852 mg, 94% purity) was dissolved in pyridine–ethanol (1:1, 10 ml) containing hydroxylamine hydrochloride (900 mg). The mixture was heated under reflux for 2 hr, cooled, and evaporated *in vacuo*, and the residue was allowed to stand under 10 ml of water until it crystallized (10 hr). Recrystallization from *n*-hexane yielded compound **6**: mp 123–125°; 580 mg (64%). One more recrystallization from *n*-hexane afforded analytically pure material: mp 124.5–126°; $[\alpha]^{27}D$ +155.3° (*c* 1.54 in CH_3OH); uv max (C_2H_5OH) 203 mμ (ε 6000); nmr, δ 1.48 (d, 3, *J* = 6 Hz, C-6-C*H*$_3$), 1.6 [d, 6, >C(C*H*$_3$)$_2$], 3.44 (s, 3, C-1-OC*H*$_3$), 4.38 (d, 1, *J* = 7.5 Hz, C-2-*H*), 4.63 (s, 1, C-1-*H*), and 4.78 (d, 1, *J* = 7.5 Hz, C-3-*H*) superimposed on 4.89 ppm (q, 1, *J* = 6 Hz, C-5-*H*).

Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 52.12; H, 7.40; N, 6.20.

Methyl 4-Amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (7).—A solution of oxime **6** (1.0 g) in dry tetrahydrofuran (2 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (0.5 g) in tetrahydrofuran (10 ml). After the addition was complete (1 hr), the reaction mixture was heated under reflux for an additional 20 hr. The reaction mixture was cooled to room temperature, and the excess hydride was decomposed with ethyl acetate followed by water, care being taken not to add a large excess of either reagent. The white precipitate was removed by filtration and washed with ethyl ether to yield compound **7** as a pale yellow oil, 895 mg (95%). Vpc analysis using column a (160°) showed one peak (trailing). The oil contained a small amount of the *manno* derivative **13** which was not detected at this stage. The oil was used without purification for subsequent reactions and characterized as the 2,4-dinitroanilino and the *N*-acetyl derivatives.

Methyl 4,6-Dideoxy-4-(2,4-dinitroanilino)-2,3-*O*-isopropylidene-α-D-talopyranoside (8).—Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**) was treated according to the method of Lloyd and Stacey[13] to give **8** in 67% yield following recrystallization from methanol with mp 138–140°. Recrystallization from chloroform–*n*-pentane and ethanol gave **8** having mp 139–140°, $[\alpha]^{27}D$ −20° (*c* 1.23 in chloroform).

Methyl 4-Acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (9) and Methyl 4-Acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (14).—Impure methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**, 634 mg), containing a small amount of the *manno* isomer **13**, was treated with acetic anhydride (1 ml) and pyridine (3 ml) at room temperature for 0.5 hr. The solvents were removed *in vacuo* with azeotroping (toluene) to give a light brown oil which crystallized. Recrystallization from ethyl acetate afforded pure **9**: yield, 460 mg (61%); mp 149–150°; $[\alpha]^{27}D$ +27.1° (*c* 0.51 in methanol).

Anal. Calcd for $C_{12}H_{21}NO_6$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.52; H, 8.34; N, 5.70.

An additional 40 mg (5%) of **9**, mp 148.5–150°, was obtained by repeated crystallizations from the mother liquor. The mother liquor was concentrated *in vacuo* to yield an oil (183 mg). The oil was applied to a preparative thin layer plate and developed in system b. Removal and processing of the band corresponding to the *talo* isomer **9** yielded another 40 mg (5%) of **9**, mp 148.5–

(21) P. M. Collins and W. G. Overend, *J. Chem. Soc.*, 3448 (1965).

150°, after recrystallization from ethyl acetate–*n*-hexane. The total yield of compound **9** was 71%.

Processing of the slower running band corresponding to the *manno* derivative **14** afforded 10.46 mg (1.3%), mp 86–92°, following crystallization from an ethyl ether–*n*-hexane mixture. An additional recrystallization afforded 4.0 mg of compound **14**, mp 96–98°, with prior softening at 92°. An infrared spectrum (chloroform) was very similar to that of compound **9**.

Methyl 4-Acetamido-4,6-dideoxy-α-D-mannopyranoside (15).—Methyl 4-acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**14**, 3.03 mg) was dissolved in water (0.5 ml). The mixture was brought to pH 3.0 (pH paper) by the addition of two drops of 0.1 *N* hydrochloric acid. The reaction mixture was heated at 95° for 0.5 hr, cooled, and lyophilized to afford a white solid. The solid was crystallized from an ethanol–ethyl ether–*n*-hexane mixture to yield compound **15** as needles: yield, 1.76 mg (69%); mp 182–183°. A mixture melting point with authentic **15**,[22] mp 184–185°, was undepressed and the infrared spectra (KBr) of the two compounds were identical.

Methyl 4-Amino-4,6-dideoxy-α-D-talopyranoside Hydrochloride (16).—Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**, 249.5 mg) was dissolved in water (5 ml) at pH 3.0 (pH paper, hydrochloric acid) and heated at 95° for 2 hr. The solution was treated with charcoal and concentrated *in vacuo* at room temperature to yield a hygroscopic semisolid. Absolute ethanol was added followed by dry ethyl ether (dropwise to the turbidity point) to effect crystallization of compound **7**: 154.5 mg (63%); mp 169–170.5° dec. Two recrystallizations from an absolute ethanol–dry ethyl ether mixture yielded pure **16** as needles: mp 177–177.5° dec; $[\alpha]^{27}D$ +99.3° (*c* 0.66 in water); pK_a 8.45.

Anal. Calcd for $C_7H_{16}ClNO_4$: C, 39.35; H, 7.55; N, 6.56. Found: C, 39.36; H, 7.50; N, 6.75.

Methyl 4-Acetamido-4,6-dideoxy-α-D-talopyranoside (17).—Methyl 4-acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**9**, 200 mg) was added to 3 ml of water at pH 3.0 (pH paper, hydrochloric acid) and heated at 95° for 1 hr. Lyophilization of the solution afforded **17** as a solid: 158 mg (94%); mp 166–168° dec, turning brown at 120°. Recrystallization from an ethanol–ethyl ether–*n*-pentane mixture yielded 100 mg (59%) of pure **17**: mp 182–183° dec, with some softening at 168°; $[\alpha]^{27}D$ + 167.5° (*c* 0.69 in methanol); $[\alpha]^{27}D$ +139.5° (*c* 0.38 in water). An infrared spectrum showed *N*-acetyl absorption at 5.95 μ and no *O*-acetyl absorption. A mass spectrum was essentially identical with the mass spectra of other 4-acetamido sugars except for minor variations in peak intensity. A mixture melting point with authentic *manno* derivative **15** was depressed.

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.46; H, 7.96; N, 6.26.

Methyl 4-Acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-talopyranoside (18). A.—Methyl 4-acetamido-4,6-dideoxy-α-D-talopyranoside (**17**, 65.5 mg) was dissolved in acetic anhydride (0.5 ml) and pyridine (0.5 ml) and allowed to stand at room temperature for 18 hr. Processing in the usual manner afforded pure **18** [79.3 mg (88%); mp 135–135.5°; $[\alpha]^{27}D$ +82° (*c* 0.49 in chloroform); $[\alpha]^{27}D$ + 67.8° (*c* 0.82 in methanol)] after one recrystallization from an ethyl ether–*n*-pentane mixture. The mass spectrum of **18** was essentially identical with the mass spectra of other triacetates of 4-amino sugars except for minor variations in peak intensity. The nmr of compound **18** showed δ 1.15 (d, 3, J = 6.8 Hz, C-6-CH_3), 1.96 [s, 3, axial[23] C-4-NHC(O)CH_3], 2.03 [s, 3, equitorial[23] C-3-OC(O)CH_3], 2.14 [s, 3, axial[23] C-2-OC(O)CH_3], 3.37 (s, 3, C-1-OCH_3), *ca.* 4.2 (m, 2, C-4-*H*, C-5-*H*), 4.62 (broad s, $J_{1,2}$ = 0–1 Hz, C-1-*H*), 5.1 (d, 1, $J_{1,2}$ = 0–1 Hz, $J_{2,3}$ = 4 Hz, C-2-*H*), 5.25 (t, 1, $J_{2,3}$ = 4 Hz, $J_{3,4}$ = 4 Hz, C-3-*H*), and 6.16 ppm (broad d, 1, C-4-N*H*).

Anal. Calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62. Found: C, 51.76; H, 6.98; N, 4.88.

B.—Methyl 4-amino-4,6-dideoxy-α-D-talopyranoside hydrochloride (**16**, 15.16 mg) was converted into its free base using methanolic Dowex 1 (–OH). The free base was dissolved in pyridine (1 ml) and acetic anhydride (2 ml) and allowed to stand at room temperature for 14 hr. Processing in the usual manner yielded a gum which crystallized: yield, 17.7 mg (84%); mp 128–132°. Recrystallization from a chloroform–*n*-hexane mixture gave compound **18**: yield, 12.2 mg (57%); mp 134–136°. A mixture melting point determination with a sample of **18** prepared from *N*-acetyl derivative **17** was undepressed.

Methyl 4,6-Dideoxy-2,3-*O*-isopropylidene-4-(*N*-methylamino)-α-D-talopyranoside Hydrochloride (11).—Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**, 497 mg) was added to a mixture of chloroform (2 ml), water (4 ml), and sodium bicarbonate (300 mg) at 0°. Ethyl chlorocarbonate (0.5 ml) in chloroform (2 ml) was added dropwise with vigorous stirring over a period of 2 hr. The layers were separated and the aqueous layer was extracted with two additional 4-ml portions of chloroform. The extracts were combined, dried (K_2CO_3), and concentrated *in vacuo* to yield **10** as a heavy oil. Compound **10** was crystalline below room temperature. Without purification, the *N*-carboethoxy derivative (**10**) was treated with lithium aluminum hydride (430 mg) in 10 ml of ethyl ether under reflux for 12 hr. The reaction mixture was cooled and the excess hydride decomposed with ethyl acetate and water, care being exercised not to add an excess of either reagent. The inorganic salts were removed by filtration and washed well with ethyl ether. The combined washings and filtrate were concentrated *in vacuo* to afford an oil. The oil was rendered anhydrous by repeated evaporation with absolute ethanol and dissolved in absolute ethanol (2 ml) and dry ethyl ether (5 ml). Anhydrous hydrogen chloride in isopropyl alcohol was added dropwise with swirling to pH 3–4 (pH paper). Ethyl ether and *n*-pentane were added to incipient turbidity to effect crystallization of the amine hydrochloride **11** as dense crystals: yield, 400 mg; mp 174–175° dec; $[\alpha]^{28}D$ +86.2° (*c* 0.76 in methanol); pK_a 7.08. A second crop of 60 mg, mp 173–174.5° dec, was also obtained. The total yield was 76%.

Anal. Calcd for $C_{11}H_{22}ClNO_4$: C, 49.33; H, 8.28; N, 5.23. Found: C, 49.52; H, 8.50; N, 5.36.

Methyl 4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-2,3-*O*-isopropylidene-α-D-talopyranoside Hydrochloride (12).—Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**, 619.6 mg) was stirred under hydrogen, at atmospheric pressure in distilled *p*-dioxane (2 ml) containing aqueous 36% formaldehyde (0.52 ml) and 10% palladium on carbon (500 mg). After 4 days, vpc analysis using column a (150°) showed no starting material (retention time 10.5 min) and two peaks with retention times of 3.4 (4%) and 5.1 min (96%). The catalyst was removed by filtration using a Hyflo Supercel bed and washed well with absolute ethanol The washings and filtrate were combined and evaporated *in vacuo*. The resulting oil was azeotroped twice with absolute ethanol (3 ml), dissolved in absolute ethanol (1 ml) and dry ethyl ether (3 ml), and adjusted with dry hydrogen chloride in isopropyl alcohol to pH 4 (pH paper). Addition of ethyl ether to incipient turbidity effected crystallization of the *N*,*N*-dimethylamino derivative **12**: yield, 600 mg (75%); mp 196–198° dec. Recrystallization using an ethanol–ethyl ether mixture afforded 540 mg (68%), mp 202–203° dec. A small portion was recrystallized from an ethanol–ethyl ether and a methanol–ethyl ether mixture to give pure compound **12**: mp 205–206° dec; $[\alpha]^{28}D$ +90° (*c* 0.65 in methanol); pK_a 6.69.

Anal. Calcd for $C_{12}H_{24}ClNO_4$: C, 51.14; H, 8.58; N, 4.97. Found: C, 51.42; H, 8.52; N, 5.18.

Methyl 4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside Picrate (19).—Methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-2,3-*O*-isopropylidene-α-D-talopyranoside hydrochloride (**12**, 100.9 mg) was heated in water (2 ml) at pH 3.0 (pH paper, hydrochloric acid) at 95° for 20 hr. The reaction mixture was cooled and lyophilized to yield a yellow hard foam. The foam was dissolved in methanol. The solution was placed on a Dowex 1 (–OH) column and eluted with methanol. The eluent was concentrated *in vacuo* to yield the free base of compound **19** as a gum. The gum was dissolved in absolute ethanol and picric acid (82 mg) in ethanol was added. The solvent was removed *in vacuo* to yield a gum which crystallized when triturated under ethyl ether: yield, 145 mg (94%); mp 172–174°. Recrystallization from hot ethyl acetate afforded material with mp 173–174.5°; $[\alpha]^{27}D$ +62.8° (*c* 0.88 in methanol); pK_a 7.70. Further recrystallizations failed to raise the melting point.

Anal. Calcd for $C_{15}H_{22}N_4O_{11}$: C, 41.48; H, 5.11; N, 12.85. Found: C, 41.72; H, 5.30; N, 13.46.

Methyl 4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside Methiodide (20).—Methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-2,3-*O*-isopropylidene-α-D-talopyranoside hydrochloride (**12**, 44.84 mg) was hydrolyzed as described in the preparation of compound **19** to obtain the free base of compound **19**. The

(22) A sample was generously provided by Mr. S. K. Gupta of this laboratory.

(23) L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964).

free base was dissolved in methyl iodide (2 ml) and methanol (1 ml) and refluxed for 0.5 hr. Dilution of the reaction mixture with ethyl ether after cooling induced crystallization. The product was recrystallized from a methanol–ethyl ether mixture to yield compound **20** as needles: yield, 29.12 mg (65%); mp 234–236° dec. Three additional recrystallizations gave a pure product having constant mp 238–238.5° dec; $[\alpha]^{29}D$ +50.7° (*c* 0.523 in methanol).

Anal. Calcd for $C_{10}H_{22}INO_4$: C, 34.59; H, 6.40; N, 4.03. Found: C, 34.86; H, 6.69; N, 4.10.

Methyl 2,3-Di-*O*-acetyl-4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside (21).—Methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-2,3-*O*-isopropylidene-α-D-talopyranoside hydrochloride (**12**, 200 mg) was hydrolyzed as described in the preparation of compound **19** to obtain the free base of compound **19** as a gum, 121 mg (88%). The gum was dissolved in acetic anhydride (1 ml) and pyridine (1 ml) and allowed to stand at room temperature for 3 days. Removal of the solvents *in vacuo* with azeotroping (toluene) yielded 170 mg of crude solid. Recrystallization from hot *n*-hexane gave 110 mg (54% for two steps): mp 84–86°; $[\alpha]^{29}D$ +107° (*c* 6.60 in methanol); pK_a 5.78; nmr δ 1.44 (d, 3, $J_{5,6}$ = 7 Hz, C-6-CH_3), 2.0 [s, 3, equitorial[23] C-2-OC(O)CH_3], 2.13 [s, 3, axial[23] C-3-OC(O)CH_3], 2.2 [s, 6, -N(CH_3)$_2$], 2.44 (q, 1, $J_{3,4}$ = 3 Hz, $J_{4,5}$ = 5.5 Hz, C-4-*H*), 3.44 (s, 3, C-1-OCH_3), 4.35 (octet, 1, $J_{5,6}$ = 7 Hz, $J_{5,4}$ = 5.5 Hz, C-5-*H*), 4.73 (d, 1, $J_{1,2}$ = 0 Hz, $J_{2,3}$ = 1.2 Hz, C-2-*H*), 4.79 (s, 1, $J_{1,2}$ = 0 Hz, C-1-*H*), and 5.66 ppm (unresolved q, 1, C-3-*H*).

Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84. Found: C, 54.15; H, 8.26; N, 4.73.

The hydrochloride salt of compound **21**, compound **22**, had mp 209–210° dec.

4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-β-D-talopyranose Hydrochloride (23), and 4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranose Hydrochloride (24).—Methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-2,3-*O*-isopropylidene-α-D-talopyranoside (compound **12**, 257.1 mg) was heated at 95° in 1.0 *N* hydrochloric acid (3 ml) for 20 hr. The reaction mixture was treated with charcoal, cooled, and lyophilized to yield a foam. The foam was azeotroped twice with an ethanol–toluene mixture. Crystallization of the reaction mixture was accomplished by dissolving it in hot methanol (*ca.* 5 ml), cooling, and adding ethyl ether to incipient turbidity. As crystals deposited over a period of several days, more ethyl ether was added. The yield was 170 mg (96%) of a mixture of anomers **23** and **24**, as evidenced by a mp 140–175° dec. A predominance of the β anomer **23** was obtained by slow recrystallization from a dilute methanol–ethyl ether mixture seeded with the β anomer. After two recrystallizations the yield was 90 mg (51%): mp 154–156° (slight turbidity in melt, cleared at *ca.* 170°) (one more recrystallization lowered the melting point to 152–154°); $[\alpha]^{29}D$ *ca.* 7 → 21° (0.5 hr) (*c* 0.5 in water); pK_a 8.22.

Anal. Calcd for $C_8H_{18}ClNO_4$: C, 42.20; H, 7.97; N, 6.15. Found: C, 42.46; H, 7.98; N, 6.42.

The α anomer **24** was obtained by extracting the crude mixture of α and β anomers, mp 140–175° dec, with several small volumes of hot ethanol. The residue was compound **24**: mp 180–182° dec, with slight softening at 155°; $[\alpha]^{24}D$ 30.8 → 19.0° (0.75 hr) → 19.5° (22 hr); pK_a 7.60.

Anal. Calcd for $C_8H_{18}ClNO_4$: C, 42.20; H, 7.97; N, 6.15. Found: C, 41.97; H, 7.84; N, 6.07.

Registry No.—**2**, 15830-63-4; **4**, 15830-64-5; **5**, 15830-76-9; **6**, 15830-65-6; **7**, 15830-66-7; **8**, 15830-67-8; **9**, 15856-43-6; **11**, 15889-54-0; **12**, 15830-68-9; **14**, 15856-44-7; **15**, 15856-45-8; **16**, 15830-69-0; **17**, 15856-46-9; **18**, 15856-47-0; **19**, 15830-70-3; **20**, 15830-71-4; **21**, 15830-72-5; **22**, 15830-73-6; **23**, 15830-74-7; **24**, 15830-75-8.

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Nucleosides. L. Synthesis of 2,3′-Imino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine and Related Derivatives[1]

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Reaction of 5′-deoxy-5′-iodo-3′-*O*-mesylthymidine (**3**) with silver acetate in methanol afforded the 2,5′-anhydro derivative of 3′-*O*-mesylthymidine (**4**) in good yield which, by treatment with liquid ammonia, gave 2,3′-imino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (**6a**). Compound **6a** was also prepared from the 2-*O*-methyl derivative **8**. Reaction of the 2,5′-anhydro nucleoside **4** with methylamine, hydroxylamine, and hydrazine yielded the corresponding cyclic *N*-methyl, *N*-hydroxy, and *N*-amino derivatives **6b–d**. In the above reactions of **4** or **8** with amines the 2,3′-imino derivatives **6** formed *via* the isocytosine intermediate **5**. The reactions and ultraviolet, pK_a, and pmr data of the 2,3′-imino derivatives **6** are reported and discussed.

Arabinosylcytosine,[3] arabinosyl-5-fluorouracil,[4] and arabinosyl-5-fluorocytosine[5] have demonstrated interesting biochemical and chemotherapeutic activity.[6] In the synthesis of these biologically active compounds, 2,2′-anhydro-1-(β-D-arabinofuranosyl) uracil,[7] and 5-fluorouracil[4] and -cytosine[3,8] (**1a** and **b**, Figure 1) have been important intermediates. In order to obtain pyrimidine nucleosides of modified biological activity, the synthesis of the nitrogen isostere (**6**, Figure 2) of 2,3′-anhydro-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine[9] (**2**, Figure 1) was undertaken. The chemistry of **2** and its derivatives have been studied extensively in this and other laboratories.[9–11] Our recent chemical studies[8] on 2-aminopyrimidine nucleosides suggested that a 2,2′- or 2,3′-imino nucleoside may conceivably act as a chemical precursor for the synthesis of nucleosides containing an amino group in the "up" configuration in the sugar moiety.

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