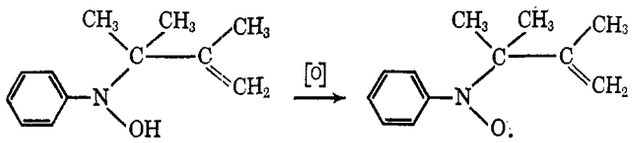
mechanism recently discussed by Hill and Rabinovitz[45] for the addition of olefins to dienophiles.)

The hydroxylamine which is initially formed, being quite reactive, is readily oxidized by unreacted nitrosobenzene (which would account for the low yield based on nitrosobenzene)[46] or oxygen to the corresponding



nitroxide. Although further study would be necessary to establish this mechanism definitely, it appears to be consistent with all the facts.

The hydroxylamine intermediate has not been isolated and unequivocally identified; however, the following observations lend support to its presence. While attempting to reduce a benzene solution of I with hydrogen over Pt–C, it was found that, after a short reaction period, the esr spectrum disappeared, whereas upon standing in air a similar esr signal reappeared and increased in intensity with time. Increasing the reaction temperature and time period resulted in a product which did not revert to the free radical upon exposure to air. Preparative gas chromatography on the initial solution after partial reduction resulted in the isolation of a component which had the characteristic infrared bands one would expect to find in the corresponding hydroxylamine. These observations strongly indicate that the hydroxylamine is an intermediate.

Acknowledgments.—The author wishes to thank Drs. M. J. S. Dewar and W. H. Urry for their suggestions with regard to this work. Also, A. B. S. thanks Dr. G. R. Wilder for his assistance in obtaining evidence to support the proposed free radical structure together with his suggestions and comments. Lastly, the author is indebted to Mr. D. D. Mullins who prepared most of the nitroso compounds used in this study.

(45) R. K. Hill and M. Rabinovitz, *J. Am. Chem. Soc.*, **86**, 965 (1964).

(46) One mole of nitrosobenzene could reduce 2 moles of hydroxylamine in which event the maximum free-radical yield would be 67% based on nitrosobenzene.

Synthesis and Chemistry of 4-Amino-4,6-dideoxy Sugars. I. Galactose[1]

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The synthesis of 4-amino-4,6-dideoxy-D-galactose, Ia, and its N-methyl and N,N-dimethyl homologs is described starting from methyl-α-D-glucopyranoside.

The recently described synthesis of amosamine[2] marked the first synthesis of a 4-amino-4,6-dideoxy hexose, a new class of carbohydrate. The increasing frequency of isolation of class members from natural sources[1] emphasizes their fundamental biological importance. Accordingly, we have inititated a program of synthesis of several member amino sugars so that the scope and mechanism of their biological activity may be the more rapidly elucidated. Further, a successful synthetic program would also result in an expanded knowledge of the fundamental chemistry of carbohydrates, and, in particular, chemistry of the 4-carbon site of hexoses.

4-Amino-4,6-dideoxy-D-galactose, Ia, is naturally occurring being found in the cell extracts of *Escherichia coli* strain Y10.[1] This amino sugar is also an anticipated constituent of thirteen other bacterial types and strains.[1] The N-alkyl homologs of Ia have not been found in nature to date.

4-Amino-4,6-dideoxy-D-galactose (Thomosamine).[3]—The starting material for Ia was methyl 2,3-di-O-benzyl-α-D-glucopyranoside which was made from methyl-α-D-glucopyranoside by known procedures[4] in 60% over-all yield for the three steps. Subsequent dimesylation afforded IIa in 98% yield. Selective displacement of the primary 6-mesyloxy group with iodide ion was smoothly effected in refluxing 2-butanone affording IIb in 85% yield. At 105° in acetone some displacement of the 4-mesyloxy function occurred giving, in addition to IIb, 11% of a diiodo derivative, most probably a mixture of C-4 epimers.[5]

Reduction of the 6-iodo group was conveniently done on a large scale with lithium aluminum hydride in tetrahydrofuran solvent. To obtain convenient reaction times it was necessary to use excess hydride and this resulted in reductions at sites other than position 6. Thus, from reduction of IIb for 6 hr in refluxing tetrahydrofuran there was obtained 82% of the desired 6-deoxy-4-mesylate IIc. An infrared spectrum of the mother liquors was devoid of mesylate absorption (ν_{SO_2} 8.50 μ) and indicated the presence of a hydroxyl group. Remesylation of the mother liquors afforded additional IIc indicating the presence in the original reaction mixture of about 12% of the 4-hydroxy compound IIIa which arose from O–S cleavage by hydride. Also, from chromatography of the remesylation there was obtained as a liquid 3% of the 4,6-dideoxy derivative IIIb and about 1% of starting 6-iodo-4-mesylate IIb. In all, then, conversion of IIb to IIc could be effected in a yield of 94%.

Introduction of the nitrogen function was effected by displacement with azide ion of the 4-mesyloxy group. Subsequent lithium aluminum hydride reduction of the

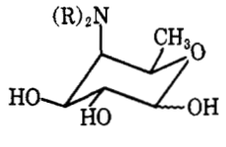
(1) A preliminary account of a portion of this work has appeared: C. L. Stevens, P. Blumbergs, D. H. Otterbach, J. L. Strominger, M. Matsuhashi, and D. N. Dietzler, *J. Am. Chem. Soc.*, **86**, 2937 (1964).

(2) Paper II of this series: C. L. Stevens, P. Blumbergs, F. A. Daniher, D. H. Otterbach, and K. G. Taylor, *J. Org. Chem.*, **31**, 2822 (1966), and references therein cited.

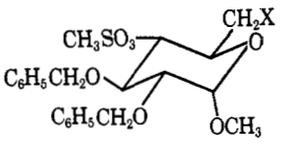
(3) The name thomosamine is proposed for this amino sugar in honor of Olin E. Thomas, vice-president and treasurer of Wayne State University.

(4) (a) K. Freudenberg and E. Plankenhorn, *Ber.*, **73B**, 621 (1940); (b) D. J. Bell and J. Lorber, *J. Chem. Soc.*, 453 (1940).

(5) Treatment of IIc under similar conditions afforded a mixture of epimeric iodides: C. L. Stevens, K. G. Taylor, and J. A. Valicenti, *J. Am. Chem. Soc.*, **87**, 4579 (1965).

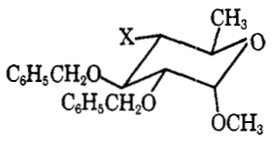


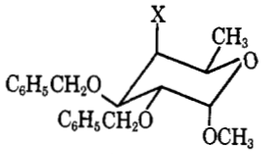
·HCl



Ia, R = H
c, R = CH_3

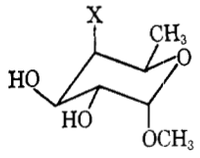
IIa, X = CH_3SO_3
b, X = I
c, X = H

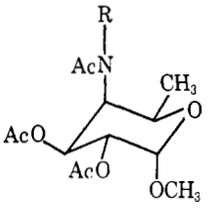




IIIa, X = OH
b, X = H

IVa, X = N_3
b, X = NH_2
c, X = NHAc
d, X = $NHCO_2C_2H_5$
e, X = $NHCH_3$
f, X = $N(CH_3)_2$





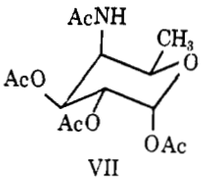
Va, X = NH_2
b, X = $NHCH_3$
c, X = $N(CH_3)_2$
d, X = NHAc

VIa, R = H
b, R = CH_3

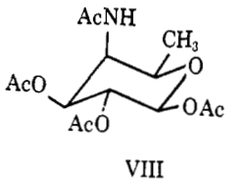
azide IVa, a crystalline solid, afforded IVb as a viscous oil in 89% yield. A hydrochloride salt and the N-acetyl compound IVc were prepared as solid derivatives. Catalytic hydrogenolysis of the benzyl protecting groups of IVb in the presence of excess hydrochloric acid yielded the glycoside Va hydrochloride as a crystalline solid in 93% yield. The free base, Va, was also crystalline. Catalytic reduction of the acetamido derivative IVc was accomplished in the absence of acid and yielded Vd as an amorphous solid. Vd was also prepared by selective N-acylation of Va. Chromatography over Florisil was necessary before the N-acetyl derivative became crystalline. The triacetyl derivative VIa could not be crystallized even after extensive chromatography and had to be characterized as an oil.

At this point attention was turned toward the preparation of the free sugar, Ia itself. This proved to be an exceptionally difficult task but was finally accomplished after numerous experiments. It was soon discovered that the hydrolytic conditions and route successfully employed for the preparation of the *gluco* isomer of Ia[2] were not applicable to the case of Ia itself. Thus heating the acetamido derivative Vd in 3 *N* hydrochloric acid at 100° cleanly hydrolyzed the N-acetyl group in 3 hr and afforded Va in 80% yield. Further attempts at hydrolysis were then attempted on the hydrochloride of Va and were unsuccessful under a variety of acidic conditions. Usually conditions vigorous enough to cleave the 1-methoxy were too severe for survival of the free sugar product. Finally, an attempt at hydrolyzing the dibenzyl derivative IVb also afforded Va, in 72% yield.

Attempts were then directed toward the synthesis of Ia *via* a 1-O-acetyl derivative, either VII or VIII. Triacetate VIa was subjected to acetolysis in acetic anhydride with sulfuric acid as catalyst. Such treatment was expected to yield a predominance of the α anomer VII,[6] and VII was the only crystalline product isolated,



VII

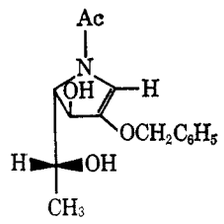


VIII

but only in 31% yield. The pyranose formulation VI was supported by elemental analysis and the infrared spectrum which, in addition to strong O-acetate carbonyl absorption, had absorption at 2.92 (NH), 5.95 (secondary amide), and 6.62 μ (NH). The α configuration for VII was indicated by its specific rotation of +95°. Acid hydrolysis of VII under carefully controlled conditions was successful for synthesis of Ia hydrochloride which could only be obtained in 36% yield as an amorphous solid. Attempts to obtain other salts in crystalline form were no more successful. The hydrochloride was unstable even in the solid state at refrigerator temperatures slowly liberating ammonium chloride. Acetylation of freshly prepared Ia at 65° in pyridine afforded the β-tetraacetyl derivative VIII in 57% yield. A small amount, <1%, of VII was the only other crystalline product isolated from the reaction. Infrared and analytical data supported the pyranose structure proposed for VIII and its low specific rotation 24.1°, indicated its anomeric configuration. After standing for 1 day, Ia failed to yield any crystalline VIII on acetylation in pyridine.

In an effort to raise the yields of formation of tetraacetyl derivative VII, an acetolysis reaction was carried out on the di-O-benzyl derivative IVc. The results of this experiment gave the first evidence of formation of pyrrolidine sugars in this *galacto* series. Thus, tetraacetate VII was only a minor product (8%) of this reaction. One of the major components (30%) was a C_{19} compound which, by infrared, contained O-acetate groups (5.75 and 8.05 μ) and a tertiary amide (6.06 μ). Conspicuously absent from the infrared spectrum were both the N–H stretching and N–H bending absorptions (2.90 and 6.6 μ, respectively) which have characterized all the 4-acetamido compounds possessing the pyranose ring.[2] A second major component (~30%) was a C_{15} compound which lacked infrared absorption for O-acetyl groups. In the carbonyl region there was strong absorption at 5.97 μ, but again the characteristic 2.90- and 6.6-μ peaks of secondary amides were absent. The compound gave a positive bromine test for unsaturation but failed to reduce Fehling's and Benedict's reagents. The position of the carbonyl absorption was indeed consistent with that of a vinyl-type acetamide[7] and thus structure IX is a possibility for the C_{15} product.

(6) C. S. Hudson and H. O. Parikr, *J. Am. Chem. Soc.*, **37**, 1589 (1915).
(7) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 46; also L. J. Bellamy, "Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p 213.



IX

Complete analysis for both the C_{19} and C_{15} compounds is necessary for an unequivocal statement of structure and this is in progress. The present data do indicate, however, pyrrolidine structures for both compounds in question.

The results of these experiments were in sharp contrast to analogous experiments in the *gluco* series wherein the pyranose form greatly predominated.[2] Unfortunately, nmr experiments on the amorphous hydrochloride of Ia were poorly resolved and not at all definitive so that pyranose $\rightleftharpoons$ pyrrolidine equilibrium data comparable with that obtained for the *gluco* isomer[2] are not available at present.

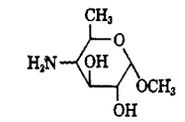
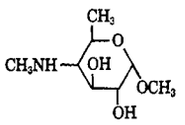
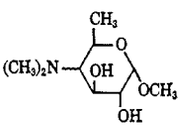
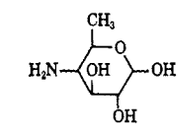
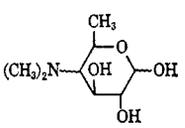
Mono-N-Methyl Homologs.—The starting material for synthesis of N-methyl homologs was the dibenzyl derivative IVb. Acylation with chloroethyl formate (yielding IVd) and subsequent hydride reduction gave the methylamino compound IVe as a viscous oil which could be characterized. The hydrochloride salt was readily crystallized and provided a solid derivative. The benzyl groups of IVe were easily hydrogenolyzed in the presence of excess acid affording Vb in 86% yield. In contrast with the amino derivative Va, Vb was acetylated to a *crystalline* triacetate, VIb.[8] Hydrolysis attempts to prepare a free sugar were not successful.

Dimethylamino Homologs.—The starting material for this series of homologs was, again, IVb. Clarke–Eschweiler methylation afforded the oily dimethylamino derivative IVf. Again, a hydrochloride salt provided a solid derivative. Hydrogenolysis of IVf's benzyl groups afforded the same dimethylamino sugar, Vc, as was obtained by Clarke–Eschweiler methylation of amino glycoside Va. With the dimethylamino function present complications arising from a pyranose–pyrrolidine equilibrium in a free sugar should be eliminated. Interestingly, in this regard, hydrolysis of Vc in 3 *N* hydrochloric acid at 100° yielded Ic hydrochloride in 67% yield.

Amino Sugar Basicities.—Some interesting, but not understood, relationships exist between amino sugar stereochemistry and basicity. In considering the data of Table I it is seen that, contrary to results in simpler systems,[9] the axial amines (*galacto*) are more basic than the equatorial ones (*gluco*), and this may well hold true to the cases of the *ido* and *altro* configurations (footnote *c*). It is known that an adjacent *cis* hydroxyl group will enhance the basicity of a neighboring amine function relative to a *trans* isomer.[10] This could be cited as the case when comparing *gluco* with *galacto* but fails to account for the opposite results when comparing *ido* with *altro*. A last observation is that by changing the configuration of a remotely situated 1-methoxyl group from α to β orientation, the basicity of the *galacto* isomer drops by 0.4 pK_a units (footnote *b*).

TABLE I

BASICITIES OF 4-AMINO-4,6-DIDEOXYHEXOSE SALTS

Compd	pK_a,[a] *galacto*	pK_a,[a] *gluco*
	7.87[b,c]	7.30[c]
	8.25	7.50
	7.65	7.00
	7.60	7.10
	7.30	6.90

[a] Determined in 50% methanol at room temperature on apparatus previously described. A. M. Wilson and M. E. Munk, *Anal. Chem.*, **34**, 443 (1962). [b] pK_a of β-glycoside is 7.49. [c] pK_a of α-idoside is 7.90 and of α-altroside is 7.65: C. L. Stevens, P. Blumbergs, J. P. Dickerson and D. Chitharanjan, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 5c.

Experimental Section

Melting points are uncorrected and were obtained on a Thomas–Hoover capillary melting point apparatus.

Methyl 2,3-Di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside.—The need for greater quantities of this compound made an improvement of the lit.[4a] procedure necessary. A slurry of 490 g of the crude methyl 4,6-O-benzylidene-α-D-glucoside (1.74 moles) mixed with excess of powdered technical sodium hydroxide (1.5 kg) in 8000 ml of technical toluene was refluxed under a water separator with vigorous stirring for 1 hr. Excess (3–4 moles) of α-chlorotoluene was added in five lots at ~30-min intervals. The mixture was stirred at 100–110° for a total reaction time of 4 hr. The use of a water separator during refluxing prevents the reaction mixture from becoming sticky owing to water formed in the reaction. The product was mixed with 2 l. of water and steam distilled *in vacuo*, until all volatile substances were removed. The residue, which crystallized, was washed with water, dried, and recrystallized once from aqueous ethanol to yield 638 g (80%) of the 2,3-di-O-benzyl compound, mp 96–98° (lit. 66%, mp 93–99°).

Methyl 2,3-Di-O-benzyl-4,6-di-O-methylsulfonyl-α-D-glucopyranoside, IIa.—To a solution of 321 g (0.86 mole) of methyl 2,3-di-O-benzyl-α-D-glucopyranoside[2a] in 600 ml of dried tetrahydrofuran and 271 g (4 equiv) of pyridine was added, with stirring, 295 g (3 equiv) of methanesulfonyl chloride. The reaction mixture was stirred at room temperature overnight; on ad-

(8) This triacetate was prepared for comparison with the crystalline triacetate of the naturally occurring methylamino sugar bamosamine, which was, however, shown to be of the *gluco* configuration; *cf.* paper II of this series.[2]

(9) With the 4-*t*-butylcyclohexylamines, the *cis* (axial) and *trans* (equatorial) isomers have pK_a' values of 9.24 and 9.50, respectively: M. Tichy, J. Jonas, and J. Sicher, *Collection Czech. Chem. Commun.*, **24**, 3434 (1959); *Chem. Abstr.*, **54**, 2208*i* (1960).

(10) J. Sicher and M. Svoboda, *Chem. Listy.*, **52**, 1596 (1958); *Chem. Abstr.*, **53**, 1188*d* (1959), for example, and unpublished observations.

dition of 5 l. of water the product IIa precipitated. It was washed with water and recrystallized from ethanol–water (8:2) to yield 446 g (98%), mp 120.5–122°.

For analysis a sample was recrystallized once more from 80% ethanol, mp 121.5–123°, $[\alpha]^{25}D$ +57° (*c* 1.14, $CHCl_3$).

Anal. Calcd for $C_{23}H_{30}O_{10}S_2$: C, 52.06; H, 5.70; S, 12.09. Found: C, 52.32; H, 5.75; S, 12.03.

Methyl 2,3-Di-O-benzyl-6-iodo-4-O-methylsulfonyl-α-D-glucopyranoside, IIb.—A solution of 92 g of the IIa in 700 ml of 2-butanone was refluxed with excess of sodium iodide (45 g) for 6 hr. The solution was filtered and the precipitate washed with acetone to yield 19.85 g (97% of 1 mole) of sodium mesylate. The solution was concentrated to dryness, and to this was added an aqueous 10% sodium thiosulfate solution and chloroform. The chloroform extract was washed with water and dried. Removal of chloroform *in vacuo* left a white crystalline solid. Recrystallization from absolute ethanol yielded 81.2 g (85%) of IIb, mp 131–132°. One further recrystallization from chloroform–pentane gave an analytical sample, mp 133–134°, $[\alpha]^{25}D$ +41.3° (*c* 1.15, $CHCl_3$).

Anal. Calcd for $C_{22}H_{27}IO_7S$: C, 46.98; H, 4.84; S, 5.71. Found: C, 46.83; H, 5.05; S, 5.75.

When the preparation of IIb was done by heating the dimesylate IIa with sodium iodide in acetone for 3 hr at 105–110° (sealed tube) some displacement of the 4-mesyl group took place. Excess (126%) of 1 mole of sodium mesylate was formed, and the reaction product had to be purified by chromatography over alumina, which afforded 72% of the 6-iodo-4-mesylate IIb (mp 133.5–134°) and 11% of an oily diiodo compound. Analysis confirmed a diiodo formulation for this oil.

Anal. Calcd for $C_{21}H_{24}I_2O_4$: C, 42.44; H, 4.07; I, 42.71. Found: C, 42.43; H, 4.04; I, 42.97.

Methyl 2,3-Di-O-benzyl-6-deoxy-4-O-methylsulfonyl-α-D-glucopyranoside, IIc.—To a mixture of 5 l. of dry tetrahydrofuran and 67.8 g (1.78 mole) of lithium aluminum hydride was added 500 g (0.89 mole) of the iodo glycoside IIb. The mixture was stirred, and refluxed for 6 hr. The excess of hydride was destroyed with ethyl acetate; the solvents were removed on a rotary evaporator. To the resulting solid 1 l. of ether was added, and the complex decomposed by slow addition of water, until all aluminum salts were precipitated. The clear ether solution was decanted, and the inorganics were washed three times with wet ether. The combined ether extracts were dried and evaporated. The remaining crystalline solid was recrystallized from ethanol and afforded 320 g (82%) of the desired IIc, mp 110–111°. The evaporation of the mother liquor left about 65 g of a brown oil. The infrared spectrum of this oil showed absence of mesylate, but indicated the presence of a hydroxyl group. This crude oil was subjected to remesylation in 150 ml of dry tetrahydrofuran, 53 g (~4 equiv) of pyridine and 57.5 g (~3 equiv) of methylsulfonyl chloride. Standard work-up gave a brown syrup which was taken up in ethanol and treated with Norit. Upon cooling 30 g of the mesylate IIc were collected, mp 110–111°. The mother liquor was chromatographed over alumina (Woelm grade I) and afforded the following fractions.

Petroleum ether (30–60°) gave 9.2 g of dideoxy compound IIIb, bp 148° (0.003 mm), $[\alpha]^{24}D$ 42.1° (*c* 2.42, $CHCl_3$).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.67; H, 7.65. Found: C, 73.61; H, 7.70.

Petroleum ether–ether (80:20) gave 16 g of mesylate IIc, mp 110–111°, $[\alpha]^{25}D$ 38° (*c* 1.38, $CHCl_3$).

Anal. Calcd for $C_{22}H_{28}O_7S$: C, 60.53; H, 6.46; S, 7.35. Found: C, 60.78; H, 6.60; S, 7.50.

Petroleum ether–ether (70:30) gave 5.6 g of unreacted 6-iodo compound IIb.

Total inventory was 366 g (94%) of IIc, 9.2 g (3%) of IIIb, and 5.6 g (1%) of starting IIb.

Methyl 2,3-Di-O-benzyl-4-azido-4,6-dideoxy-α-D-galactopyranoside, IVa.—A solution of 50 g (0.15 mole) of IIc and 25 g (about fourfold excess) of sodium azide in 250 ml of dimethylformamide (DMF) containing 3 ml of water was refluxed 4 hr. After cooling the reaction mixture was poured into 1.5 l. of water and extracted five times with the total volume of 1 l. of petroleum ether. The extract was dried and evaporated to yield 42 g (96%) of IVa as a slightly yellow oil. This product was pure enough for the further steps as shown by thin layer chromatography (system, ether–petroleum ether, 1:1) and by its infrared spectrum (absence of a mesyl band).

By chromatography over alumina (Woelm grade I; eluent, petroleum ether–ether 9:1) the 4-azidoglycoside IVa was obtained in crystalline form. Recrystallization from pentane gave an analytical sample, mp 54°, $[\alpha]^{25}D$ 11.3° (*c* 1.94, in $CHCl_3$).

Anal. Calcd for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.70; H, 6.82; N, 10.90.

Methyl 2,3-Di-O-benzyl-4-amino-4,6-dideoxy-α-D-galactopyranoside, IVb, and Its Hydrochloride.—A solution of 63 g of azide IVa in 50 ml of dry dioxane was added dropwise to a vigorously stirred solution of 12 g of lithium aluminum hydride (2 moles) in 250 ml of dioxane. After vigorous nitrogen evolution had ceased, the mixture was refluxed for 0.5 hr. The excess of hydride was decomposed by the addition of ethyl acetate, and the solvents were evaporated on the rotary evaporator to dryness. The dry residue was dissolved in 300 ml of ether, and water slowly added until the aluminum hydroxide coagulated. The precipitate was washed several times with ether and the combined ether extracts were dried and evaporated to give 58 g (89.5%) of a colorless, viscous oil. For analysis a small amount was distilled evaporatively.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.36; H, 7.88; N, 3.83.

For the preparation of the hydrochloride 3 g of the oily amine were dissolved in 20 ml of ether and a slight excess of isopropanol–hydrogen chloride added. As soon as the hydrochloride was precipitated the solvents with the excess of hydrogen chloride were decanted. The crude precipitate was recrystallized from 2-propanol–ether–pentane to yield 2.6 g (79%) of the hydrochloride, mp 196–198° dec. For analysis a sample was recrystallized from the same solvent mixture, mp 199–200° (without decomposition), $[\alpha]^{25}D$ 88.5° (*c* 0.89, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}ClNO_4$: C, 64.03; H, 7.16; Cl, 9.00. Found: C, 63.83; H, 7.42; Cl, 9.20.

Methyl 4-Amino-4,6-dideoxy-α-D-galactopyranoside (Va) and Its Hydrochloride.—A solution of 58 g of the oily amine IVb in 200 ml of methanol was hydrogenated at atmospheric pressure with 850 mg of 10% palladium on charcoal as catalyst. After the addition of excess of concentrated hydrochloric acid (34 ml, 2 equiv) the hydrogen uptake was very rapid, and the hydrogenation was completed after 2 hr. The catalyst was filtered off and the solvents were evaporated at aspirator pressure and then at 1-mm pressure. The white crystalline residue was recrystallized from absolute ethanol to yield 32.7 g (93.5%) of Va hydrochloride, mp 233–234°, $[\alpha]^{24}D$ 209° (*c* 1.81, in H_2O).

Anal. Calcd for $C_7H_{18}ClNO_4$: C, 39.35; H, 7.55; N, 6.58; Cl, 16.59. Found: C, 39.28; H, 7.53; N, 6.64; Cl, 16.46.

For preparation of the free base 5 g of the hydrochloride dissolved in methanol was passed over a column of Dowex 50-X2. The column was washed neutral with methanol (~250 ml), and then eluted with 300 ml of 2% methanolic ammonia. Evaporation of the solvent left a slightly yellow oil which crystallized on standing. The crystals were recrystallized from ethanol–ether–pentane to yield 3.78 g (91%), mp 102–102.5°.

Anal. Calcd for $C_7H_{15}NO_4$: C, 47.45; H, 8.53; N, 7.90. Found: C, 47.54; H, 8.71; N, 7.84.

Methyl 2,3-Di-O-benzyl-4-acetamido-4,6-dideoxy-α-D-galactopyranoside, IVc.—A solution of 8 g of the oily IVb in pyridine was treated with excess of acetic anhydride overnight. The reaction mixture was evaporated at 1-mm pressure, and the oily residue partitioned between water and chloroform. The chloroform layer was dried and evaporated. The resulting oily residue crystallized on standing, and was recrystallized from ethyl acetate–ether–pentane to yield 8.6 g, mp 94–95°. For analysis a small sample was recrystallized from chloroform–pentane, mp 94–95°, $[\alpha]D$ +64.3° (*c* 0.98, $CHCl_3$).

Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.50. Found: C, 68.96; H, 7.52; N, 3.36.

Methyl 4-Acetamido-4,6-dideoxy-α-D-galactopyranoside, Vd, Method A.—A solution of 6.6 g of analytically pure IVc in 100 ml of methanol was hydrogenated at atmospheric pressure with 200 mg of 10% palladium on charcoal as catalyst. The hydrogen uptake was quantitative after 6 hr. The catalyst was filtered off and the solvents evaporated *in vacuo* leaving an amorphous glass. All attempts to directly crystallize this product failed. It could be precipitated as a fluffy amorphous solid, 2.25 g (62%), which had a melting range from 76–84°. Thin layer chromatography indicated the uniformity of this product. For analysis a small sample was sublimed, at 125–130° (0.001 mm), mp 77–83°, $[\alpha]^{25}D$ 170.5° (*c* 1.86, H_2O). It could be crystallized, however, after chromatography (see below).

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.19; H, 8.00; N, 6.32.

Method B.—A solution of 2.4 g of Va (free base) in 35 ml of methanol was cooled (0°) and a twofold excess (2.4 g) of acetic anhydride was added in four portions over a period of 30 min. After standing for another 30 min at room temperature the reaction mixture was passed over a column of Dowex 50-X2 in order to separate the product from unreacted starting material. The evaporation of the solvent left a foam. Thin layer chromatography and an infrared spectrum proved this compound to be identical with the one obtained according to method A. A solution of 800 mg of the above foam in the minimum amount of chloroform was passed over a Florisil column. Elution with chloroform removed mixtures containing both O- and N-acetyl groups. Elution with 10% acetone–chloroform afforded 230 mg of crystalline Vd. A small sample was recrystallized from acetone–pentane, mp 163–165°, for an elemental analysis which was satisfactory.

4-Acetamido-1,2,3-tri-O-acetyl-4,6-dideoxy-α-D-galactopyranoside, VII.—The hydrochloride of Va, (15 g) was converted to its free base using Dowex 50 which was acetylated using excess acetic anhydride in pyridine at room temperature overnight. Standard work-up gave 14.9 g (75%) of the oily triacetyl derivative VIa which could not be crystallized. Thin layer chromatography and good elemental analysis indicated the purity of the product.

Anal. Calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98. Found: C, 51.70; H, 6.95.

The 14.9 g of triacetate glycoside VIa were dissolved in 300 ml of acetic anhydride; after cooling to 0° 5 ml of concentrated sulfuric acid was added while stirring. The reaction mixture was kept at room temperature for 7 hr and then poured into 2 l. of ice–water and extracted three times with chloroform. After drying and evaporation of the chloroform a dark brown oil remained which was purified by chromatography over alumina (Woelm grade I). The chromatography yielded after recrystallization from ether–pentane 5.13 g (31%) of white crystals, mp 207–208°, $[\alpha]^{25}D$ 95° (*c* 1.10, $CHCl_3$).

Anal. Calcd for $C_{14}H_{21}NO_8$: C, 50.75; H, 6.39; N, 4.23. Found: C, 50.80; H, 6.54; N, 4.30.

4-Amino-4,6-dideoxy-D-galactose Hydrochloride (Thomosamine), Ia. A. Acid Hydrolysis of VII.—A solution of 500 mg of the tetraacetate VII in 70 ml of 3 *N* hydrochloric acid was heated to 55° for 5 hr. The slightly brown solution was stirred with Norit for 30 min and filtered. The colorless solution was carefully evaporated to dryness (at 35°, 0.1 mm). The glassy residue was dissolved in ethanol but did not crystallize. Upon dropwise addition of ether an off-white, fluffy, amorphous solid precipitated. This was filtered and reprecipitated again from ethanol–ether to yield a white amorphous solid, 108 mg (36%), mp 79–83°. The material traveled as a single spot on paper chromatography with $R_{glucose}$ 1.13 in 1-butanol–ethanol–water, 13:8:4, and $R_{glucose}$ 2.09 in pyridine–ethyl acetate–water, 1:3.6:1.1.

Anal. Calcd for $C_3H_{14}ClNO_4$: C, 36.10; H, 7.07; N, 7.02. Found: C, 36.45; H, 7.36; N, 6.61.

Attempts to purify Ia hydrochloride further and attempts at preparation of other salts were unsuccessful. Ia hydrochloride decomposed both in solution and in the solid state with the liberation of ammonium chloride.

The alternate routes described below were unsuccessful for the preparation of Ia. The experimental results of these attempts may be useful.

B. Acid Hydrolysis of Vd.—Treatment of pure Vd with 50 ml of 3 *N* hydrochloric acid at steam-bath temperatures for 3 hr afforded an 80% yield of the deacetylated product Va hydrochloride, mp 232–234°. Identical conditions successfully hydrolyzed the glycoside group of the *gluco* isomer of Vd.

C. Acid Hydrolysis of Va.—Treatment of Va with 1 *N* sulfuric acid for 2 days with a gradual rise in temperature up to 98° afforded a mixture of about equal amounts of Ia and starting Va by paper chromatography. This technique minimized decomposition. Unfortunately, Dowex-50 chromatography failed to separate the components.

4-Acetamido-1,2,3-tri-O-acetyl-4,6-dideoxy-β-D-galactopyranoside, VIII.—The α-tetraacetate VII (500 mg) was hydrolized according to the above procedure. The glassy solid obtained after careful evaporation was immediately dissolved in excess of pyridine, and reacetylated with excess of acetic anhydride at 65° for 14 hr. After the usual work-up procedure for this type of acetylation, evaporation of the slightly yellow chloroform extract left a viscous oil, from which, after addition of a minimum amount of ether, 3.9 mg (0.8%) of the α-tetraacetate VII crystallized. From the mother liquor, by addition of pentane, the β-tetraacetate VIII crystallized: 285 mg (57%), mp 87–89°, $[\alpha]^{25}D$ + 24.1° (*c* 1.11, $CHCl_3$). After several crystallizations from ether–pentane a sample with constant rotation and mp 89–90° was obtained: $[\alpha]^{25}D$ + 21° (*c* 1.26, $CHCl_3$). When the product of hydrolysis of VII was allowed to stand for 1 day before reacetylation, no VIII was obtained.

Anal. Calcd for $C_{14}H_{21}NO_8$: C, 50.75; H, 6.39; N, 4.23. Found: C, 50.83; H, 6.41; N, 4.07.

Acetolysis of IVc.—A solution of 8.36 g of IVc in 150 ml of acetic anhydride was cooled to 0° and treated with 4 ml of concentrated sulfuric acid. This was left at room temperature for 7 hr and subjected to the same work-up as used in the case of VIa. The resulting dark brown oil was subjected to alumina chromatography (Woelm grade I) and the following compounds were isolated.

(1) A C_{19} monobenzyl compound which melted at 167–167.5° after recrystallization from ether–pentane: 2.3 g (~30%); infrared ($CHCl_3$) 5.75, 6.06 and 8.05 μ.

Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.13; H, 6.63; N, 3.89.

(2) α-Tetraacetate VII, 555 mg (8%), mp 205–207° after recrystallization from ether–pentane.

(3) An unsaturated, C_{15} compound (tentatively assigned structure IX): 1.6 g (~30%); mp 157–158° after recrystallization from chloroform–carbon tetrachloride; positive bromine unsaturation test and negative Fehling and Bendict tests were obtained; infrared ($CHCl_3$), 3 (broad), 5.97, and 10.13 μ.

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.23; H, 6.73; N, 5.22.

Methyl 2,3-Di-O-benzyl-4-carbethoxyamino-4,6-dideoxy-α-D-galactopyranoside, IVd.—A solution of 10 g of oily amine IVb in 75 ml of chloroform was added to a solution of 8 g of sodium bicarbonate in 100 ml of water and the mixture was cooled to 0°. A solution of 3 g of ethylchloroformate in 15 ml of chloroform was added in small portions with vigorous shaking. After 45 min the addition was complete and the chloroform layer was separated, dried, and evaporated to give a crystalline solid. This product was recrystallized from ether–pentane to yield 10.2 g (85%), mp 83–84°. For analysis a small sample was recrystallized again from the same solvent pair, mp 83.5–84.5°, $[\alpha]D$ 46.7° (*c* 1.93, $CHCl_3$).

Anal. Calcd for $C_{24}H_{30}NO_6$: C, 67.27; H, 7.06; N, 3.26. Found: C, 67.29; H, 7.36; N, 3.21.

Methyl 2,3-Di-O-benzyl-4-methylamino-4,6-dideoxy-α-D-galactopyranoside, IVe.—A solution of 4 g of the N-carboethoxy glycoside IVd in 150 ml of ether was treated with 2 g of lithium aluminum hydride at reflux for 3 hr. Excess of hydride was decomposed by the addition of ethylacetate and then water was added until the precipitate coagulated. The ether was decanted, the aluminum hydroxide washed three times with 50-ml portions of ether with vigorous shaking. The combined ether extracts were dried and evaporated to yield 3.5 g (95%) of a clear, viscous oil. This product is pure enough for the further reactions. For analysis a small sample was distilled at 90–100° (0.001 mm).

Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.38; H, 7.92; N, 3.82.

For preparation of the hydrochloride, the crude oily product was dissolved in ether and the salt precipitated by the addition of sufficient 2-propanol–hydrogen chloride. One recrystallization from 2-propanol–ether yielded the analytically pure compound, mp 185–187°, $[\alpha]^{25}D$ 100° (*c* 1.15, methanol). The yield of IVe hydrochloride from amine IVb was 78%.

Anal. Calcd for $C_{22}H_{30}ClNO_4$: C, 64.77; H, 7.41; N, 3.43; C., 8.69. Found: C, 64.78; H, 7.53; N, 3.54; Cl, 8.84.

Methyl 4,6-Dideoxy-4-methylamino-α-D-galactopyranoside, Vb.—A solution of 2 g of the crude oily IVe in 50 ml of methanol was hydrogenated with 10% palladium on charcoal as catalyst. When 1 ml of concentrated hydrochloric acid was added the hydrogen uptake was completed within 20 min. The usual work-up procedure using Dowex 50 yielded an oil which crystallized on standing. The recrystallization from ether–pentane yielded 885 mg (86.5%), mp 119–120°. For analysis a small sample was sublimed at 80–90° (0.01 mm) and recrystallized once more from ether–pentane, mp 120–121°, $[\alpha]^{25}D$ 255° (*c* 0.985, $CHCl_3$).

Anal. Calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.32. Found: C, 50.27; H, 8.97; N, 7.14.

Methyl 2,3-Di-O-acetyl-4-N-methylacetamido-4,6-dideoxy-α-D-galactopyranoside, VIb.—A solution of 156 mg of the glycoside Vb in pyridine was treated with excess acetic anhydride at 50° for 2 days. The usual work-up procedure (evaporation, distribution between water–chloroform, drying, and evaporation), and recrystallization from ether–pentane yielded 171 mg (78%), mp 119–120°, $[\alpha]^{25}D$ +89° (*c* 1.13, $CHCl_3$).

Anal. Calcd for $C_{14}H_{23}NO_7$: C, 53.00; H, 7.30; N, 4.41. Found: C, 53.31; H, 7.40; N, 4.43.

Methyl 2,3-Di-O-benzyl-4-dimethylamino-4,6-dideoxy-α-D-galactopyranoside, IVf.—A solution of 1.8 g of the oily amine IVa in 10 ml of 80% formic acid and 1.5 ml of 40% formalin was heated on a steam bath for 10 hr. After evaporation of the solvents *in vacuo* the residual yellow oil was dissolved in 50 ml of methanol, and passed over a column of Dowex 50-X2 (acid form). The column was washed with 200 ml of methanol, and then eluted with 20 ml of 2% ammonia in methanol. The solvent was evaporated *in vacuo* and the remaining viscous oil was distilled evaporatively at 125° (0.001 mm) to give an oil, 1.9 g (98%).

Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.36. Found: C, 71.45; H, 8.04; N, 3.61.

For preparation of the hydrochloride the free base was dissolved in ether and sufficient 2-propanol containing dry hydrogen chloride gas was added until all material was precipitated. The while crystalline product was recrystallized from 2-propanol-ether to yield 1.72 g (81%), mp 185–187°, $[\alpha]^{25}D$ 54° (*c* 1.42, methanol).

Anal. Calcd for $C_{23}H_{32}ClNO_4$: C, 65.47; H, 7.64; N, 3.32; Cl, 8.40. Found: C, 65.66; H, 7.64; N, 3.50; Cl, 8.59.

Methyl 4-Dimethylamino-4,6-dideoxy-α-D-galactopyranoside, Vc. Method A.—A methanol solution containing 500 mg of IVf hydrochloride was hydrogenated at atmospheric pressure using palladium (10%) on charcoal as catalyst. After the addition of three drops of hydrochloric acid the uptake was finished within 0.5 hr. The reaction solution was filtered and passed over Dowex 50-X2. The column was washed neutral with methanol and eluted with 2% ammonia in methanol. Evaporation of the solvent left crystalline solid which was sublimed to yield 218 mg (96%), mp 96.5–97.5°.

Method B.—In an alternate procedure 1.0 g of Va was methylated using 7.2 ml of 86% formic acid and 1.6 ml of 40% formalin solution with heating on a steam bath for 14 hr. After evaporation of the solvents, the residual dark brown oil was dissolved in 30 ml of methanol, and, after cooling to 0°, was treated with 3 portions of 10 drops of acetic anhydride over a period of 30 min. The reaction mixture was then passed over a Dowex 50 column and washed with methanol; the basic product was finally eluted with 2% ammonia in methanol. The evaporation left a viscous oil, which crystallized on standing. The crystals were recrystallized from ether–pentane to yield 732 mg (63%) of Vc, mp 95–97°.

For analysis a small sample was sublimed at 100° (0.01 mm) and recrystallized once more from the same solvent pair, mp 96.5–97.5°, $[\alpha]^{24}D$ 134 (*c* 1.17, CHClC).

Anal. Calcd for $C_9H_{19}NO_4$: C, 52.58; H, 9.46; N, 7.06. Found: C, 52.67; H, 9.33; N, 6.82.

For preparation of the hydrochloride the crystalline free base was dissolved in ether, and the salt precipitated by addition of sufficient 2-propanol hydrogen chloride. The gum which was formed was dissolved in a ethanol–chloroform mixture (1:3) and acetone was added to turbidity. From this solution the hydrochloride crystallized after standing for several days. The usual procedure for crystallizing similar salts (ethanol–ether–pentane or 2-propanol–ether mixtures) failed in this case. The yield of salt from free base Vc was 48%, mp 164–165°.

Anal. Calcd for $C_9H_{20}ClNO_4$: C, 44.72; H, 8.34; N, 5.79. Found: C, 44.84; H, 8.33; N, 5.70.

4-Dimethylamino-4,6-dideoxy-D-galactose Hydrochloride, Ic.—A solution of 306 mg of glycoside Vc in 50 ml of 3 *N* hydrochloric acid was heated on a steam bath for 6 hr. The colorless reaction mixture was evaporated to dryness and the residual glass was dissolved in the minimum amount of ethanol. On standing at room temperature, and then for several days in the refrigerator, 288 mg (67%) of Ic crystallized: mp 193°; $[\alpha]^{24}D$ (initial) 70°; (24 hr) 10.3° (*c* 1.55, H_2O). The sample for analysis was recrystallized a second time, mp 193°.

Anal. Calcd for $C_8H_{17}ClNO_4$: C, 42.20; H, 7.97; H, 6.15; Cl, 15.57. Found: C, 42.44; H, 8.01; N, 6.27; Cl, 15.44.

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Synthesis and Chemistry of 4-Amino-4,6-dideoxy Sugars. II. Glucose[1]

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The stereospecific syntheses of 4-amino-4,6-dideoxy-D-glucose, Ia, and its N-methyl and N,N-dimethyl homologs, Ib and c, are described. The utility of intermolecular inversions at the 4-carbon atom of sugars is amply demonstrated. Nmr analyses of Ia and selected derivatives are consistent with the *gluco*-pyranose configuration and indicate the expected chair conformation. The N-methyl homolog, Ib, was shown to be identical with the amino sugar moiety of the antibiotic bamicetin.[3]

To date 4-amino-4,6-dideoxy-D-glucose and its N-methyl and N,N-dimethyl homologs have been isolated from at least four natural sources: (1) from *Streptomyces plicatus*[3] and (2) *Streptomyces vinaceus-drappus*[4] as components of the antibiotics amicetin and bamicetin; and from cell extracts of (3) *Chromobacterium violaceum*[1b] and (4) *Escherichia coli* strain B.[1c] This paper describes the synthesis of these sugars.

4-Amino-4,6-dideoxy-D-glucose (Viosamine,[1b] Ia).—Two synthetic routes were successful for the synthesis of Ia. The starting material for the first approach was IIa, a known 4,6-ditosylate derivative of D-galactose.[5] Selective displacement of the primary 6-O-tosylate group with iodide ion was not realized. However, the desired 6-iodo compound IIb could be isolated in fair yield when IIa was heated at 110° with 1.5 equivalents of sodium iodide in acetone. Alumina chromatography provided the desired separation of reaction products and resulted in a 32% yield of the

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