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.

Acknowledgment.—The authors wish to thank Miss A. Balys for determining some of the pK_a values. Financial assistance from the National Institutes of Health, Grant GM 11520, is gratefully acknowledged.

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

(1) Preliminary accounts of portions of this work have appeared: (a) C. L. Stevens, P. Blumbergs and F. A. Daniher, *J. Am. Chem. Soc.*, **85**, 1552 (1963); (b) C. L. Stevens, P. Blumbergs, F. A. Daniher, R. W. Wheat, A. Kujomoto, and E. L. Rollins, *ibid.*, **85**, 3061 (1963); (c) C. L. Stevens, P. Blumbergs, F. A. Daniher, J. L. Strominger, M. Matsuhashi, D. N. Dietzler, S. Suzuki, T. Okazaki, K. Sugimoto, and R. Okazaki, *ibid.*, **86**, 2939 (1964).

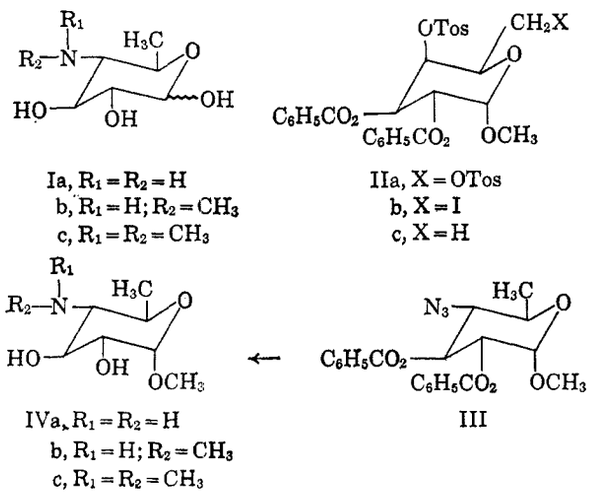
(2) National Science Foundation Predoctoral Fellow.

(3) T. H. Haskell, *J. Am. Chem. Soc.*, **80**, 747 (1958) and references cited therein.

(4) J. W. Hinman, E. L. Caron, and C. DeBoer, *ibid.*, **75**, 5864 (1953).

(5) E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **24**, 1618 (1959).

crystalline 6-iodo compound, IIb, and a 20% recovery of the starting ditosylate IIa. A third, oily reaction product was isolated whose physical properties and elemental analysis were consistent with a dideoxy-diiodo sugar derivative. The high yield of this compound, ~45%, provides evidence indicating that the primary and secondary tosyloxy groups of IIa are of



Ia, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$

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

IVa, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$

III

comparable reactivity toward nucleophilic displacement. This relative reactivity can be roughly estimated from data available in the literature. Thus, the relative reactivity at C-6:C-4 of the *gluco* configuration[6] roughly agrees with the ~100-fold difference seen for model primary and secondary alkyl bromides.[7] Further, it can be seen that the 6 position of glucose is about 50 times as reactive as a comparable galactose derivative.[8] From this, one may expect the reactivity of the 4 and 6 positions of galactose to be comparable and certainly of the same order of magnitude.

Raney nickel catalyzed hydrogenolysis of the 6-iodo group of IIb was facile and gave the 6-deoxy derivative, IIc, in 72% yield. Conversion of the *galacto* to the *gluco* configuration was effected by azide ion displacement of the 4-O-toxyl group of IIc. The resulting azide III, following a cursory infrared characterization was immediately converted to the amino sugar glycoside IVa in 50% yield by successive catalytic hydrogenation and basic saponification reactions. Periodate studies confirmed the presence of a 4-amino group. Thus, IVa consumed 2 moles at a rate similar to that of α-methyl-D-glucopyranoside while the mono-N-acetyl derivative Va consumed only 1 mole of periodate, and at a much slower rate.

Cleavage of the methyl glycoside was best effected by acid hydrolysis of the N-acetyl derivative Va. Thus, crystalline viosamine hydrochloride, Ia, could be obtained from Va in yields up to 85%. The over-all yield from commercially available D-galactose was of the order of 0.5% for twelve steps.

(6) Paper I of this series: C. L. Stevens, P. Blumbergs, and D. H. Otterbach, *J. Org. Chem.*, **31**, 2817 (1966).

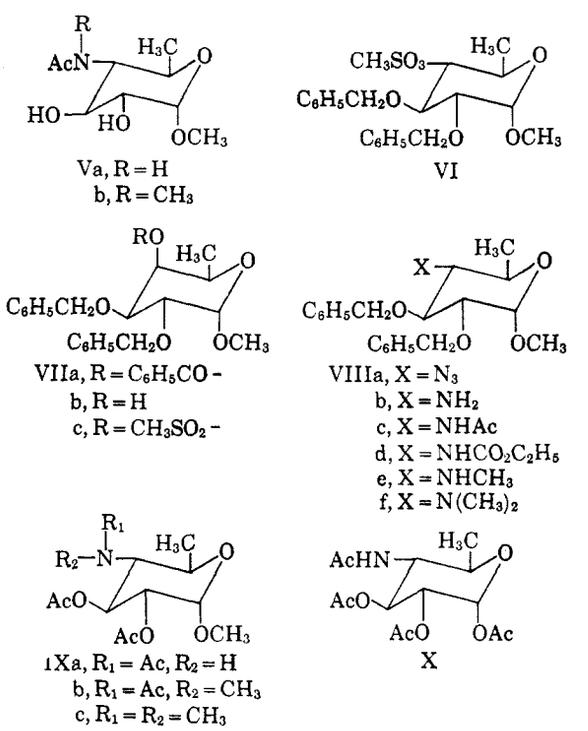
(7) *k*:*k* isobutyl bromide:cyclohexyl bromide equals 100; *cf.* A. J. Streitweiser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., New York, N. Y., 1962, p 13; H. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1962, p 178.

(8) Deduced from the data of J. M. Sugihara and W. J. Terrlink [*J. Org. Chem.*, **29**, 550 (1964)] and S. Nadkarni and N. R. Williams [*J. Chem .Soc.*, 3496 (1965)] who attribute the lowered reactivity at C-6 of galactose to field effects.

A superior method for synthesis of I was developed in conjunction with the synthesis of 4-amino-4,6-dideoxy-D-galactose[6] which used the readily available methyl α-D-glucopyranoside as starting material. The method employs a double inversion reaction sequence at the 4-carbon of the 6-deoxy-4-O-mesyl-*gluco* derivative VI,[6] the last compound common to both of the synthetic routes leading to the *gluco* and *galacto* 4-amino sugars.

Treatment of the mesylate VI with sodium benzoate in refluxing dimethylformamide[9] followed by a basic hydrolysis of the intermediate 4-O-benzoate VIIa afforded methyl 2,3-di-O-benzyl-6-deoxy-α-D-galactopyranoside (VIIb) in up to 86% over-all yield. Subsequent mesylation of VIIb in pyridine provided the C-4 epimer of VI, compound VIIc, thus completing the first steps in the double inversion sequence.

Sodium azide displacement was smoothly effected in dimethylformamide and the resulting azide VIIIa, an oil, was completely characterized. Lithium aluminum hydride reduction of VIIIa afforded an oily 4-amino compound VIIIb which was characterized as its hydrochloride salt and N-acetyl derivative VIIIc. The



Va, R = H
b, R = CH_3

VI

VIIa, R = C_6H_5CO-
b, R = H
c, R = CH_3SO_2-

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

IXa, R_1 = Ac, $R_2 = H$
b, R_1 = Ac, $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$

X

benzyl protecting groups could be removed by hydrogenation of the hydrochloride salt of VIIIb in the presence of additional acid. Under optimized conditions and without purification of intermediates, the conversion of mesylate VIIc to the N-acetyl derivative VIIIc could be effected in 94% over-all yield. Catalytic reduction of VIIIc also effected cleavage of the benzyl protecting groups and led to the N-acetyl derivative Va in 98% yield. Since Va was the derivative most suitable for acid hydrolysis to the free amino sugar Ia, the double inversion sequence resulted in a marked increase in over-all yield, 16% for thirteen steps from methyl α-D-glucoside.[10] The high yields throughout the se-

(9) Conditions similar to those employed by Reist, *et al.*, were used: E. J Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **24**, 1618 (1959).

(10) The yield of the 6-deoxy-4-mesylate VI was 30% from methyl glucoside[6] and Ia was 54% from VI.

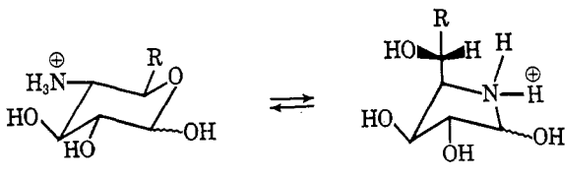


Figure 1.

quence demonstrate well the utility of displacement reactions, without intervening neighboring group participation, at the 4 position of hexoses, and for synthetic purposes, axial and equatorial mesylates are displaced with comparable facility.[11]

Acetylation experiments were carried out on three derivatives, VIIIc, IXa, and Ia. Treatment of the triacetate IXa with acetic anhydride employing sulfuric acid catalyst cleaved the glycosidic group and afforded the tetraacetyl derivative X in 71% yield. The high specific rotation (+142°) of X indicated the α configuration at carbon 1. Interestingly, the benzyl groups of VIIIc could also be cleaved under identical conditions, affording, again, X in 83% yield. The high proportion of the α-acetoxy derivative from these experiments is in accord with previous experimental findings with glucose itself.[12] Although viosamine hydrochloride, Ia, crystallizes with the β configuration at the anomeric carbon (see nmr studies below), acetylation in pyridine at 50° caused anomeric interconversion. Thus, while a similar reaction had afforded 4-acetamido-4,6-dideoxy-1,2,3-tri-O-acetyl-β-D-*galacto*-pyranoside,[6] this present experiment afforded the *gluco* α-acetoxy derivative X in 89% yield.

4,6-Dideoxy-4-methylamino-D-glucose (Bamosamine).—For synthetic entry into the monomethyl amino sugars, a class rarely found in nature,[13] di-O-benzyl derivative VIIIb was deemed suitable. N-Carbethoxy derivative VIIId was readily prepared but reduction to VIIIe with lithium aluminum hydride was only effected at the temperature of refluxing dioxane. Attempted reductions at the lower temperatures of refluxing tetrahydrofuran and ether resulted in recovery of the starting VIIId. This was completely unexpected since the axial N-carbethoxy group of the corresponding *galacto* isomer was readily reduced in refluxing ether.[6] Hydrogenolysis of the benzyl groups of VIIIe was smoothly accomplished in the presence of acid and afforded glycoside IVb in 71% over-all yield from VIIIb. Acetylations in methanol or pyridine afforded the crystalline acetyl derivatives Vb and IXb respectively. Numerous attempts to prepare Ib by the acid hydrolyses of synthetic IVb and Vb did not afford a crystalline product. However, the free sugar Ib could be characterized as a basic, reducing spot on paper chromatography.

Acidic methanolysis of bamicetin[3] afforded a basic fraction, which, on acetylation in methanol gave in about 75% yield a mixture (mixture A) of N-acetyl α- and β-methyl bamosaminides. By way of a preliminary identification of bamosamine, vapor phase and paper chromatographic comparisons were made. Vpc of the trimethylsilyl derivatives[14] of mixture A showed two peaks of approximately equal intensity. The intensity of the peak with the shorter retention time was approximately doubled when the natural mixture was innoculated with the approximate amount of the trimethylsilyl derivative of synthetic Vb. The second peak of the pair was presumed to be the β-glycoside of mixture A and its retention time relative to Vb was consistent with the relative retention times of previously observed α,β-anomeric hexose pairs.[14] Further, the acid hydrolysis of mixture A and the hydrolysis of Vb gave identical free sugar spots on paper chromatography in three systems. Conclusive proof for the structure of bamosamine was provided by comparison of a further acetylated derivative. Thus, acetylation of mixture A in pyridine afforded a mixture (mixture B) of triacetyl α- and β-glycosides from which crystalline IXb could be isolated in 43% yield. The remainder of mixture B was a gum containing only isomeric triacetyl glycosides (evidenced by correct elemental analysis) in which the β anomer predominated (by optical rotation). Thus the structure of bamosamine was shown to be 4,6-dideoxy-4-methylamino-D-glucose.

4,6-Dideoxy-4-dimethylamino-D-glucose (Amosamine).—Clark–Eschweiler methylation of the methyl glycoside IVa proceeded in 87% yield to the dimethylamino sugar IVc. Acidic hydrolysis of IVc at 100° afforded amosamine, Ic, in 70% yield. Methylation by the Clarke–Eschweiler procedure was also successful on dibenzyl derivative VIIIb. Subsequent hydrogenation of the oily VIIIf in the presence of excess hydrochloric acid also afforded IVc in 93% yield.

Nmr Studies.—The question of pyranose–pyrrolidine isomerization (Figure 1) in 4-aminohexoses is an interesting one; *e.g.*, Reist, Baker, and Goodman[15] provided evidence indicating formation of both pyranose and pyrrolidine forms of 4-amino-4-deoxy-D-glucose hydrochloride (Figure 1, R = CH_2OH) on attempted preparations of that compound from various derivatives. Reist and Goodman again encountered a pyrrolidine sugar in their recently described synthesis of 4-acetamido-4-deoxy-D-ribose.[16] Thus, it is reported that acetolysis of methyl 4-acetamido-4-deoxy-α-D-ribopyranoside yielded 1,2,3,4-tetraacetyl-5-acetoxymethyl-D-ribo-2,3,4-trihydroxypyrrolidine.

In the case of viosamine hydrochloride, Ia, its nmr spectrum in D_2O[17] was decisive, indicating the presence of the pyranose form exclusively (Figure 1, R = CH_3) even on standing and at elevated temperatures. In addition, the spectrum corroborates mutarotation data (see experimental) which indicated that viosamine hydrochloride crystallized as the β anomer. When the spectrum was recorded about 15 min after dissolution in D_2O the 6-methyl group was seen as a pair of doublets.[18] Integration revealed that the lower-field doublet, δ 1.90, comprised about 75% of the total

(11) Kinetic studies have established the displacement rates of C-4 axial and equatorial iodo sugar derivatives: C. L. Stevens, K. G. Taylor, and J. A. Valicenti, *J. Am. Chem. Soc.*, **87**, 4579 (1965).

(12) W. A. Bonner, *ibid.*, **73**, 2659 (1951), and references therein.

(13) J. D. Dutcher, "Advances in Carbohydrate Chemistry," Vol. 18, M. L. Wolfrom, Ed., Academic Press Inc., New York, N. Y., 1963, p 259, provides a review of amino sugars from some natural sources.

(14) C. C. Sweeley, R. Bently, M. Makita, and W. Wells, *J. Am. Chem. Soc.*, **85**, 2497 (1963).

(15) E. J. Reist, R. R. Spencer, D. F. Calkins, B. R. Baker, and L. Goodman, *J. Org. Chem.*, **30**, 2312 (1965).

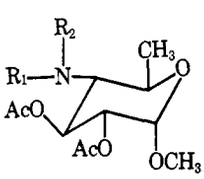
(16) E. J. Reist, L. Goodman, and D. E. Gueffroy, *J. Am. Chem. Soc.*, **87**, 677 (1965).

(17) We wish to thank Professor Robert Wheat of Duke University for providing this spectrum.

(18) The peak area of this pattern was set equivalent to 3.00 H. Further all chemical shifts herein reported are relative to tetramethylsilane as internal (organic solvents) or external standard (aqueous solvents).

methyl signal area. The higher field doublet, δ 1.85, had a J value of 6.5 cps, identical with that of its lower field partner. The lowest field portion of the spectrum revealed a small doublet (0.25 H), J = 3.5 cps,[19] at δ 5.80. Both the coupling constant and chemical shift of this signal were consistent with its assignment as the equatorial anomeric proton of the α-pyranose form of Ia. By comparison of relative areas the higher-field 6-methyl doublet, then, could also be assigned as the one due to the α anomer of Ia which was being formed by mutarotation. Indeed, both the δ 5.80 and 1.85 doublets increased in relative intensity on standing in solution, and, after 1.5 hr, reintegration of the methyl group signals indicated that the β/α ratio had decreased from the 15-min ratio of 75/25 to 65/35. This ratio is essentially identical with that found for aqueous solutions of glucose.[20] The axial anomeric proton of the β form of Ia was seen at about δ 5.2,[21] and, at room temperature, was half-obscured by a large HDO signal. At 95° the HDO signal was shifted upfield[22] clearly revealing a sharp doublet at δ 5.20, with a J value of 7.5 cps indicating the *trans* diaxial splitting of a β-pyranose.[19] With both anomeric proton signals (0.97H) now sharply defined it was evident that *only* β- and α-pyranose forms were present.[23,24] Examination of the remaining spectral features confirmed this interpretation. The C-4 proton, which would suffer only *trans* diaxial splittings in a pyranose chair form, was seen as a triplet, J = 9.5 cps, at δ 3.50, thus confirming the expected C_3 to C_6 conformation of Ia. The remaining C-2, -3, and -5 protons were displayed as a series of overlapping signals at somewhat lower field.

The nmr of diacetate IXc was instructive. When run in CCl_4, the acetyl signals were seen as sharp singlets



IXa, R_1 = Ac; R_2 = H
b, R_1 = Ac; R_2 = CH_3
c, R_1 = R_2 = CH_3

at δ 1.92 and 1.96 indicating that they were probably both equatorially disposed,[25] as anticipated. The remaining signals served to confirm the expected chair conformation of IXc: H-5, δ 3.69, octet with J's of 6.3 and 10 cps; H-4, δ 2.3, probable triplet partially obscured by the N,N-dimethyl signal at δ 2, 3, signal width 30 cps; H-3, δ 5.39,[26] triplet,[27] $J \sim 10$ cps. The H-2 and H-1 signals were superimposed[26] at δ 4.6 giving rise to a six-line pattern from which a J_{1-2} of 3.5 cps could be obtained. The somewhat high field chemical shift of H-1 and H-2 could be due to shielding effects from inter- or intramolecular associations in the nonpolar CCl_4 solvent, since in $CDCl_3$ their signals, still overlapped, were moved downfield to the more frequently seen value of δ 4.85.[19,26] Interestingly, the hydrochloride salt of IXc, which is formed on standing in chloroform or carbon tetrachloride, exhibits an "axial" acetoxyl signal at δ 2.15. In the nmr spectrum of IVc the H-1 doublet (δ 4.82, J = 3.5 cps) and H-4 triplet (δ 2.08, J = 9.5 cps) were now clearly seen and confirmed conclusions drawn from previous spectra.

Experimental Section

Melting points are uncorrected and were obtained on a Thomas–Hoover melting point apparatus. Infrared spectra were obtained on a Beckman IR-4 and nmr spectra on Varian DP-60 and A-60 spectrometers. Several paper chromatography systems were used: A, acetone–water (9:1); B, 1-butanol–ethanol–water–ammonium hydroxide (5:1.5:0.1:3); C, pyridine–ethyl acetate–water (5:12:4); D, pyridine–ethyl acetate–acetic acid–water (5:5:3:1); E, 2-propanol–3% ammonium hydroxide (3:1); F, 1-butanol–acetic acid–water (5:1:4). Several thin layer chromatography systems were also used to follow reaction courses and determine purity of products: A, diethyl ketone–diisopropyl ketone–ligroin (99–101°) (6:3:1); B, 1-butanol–water (saturated upper layer); C, chloroform–acetone (1:7); D, benzene–methanol (3:1). Petroleum ether of boiling range 30–60° was used for the indicated recrystallizations and chromatographies.

Methyl 2,3-Di-O-benzoyl-6-deoxy-6-iodo-4-O-*p*-tolylsulfonyl-α-D-galactopyranoside (IIb).—Three sealed tubes each containing 1.7 g of methyl 2,3-di-O-benzoyl-4,6-di-O-p-tolylsulfonyl-α-D-galactopyranoside (IIa)[5] and 535 mg of sodium iodide in 40 ml of anhydrous acetone were heated at 110° for 40 hr. Sodium *p*-tolylsulfonate, 1.68 g (120%) of theory was isolated by filtration. Acetone was removed at aspirator pressure and the residual solid partitioned between chloroform and water. The chloroform layer was washed with 10% aqueous sodium thiosulfate and water and dried (sodium sulfate). The chloroform was removed at aspirator pressure to yield a foam.

The resulting foam was chromatographed over 90.0 g of Fisher neutral alumina. Elution with 15% ether–petroleum ether (bp 40–60°) yielded 2.0 g (45%) of methyl 2,3-di-O-benzoyl-4,6-dideoxy-4,6-diiodo-α-D-aldohexopyranoside as an oil.

Anal. Calcd for $C_{21}H_{20}I_2O_6$: C, 40.53; H, 3.26; I, 40.79. Found: C, 41.57; H, 3.60; I, 39.85. C, 41.63; H, 3.58.

Continued elution with 1:1 ether–petroleum ether yielded, after recrystallization from methanol, 1.51 g of methyl 2,3-di-O-benzoyl-6-deoxy-6-iodo-4-O-*p*-tolylsulfonyl-α-D-galactopyranoside, IVb, mp 132–4°, $[\alpha]^{28}D$ + 141° (*c* 1.6, $CHCl_3$).

Anal. Calcd for $C_{28}H_{27}IO_9S$: C, 50.46; H, 4.09; S, 4.83. Found: C, 50.64; H, 4.12; S, 5.03.

Finally, elution with chloroform yielded 1.03 g (20%) of starting IIa, identified by melting point, mixture melting point, and infrared spectrum.

Methyl 2,3-Di-O-benzoyl-6-deoxy-4-O-*p*-tolylsulfonyl-α-D-galactopyranoside (IIc).—To a solution of 1.4 g of IVb in 10 ml of dry dioxane and 50 ml of dry methanol was added two spatula tips full of Raney nickel W-6. The reaction mixture was hydrogenated at atmospheric pressure. During the hydrogenation, an aqueous solution of 1.5 g of sodium hydroxide in 5.0 ml of water was added in small portions whenever the hydrogen uptake appeared to stop. Hydrogen uptake was 109% of theory. The reaction mixture was filtered, the catalyst washed with methanol, and the filtrate evaporated to dryness at aspirator pressure. The solid residue was dissolved in methanol and the

(19) R. U. Lemieux, R. K. Kulnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(20) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, pp 377, 408.

(21) The δ between the axial and equatorial anomeric protons of glucose is 0.58 ppm in D_2O: L. D. Hall, *Tetrahedron Letters*, **No. 23**, 1457 (1964).

(22) The remainder of the spectrum was essentially unaltered.

(23) Forms other than pyranose would have been detected in concentrations greater than 5%. At 95°, the β form still predominated over the α 56/44.

(24) For data on the nmr characteristics of anomeric protons of furanoses, see B. Capon and D. Thacker, *Proc. Chem. Soc.*, 369 (1964).

(25) (a) The chemical shifts of axial *vs.* equatorial acetates are discussed in ref 16 and (b) also by F. W. Lichtenthaler, *Ber.*, **96**, 2047 (1963).

(26) In agreement with observations made previously on the nmr spectrum of methyl-4-acetamido-4-deoxy-2,3,6-tri-O-acetyl-α-D-glucopyranoside: H. Agahigian, G. D. Vickers, M. H. von Saltza, J. Reid, A. I. Cohen, and H. Ganthier, *J. Org. Chem.*, **30**, 1085 (1965).

(27) Each line of this signal was split again (~1 cps) so that the signal had the appearance of a doublet of triplets. This was duplicated in $CDCl_3$ solvent and is attributed to long-range or virtual long-range coupling with another ring proton. *Cf.* R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **43**, 2059 (1965).

solution de-ionized by successive passages over a column of Dowex 1 and then Dowex 50. The eluate was evaporated to yield an oil which was dissolved in 10 ml of dry pyridine and cooled in an ice bath. To the chilled solution was slowly added two equivalents of benzoyl chloride (rebenzoylation). Cooling was continued for 2 hr and then the solution was stirred magnetically overnight at room temperature. The addition of ice–water to the reaction mixture yielded a solid. The solid was filtered, washed thoroughly with water, and then recrystallized from absolute ethanol to yield 650 mg of product, mp 156–158°. The mother liquors gave an additional 80 mg, mp 151–153°. The total yield was 72%. An analytical sample was obtained by recrystallization from ether–petroleum ether, mp 157.5–158.5°, $[\alpha]^{23}D$ + 180° (*c* 1.5, $CHCl_3$).

Anal. Calcd. for $C_{28}H_{28}O_9S$: C, 62.21; H, 5.22; S, 5.93. Found: C, 62.35; H, 5.28; S, 6.05.

Methyl 4-Amino-4,6-dideoxy-α-D-glucopyranoside (IVa).—A solution of 200 mg of IIc, 95 mg of lithium azide, and 10 mg of urea in 3.5 ml of dimethylformamide was heated at 125° for 20 hr. After removing the solvent *in vacuo*, the residual solid was partitioned between chloroform and water. The chloroform solution was dried over sodium sulfate and removed at aspirator pressure to yield as a yellow oil methyl 4-azido-2,3-di-O-benzoyl-4,6-dideoxy-α-D-glucopyranoside, III. An infrared spectrum of the oil confirmed the presence of organic azide with a strong absorption at 4.75 μ.

For the reduction step, platinum oxide (50 mg) was suspended in 10 ml of methanol and reduced by stirring with hydrogen at room temperature, followed by the addition of the crude 4-azido compound in 10 ml of methanol. The reaction mixture was stirred under hydrogen for 3 hr and a slight volume increase was noted. The catalyst was removed and the methanol evaporated at aspirator pressure. The residue was heated in 10 ml of distilled water with 300 mg of barium hydroxide monohydrate on a steam bath for 2.25 hr. The barium ion was precipitated by the addition of 10% sulfuric acid to a pH of 3. The mixture was filtered through Celite, the residue washed with 10 ml of distilled water, and the filtrate concentrated to a volume of approximately 3 ml *in vacuo*. The solution was diluted with 10 ml of methanol and passed over a column of Dowex 50-X2 (acid form). The column was washed with methanol to neutrality and then eluted with 60 ml of 1% ammonia in methanol. The eluate was evaporated at aspirator pressure and the solid residue was sublimed at 95° and 0.1-mm pressure. The sublimed material weighed 32.2 mg (50%), mp 115–116°. An analytical sample was obtained by recrystallization from chloroform–petroleum ether, mp 117–118° $[\alpha]^{23}D$ +143.7° (*c* 0.85, H_2O).

Anal. Calcd for $C_7H_{15}NO_4$: C, 47.44; H, 8.53; N, 7.90. Found: C, 47.55; H, 8.34; N, 8.03.

Methyl 4-Acetamido-4,6-dideoxy-α-D-glucopyranoside (Va).—A solution of 150 mg of IVa in 5 ml of methanol was cooled to 0° in an ice bath. Acetic anhydride (0.25 ml) was added slowly and the solution stirred at 0° for 30 min. The addition was repeated and the solution was stirred at 0° for 1 hr and allowed to come to room temperature. The solvent was removed at aspirator pressure and the residue recrystallized from methanol–ether to yield 155 mg (83%) of product, mp 188–189°, $[\alpha]^{24}D$ +173° (*c* 0.39, H_2O). The melting point was not raised by further recrystallization.

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.30; H, 7.81; N, 6.39. Found: C, 49.24; H, 7.87; N, 6.44.

4-Amino-4,6-dideoxy-D-glucose Hydrochloride (Ia).—A solution of 40.4 mg of Va in 9.5 ml of 2.5 *N* hydrochloric acid was heated in an oil bath at 98–100° for 6.5 hr. The solution was cooled and evaporated to dryness at oil-pump pressure. The residue was chromatographed over a 1 × 30 cm column of acid Dowex 50-X2. The column was washed with 50 ml of distilled water and then eluted with 0.33 *N* hydrochloric acid, 10-ml fractions being taken. Fractions 4–7 contained the product which migrated as a single spot on paper chromatograms, R_f 0.39 system A. These fractions were combined, filtered through a bed of Norit and evaporated to dryness at oil-pump pressure. The residue, a clear glass, was dissolved in 0.1 ml of distilled water and diluted with 2.0 ml of absolute ethanol. Ether was then added to turbidity and the solution allowed to stand at 4° for 5 days. The solution was filtered and the crystalline residue washed with cold ethanol–ether (1:1). The material was dried at 0.1 mm for 30 min at room temperature. The product weighed 21.4 mg (58%) and melted at 130–138° dec, $[\alpha]^{21.5}D$ −12.0°, 8 min → −1.58°, 30 min → +7.24°, 1 hr → +20.1°, 22 hr (*c* 0.76, H_2O). In later, larger scale preparations the Dowex 50 chromatography step could be omitted and yields up to 85% could be obtained.

Anal. Calcd for $C_6H_{14}ClNO_4$: C, 36.10; H, 7.07; N, 7.02. Found: C, 35.91; H, 7.10; N, 6.96.

Methyl 2,3-Di-O-benzyl-6-deoxy-α-D-galactopyranoside (VIIb).—A mixture of 100 g (0.23 mole) of 4-O-mesyl derivative VI[6] and 100 g (3 equiv) of sodium benzoate in 1500 ml of dimethylformamide was heated at reflux with vigorous stirring for 24 hr. The mixture was poured into 8 l. of water, and extracted with 3 l. of ether. The ether was evaporated and left a brown semisolid presumed to be the benzoate VIIa.

This crude 4-benzoate was dissolved in 1000 ml of ethanol–water (2:1) containing 45 g of sodium hydroxide and refluxed for 4 hr on a steam bath. The ethanol was then removed *in vacuo* and the resulting turbid solution was diluted with 500 ml of water and extracted with 500 ml of ether. The ether extract was dried over potassium carbonate and concentrated to a volume of approximately 150 ml. Pentane was added to faint turbidity, and on standing overnight in the refrigerator crystals separated. The first crop, 65 g, had mp 81–83°. The mother liquors yielded an additional 6 g of product, mp 80–83°, for a total yield of 86% of VIIb. Recrystallization from carbon tetrachloride–pentane gave an analytical sample, mp 82–83°, $[\alpha]^{23}D$ +48.5° (*c* 1.04, $CHCl_3$).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.44; H, 7.40.

Methyl 2,3-Di-O-benzyl-6-deoxy-4-O-methylsulfonyl-α-D-galactopyranoside (VIIc).—To a solution of 50 g (0.14 mole) of VIIb in 200 ml of dry tetrahydrofuran and 33 g (3 equiv) of dry pyridine 32 g (2 equiv) of methanesulfonyl chloride were added while stirring. The solution was allowed to stand 4 days at room temperature whereupon the reaction mixture was decomposed by pouring it into 2 l. of ice–water. The aqueous solution was extracted with chloroform. The chloroform layer was washed with cold 3 *N* hydrochloric acid, saturated sodium bicarbonate solution, and dried over magnesium sulfate. The chloroform was removed and the resulting syrup was taken up in methanol and treated with Norit. Upon cooling 45.6 g (75%) of product VIIc was collected, mp 71–73°. From the mother liquor another less pure crop of 7.3 g of product could be recovered. For analysis a sample was recrystallized from methanol, mp 73–74°, $[\alpha]^{25}D$ +71.4° (*c* 1.05, $CHCl_3$).

Anal. Calcd for $C_{22}H_{28}O_7S$: C, 60.53; H, 6.62; S, 7.35. Found: C, 60.63; H, 6.40; S, 7.20.

Methyl 2,3-Di-O-benzyl-6-deoxy-4-azido-α-D-glucopyranoside (VIIIa).—A solution of 40 g of the inverted mesylate VIIc in 150 ml of dimethylformamide containing 1 ml of water was refluxed (~135°) with 20 g (~4 equiv) of sodium azide for 6 hr. The cooled mixture was poured into 1.5 l. of water and extracted several times with petroleum ether (total 1000 ml). The extract was dried (magnesium sulfate) and the petroleum ether distilled *in vacuo* to yield 33.7 g (96%) of a slightly yellow oil. An infrared spectrum showed the azide band at 4.75 μ and absence of a mesylate band at 8.5 μ. For analysis a small sample was chromatographed over alumina (Woelm, grade I) (eluent: ether–petroleum ether, 1:9). Thin layer chromatography in an ether–petroleum ether system (1:1) indicated that this product was homogeneous.

Anal. Calcd for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96. Found: C, 66.01; H, 6.64; N, 10.78.

Methyl 4-Amino-2,3-di-O-benzyl-4,6-dideoxy-α-D-glucopyranoside (VIIIb).—To a refluxing solution of 3 g of lithium aluminum hydride in 150 ml of dry dioxane was added, dropwise, while stirring, 13 g of the 4-azido compound VIIIa dissolved in 50 ml of dioxane. After the vigorous nitrogen evolution abated, the reaction mixture was refluxed with stirring for another hour. The excess of lithium aluminum hydride was decomposed with ethyl acetate and the dioxane removed *in vacuo*. At this time 200 ml of ether was added to dissolve the dry residue and water was then slowly added until the white gelatinous precipitate coagulated. The ether layer was decanted, and the precipitate re-extracted twice. The combined ether extracts were dried (potassium carbonate) and the ether distilled *in vacuo* to yield 9.7 g (80%) of a viscous yellow oil. By evaporatory distillation (110°, 0.002 mm) the clear, colorless amine, VIIIb, can be obtained in analytical purity.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.25; H, 7.71; N, 3.80.

The crude oil was dissolved in dry ether and about 1 equiv of saturated hydrogen chloride–2-propanol was added. The resulting crystalline solid was recrystallized from acetone–pentane to yield 7.1 g (53%) of the hydrochloride salt, mp 175–177°. An analytical sample had a mp of 180–181° after one additional recrystallization from 2-propanol–pentane, $[\alpha]^{24.5}D$ +46.2° (*c* 1.11, H_2O).

Anal. Calcd for $C_{21}H_{28}ClNO_4$: C, 64.03; H, 7.16; N, 3.56. Found: C, 63.99; H, 7.23; N, 3.74.

Methyl 4-Acetamido-2,3-di-O-benzyl-4,6-dideoxy-α-D-glucopyranoside (VIIIc).—Without isolation of intermediates, 25 g of mesylate VIIc were converted to the 4-azido derivative, VIIIa, which was reduced to the oily 4-amino compound, VIIIb. This crude oil was acetylated with excess acetic anhydride in pyridine overnight at room temperature. The reaction mixture was evaporated *in vacuo* to a heavy oil, which was taken up in chloroform. The chloroform layer was washed with water, dried over magnesium sulfate, and evaporated. The white crystalline residue was recrystallized from chloroform–pentane to yield 21.5 g (94% from VIIc) of the 4-acetamido derivative in analytical purity (VIIIc), mp 150–150.5°, $[\alpha]^{24}D$ +25° (*c* 1.08, in $CHCl_3$).

Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.00; H, 7.29; N, 3.49. Found: C, 69.15; H, 7.31; N, 3.51.

Methyl 4-Amino-4,6-dideoxy-α-D-glucopyranoside (IVa).—A solution of 3.0 g of methyl-4-amino-2,3-di-O-benzyl-4,6-dideoxy-α-D-glucopyranoside (VIIIb) hydrochloride was hydrogenated at atmospheric pressure in 50 ml of methanol with 300 mg of 10% palladium on carbon as catalyst. The hydrogenation was catalyzed by the addition of 1 ml of concentrated hydrochloric acid. A reaction time of 2 hr was required for theoretical hydrogen uptake. The catalyst was removed by filtration and the reaction mixture was passed over a column of Dowex 50-X2 (acid form). The column was washed with methanol to neutrality and the aminoglycoside eluted with 150 ml of 2% methanolic ammonia. The eluate was evaporated *in vacuo* to yield an oil which solidified on standing. For further purification the product was recrystallized from ether–pentane to yield 1.08 g (80%) of product, mp 114–116°. A mixture melting point with previously prepared material was undepressed, and the infrared spectra were superimposable.

Methyl 4-Acetamido-4,6-dideoxy-α-D-glucopyranoside by Reduction of VIIIc.—A solution of 15 g of N-acetyl derivative VIIIc in 150 ml of methanol was hydrogenated overnight at atmospheric pressure employing 500 mg of 10% palladium on carbon as catalyst. After filtration the solution was evaporated, and the crystalline residue recrystallized once from methanol–ether to yield 9.5 g (98%) of the N-acetylglycoside Va, mp 188–189°. A mixture melting point with a previously prepared sample was undepressed and the infrared spectra of both samples were superimposable.

Methyl 4-Acetamido-4,6-dideoxy-2,3-Di-O-acetyl-α-D-glucopyranoside (IXa).—A solution of 2 g of glycoside IVa in excess of acetic anhydride and pyridine was kept at room temperature overnight. Evaporation, partition between water–chloroform and evaporation of the dried organic solvent left a crystalline material. Recrystallization from chloroform–ether yielded 2.98 g of the triacetate IXa, 88%, mp 169–170°, $[\alpha]^{25}D$ +190° (*c* 1.585, $CHCl_3$).

Anal. Calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.61. Found: C, 51.62; H, 7.19; N, 4.64.

1,2,3-Tri-O-acetyl-4-acetamido-4,6-dideoxy-α-D-glucose (X). Method A.—A solution of 1.3 g of the above-described triacetate, IXa, in 60 ml of acetic anhydride was cooled in ice with stirring while 1 ml of concentrated sulfuric acid was added. The reaction mixture stood overnight at room temperature and was then poured into 300 ml of ice–water. The product was extracted with chloroform and the chloroform extract was washed thoroughly with saturated sodium bicarbonate solution. After drying (magnesium sulfate) evaporation of the chloroform left a crystalline solid, which was recrystallized from chloroform–ether–pentane, to yield 1.01 g (71%) of the α-tetraacetate X, mp 148–149°. By another recrystallization from the same solvents an analytical sample was obtained, mp 149–149.5°, $[\alpha]^{25}D$ +142 (*c* 0.895, $CHCl_3$).

Anal. Calcd for $C_{14}H_{21}NO_8$: C, 50.75; H, 6.39; N, 4.23. Found: C, 50.56; H, 6.48; N, 4.21.

Method B.—A solution of 1 g of the dibenzyl derivative VIIIc in 50 ml of acetic anhydride and 1.5 ml of concentrated sulfuric acid was prepared and left to stand as described for method A. After the same work-up procedure (method A), 798 mg (83%) of the α-tetraacetate was isolated after one recrystallization. The mixture melting point with the compound prepared according to method A was undepressed and their infrared spectra were superimposable.

Method C.—A solution of 100 mg of viosamine hydrochloride, Ia, in excess pyridine and acetic anhydride was warmed at 50° for 28 hr. The usual work-up yielded an orange gum, which was chromatographed over alumina (Woelm grade I) to yield 148 mg (89%) of the α-tetraacetate X. The identity of this product was confirmed by melting point, mixture melting point, infrared spectra, and thin layer chromatography in systems C and D.

Methyl 2,3-Di-O-benzyl-4-carbethoxyamino-4,6-dideoxy-α-D-glucopyranoside (VIIId).—A solution of 10 g of the oily VIIIb in 75 ml of chloroform was added to 100 ml of water containing 8 g of sodium bicarbonate. To this were added, with vigorous shaking at 0°, small portions of 3 g of chloroethylcarbonate in 15 ml of chloroform. The addition was complete in 45 min whereupon the chloroform layer was dried (magnesium sulfate) and evaporated to yield after one recrystallization from ether–pentane 8.0 g (77%) of carbethoxy derivative VIIId, mp 103–104°. An additional recrystallization provided an analytical sample, mp 104–105°, $[\alpha]^{24}D$ +24.7 (*c* 1.28, in $CHCl_3$).

Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.27; H, 7.06; N, 3.26. Found: C, 67.09; H, 7.26; N, 3.15.

Methyl 2,3-Di-O-benzyl-4-monomethylamino-4,6-dideoxy-α-D-glucopyranoside (VIIIe).—A solution of 6 g of the N-carboethoxyglycoside VIIId in 100 ml of dry dioxane was added dropwise to a well-stirred refluxing solution of 3 g of lithium aluminum hydride in 250 ml of dioxane. After the addition was complete the mixture was refluxed for 2 more hrs. Excess lithium aluminum hydride was decomposed by the addition of ethyl acetate and the mixture was evaporated to dryness on a rotary evaporator. The resulting solid was slurried with 300 ml of ether and water was added dropwise until the precipitate coagulated. The ether was decanted and the residual solid thoroughly washed by shaking with three 50-ml portions of ether. Evaporation of the combined, dried ethereal solutions yielded a clear viscous oil, 4.3 g (78%). A small sample was purified by evaporatory distillation at 125° (0.001 mm).

Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87. Found: C, 71.32; H, 7.96.

Preparation of the Hydrochloride.—A solution of 3.4 g of the crude oil in 1.0 ml of ether was treated with sufficient isopropanol–hydrogen chloride to precipitate the salt. Recrystallization from isopropanol–ether yielded 4.0 g of the hydrochloride in beautiful, big prisms, mp 139–140°, $[\alpha]^{25}D$ +52° (*c* 1.95, CH_3OH).

Anal. Calcd for $C_{22}H_{30}ClNO_4$: C, 64.77; H, 7.41; N, 3.43; Cl, 8.69. Found: C, 64.92; H, 7.58; N, 3.43; Cl, 8.83.

Methyl 4-Methylamino-4,6-dideoxy-α-D-glucopyranoside (IVb).—A solution of 3 g of the crystalline hydrochloride of VIIIe in 60 ml of methanol was hydrogenated using 200 mg of 10% palladium on charcoal as catalyst. After 0.5 ml of concentrated hydrochloric acid was added a rapid hydrogen uptake started. The hydrogenation was complete after 1 hr. The solution was filtered and the filtrate passed over Dowex 50-X2 (acid form). Elution with 1% methanolic ammonia yielded a basic oil which was crystallized from chloroform–ether, 1.2 g (85%) mp 64–65°, $[\alpha]^{25}D$ +175° (*c* 1.01, $CHCl_3$). This is an over-all yield of 71% for the three-step reaction starting from VIIIb, $[\alpha]^{25}D$ +153.5° (*c* 0.91, H_2O).

Anal. Calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.32. Found: C, 50.16; H, 8.89; N, 7.35.

Methyl 4-N-Methylacetamido-4,6-dideoxy-α-D-glucopyranoside (Vb).—A solution of 1.16 g of IVb in methanol was cooled to 0° and the sugar was N-acetylated according to the usual procedure. Work-up gave a viscous, colorless oil, which crystallized very slowly, 960 mg, 68%. Recrystallization from ethanol gave 929 mg, mp 157–158°, $[\alpha]^{24}D$ +133° (*c* 1.88, $CHCl_3$).

Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.48; H, 8.21; N, 6.01. Found: C, 51.46; H, 8.34; N, 6.01.

This compound was also obtained in 76% yield by N-acetylation of 200 mg of the distilled, oily VIIIe. The crude N-acetate was, without characterization, subjected to a hydrogenation in methanol with palladium on charcoal as catalyst.

Methyl 2,3-Di-O-acetyl-4-N-methylacetamido-4,6-dideoxy-α-D-glucopyranoside (IXb).—A solution of 170 mg of N-acetyl derivative Vb in pyridine was treated with excess acetic anhydride at room temperature for 24 hr. Work-up followed by chromatography (Woelm grade I alumina, ether eluent) and recrystallization from chloroform–ether–pentane (approximately 1:10:50 by volume) afforded 200 mg (86%) of white crystals, mp 119–120°, $[\alpha]^{23}D$ +119° (*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, 53.06; H, 7.51; N, 4.40.

Methanolysis[28] of Bamicetin. Preparation of Bamosamine.—Dissolution of 10 g of partially purified bamicetin[3] in hot ethanol followed by filtration removed 801 mg of insoluble material. Evaporation of the ethanol *in vacuo* afforded a yellow gum which was dissolved in 150 ml of saturated methanolic hydrogen chloride. After 24 hr at room temperature 3 g of precipitated cytimidine hydrochloride[3] was removed by filtration. The filtrate was evaporated to a gum which was redissolved in methanol and passed over a column of Dowex 1 (hydroxide form) to remove chloride ion. The methanol eluates were concentrated and passed over Dowex 50 (acid form). Elution with methanol afforded the methyl glycosides of the neutral deoxy sugar, amicetose.[28] Elution with 2% methanolic ammonia afforded a yellow gum. Dissolution of this gum in 50 ml of chloroform followed by filtration removed some insolubles. After evaporation of the chloroform solution the resulting residue was dissolved in 70 ml of methanol and cooled to 0°, whereupon 10 ml of acetic anhydride was added in 1-ml portions over a period of 40 min. The resulting solution was again passed over Dowex 50 (acid form). Elution with methanol followed by evaporation of solvents (*in vacuo*) and charcoal treatment in methanol afforded a clear gum, 2.88 g (about 75%) of N-acetylbamosamine methyl glycosides (mixture A, *cf.* discussion section). Elution of the Dowex 50 column with 2% methanolic ammonia afforded, after evaporation and acid hydrolysis, 76 mg of Ic (from amicetin present in the original sample of bamicetin).

Preliminary Characterization of Bamosamine. A. Vpc.—About 10 mg of mixture A (*vide supra*) was converted to the trimethylsilyl derivative[14] and subjected to isothermal vpc analysis on 10% Carbowax 20M on Chromosorb W at 180°. Mixture A showed two major peaks (>90% of total) of about equal intensity with relative retention times of 1.0 and 1.2. Peak 1.0 had a retention time identical with that of IVb.

B. Acid Hydrolysis.—Treatment of 10 mg of mixture A under the acidic conditions used for the preparation of Ic was followed by paper chromatography in systems B, E, and F. After 5 hr the hydrolysis showed one reducing, basic spot (R_f: B, 0.63; E, 0.66; F, 0.19) plus a spot at the origin. Identical treatment of synthetic Vb afforded identical spots. Crystallization attempts on preparative-scale hydrolyses failed.

Isolation of IXb from the Natural Source.—An aliquot, 437 mg, of mixture A (*vide supra*) was treated with excess acetic anhydride in pyridine at room temperature for 36 hr. Evaporation of the solvents *in vacuo*, distribution of the resulting gum between water and chloroform followed by drying and evaporation of the chloroform layer afforded mixture B (*cf.* discussion section). From mixture B in chloroform–ether–pentane (1:10:50) was obtained (after seeding) 62 mg of IXb, mp 119–120°. Alumina chromatography of the mother liquors (Woelm neutral, grade I, ether eluent) and two recrystallizations (same solvent mixture) afford 196 mg of IXb, mp 119–120, total yield 258 mg (43%), $[\alpha]^{23}D$ +119° (*c* 1.26, in $CHCl_3$). Mixture melting point with synthetic IXb was undepressed and infrared spectra were superimposable.

The oily residue of the mother liquors was dried at 50° (0.1 mm) for 12 hr, $[\alpha]^{24}D$ +61 (*c* 1.1, in $CHCl_3$). A sample was submitted for elemental analysis.

Anal. Calcd for $C_{14}H_{23}NO_7$: C, 53.00; H, 7.30; N, 4.41. Found: C, 53.23; H, 7.38; N, 4.26.

Methyl 4-Dimethylamino-2,3-di-O-benzyl-4,6-dideoxy-α-D-glucopyranoside (VIIIf).—A solution of 4 g of VIIIb in 12 ml of 85% formic acid, and 2 ml of 40% formalin solution was heated for 5 hr. The mixture was evaporated *in vacuo* to a viscous oil, dissolved in 30 ml of methanol and passed over a column of Dowex 50-X2 (acid form). The column was washed with 100 ml of methanol, and then eluted with 200 ml of 2% ammonia in methanol. The eluate was evaporated and the yellow oil evaporatively distilled at 130°, 0.005 mm, to yield 4.0 g of a colorless, viscous oil.

Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.12; H, 7.99; N, 3.71.

For the preparation of the hydrochloride salt the distilled oil was dissolved in 50 ml of ether and about 1.2 equiv of hydrogen chloride dissolved in 2-propanol was added. The resulting precipitate was recrystallized twice from 2-propanol–ether–pentane to yield 3.8 g (81%) of the hydrochloride of VIIId, mp 187–188, $[\alpha]^{25}D$ +55 (*c* 1.63, CH_3OH).

Anal. Calcd for $C_{23}H_{32}ClNO_4$: C, 65.47; H, 7.64; N, 3.32; Cl, 8.40. Found: C, 65.44; H, 7.58; N, 3.37; Cl, 8.65.

Methyl 4-Dimethylamino-4,6-dideoxy-α-D-glucopyranoside (IVc). Method A.—1.55 g of the distilled oily 4-dimethylamino derivative VIIIf was hydrogenated at atmospheric pressure in 50 ml of methanol with 250 mg of 10% palladium on carbon as catalyst. The addition of 5 drops of concentrated hydrochloric acid accelerated the hydrogenation considerably with uptake complete within 1 hr. The mixture was filtered and passed over Dowex 50-X2. The Dowex column was washed with 150 ml of methanol and IVc was eluted with 2% ammonia in methanol (300 ml). The solvent was evaporated at aspirator pressure, and the product recrystallized from ether–pentane to yield 770 mg (93%) of white crystalls, mp 94–95°.

Method B.—A solution of 2 g of IVa in 15 ml of 85% formic acid and 4 ml of 40% formalin was heated on a steam bath for 20 hr. The solution was evaporated to dryness *in vacuo* and the residue was taken up in warm methanol (50 ml) and passed over a Dowex 50-X2 column. The column, after washing to neutrality with methanol, was eluted with 500 ml of 2% ammonia in methanol. Evaporation of the solvent yielded an oil, which crystallized on standing. For purification the crude product was sublimed at 75°, 0.1 mm, and then recrystallized from ether–pentane to yield 2.05 g (77%), mp 94–95°, $[\alpha]^{19}D$ +144° (*c* 1.1, H_2O). An analytical sample was prepared by further recrystallizations and melted at 95–96°. By all criteria the products from A and B were identical.

Anal. Calcd for $C_9H_{19}NO_4$: C, 52.65; H, 9.33; N, 6.82. Found: C, 52.84; H, 9.53; N, 6.65.

For the preparation of the hydrochloride the free base (360 mg) was dissolved in ether and sufficient 2-propanol–hydrogen chloride was added to precipitate all the material. The solid was taken up in ethanol, and ether added to turbidity. This yielded 250 mg (58%) of material, mp 195–196°. The solution yielded upon standing 50 mg more of less pure material, mp 190–192°. Mixture melting point and infrared spectra confirmed the identity of this product with that isolated from the natural source.[28]

4-Dimethylamino-4,6-Dideoxy-D-glucose Hydrochloride (Amosamine Ic).—A solution of 500 mg of IVc in 150 ml of 3 *N* hydrochloric acid was heated on a steam bath for 5 hr. The colourless solution was evaporated *in vacuo* (~0.1 mm) to dryness. The residual glass was dissolved in a minimum amount of ethanol. After addition of a seed crystal[28], the free sugar crystallized while being kept in the refrigerator, 310 mg (56%), mp 180–182°. On paper chromatography the R_f values of Ic were identical with those of the natural product in systems A, B, C and D. Recrystallized from ethanol was 50.0 mg affording 35 mg with mp 185–186°, $[\alpha]^{25}D$ +40.4° (*c* 0.81, H_2O). The infrared spectrum of this product is superimposable with that of the natural product.[28]

Anal. Calcd for $C_8H_{18}ClNO_3$: C, 42.20; H, 7.97; N, 6.15. Found: C, 42.39; H, 8.16; N, 6.25.

Methyl 4-Dimethylamino-4,6-dideoxy-2,3-di-O-acetyl-α-D-glucopyranoside (IXc).—A solution of 60 mg of IVc in acetic anhydride was heated at 50° overnight and then evaporated *in vacuo* affording 60 mg of an oil which resisted crystallization but which was one component by thin layer chromatography. Nmr revealed that it was indeed a diacetate. The compound was characterized by preparing a hydrochloride salt, mp 199–200° after recrystallization from chloroform–pentane,[29] $[\alpha]^{24}D$ 116° (*c* 1.13, $CHCl_3$), $pK_a' = 4.78$.

(28) Conditions used were similar to those developed for methanolysis of amicetin: C. L. Stevens, K. Nagarajan, and T. Haskell, *J. Org. Chem.*, **27**, 2991 (1962).

(29) The nmr and melting point of IXc referred to in C. L. Stevens, N. A. Nielsen, P. Blumbergs, and K. G. Taylor, *J. Am. Chem. Soc.*, **86**, 5695 (1964), are those of the hydrochloride salt.

Anal. Calcd for $C_{13}H_{24}ClNO_6$: C, 47.92; H, 7.43; N, 4.29. Found: C, 47.86; H, 7.53; N, 4.19.

On attempts to prepare a crystalline free base from the pure hydrochloride by neutralization, IXc readily lost an acetyl group yielding an oily monoacetate.

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The Addition of Aromatic Nitroso Compounds to Conjugated Dienes. II

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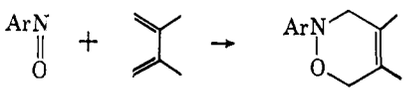
The addition of seven *para*- or *meta*-substituted arylnitroso compounds to 2,3-dimethyl-1,3-butadiene has been studied kinetically between 2 and 30° in dichloromethane. Rate constants and activation parameters have been obtained. A considerable substituent effect is observed ($\rho = +2.53$). The reaction appears to obey the isokinetic relationship, with $\beta = 470°K$.

In an earlier paper[2] we established that the 1,4-cycloaddition reaction between 2,3-dimethyl-1,3-butadiene and *p*-bromonitrosobenzene has a first-order kinetic dependence on the conjugated diene and on the nitroso derivative. In order to suppress an alternative reaction path, the Guggenheim method[3]



was employed to provide kinetic data for the reaction between nitrosobenzene and the same conjugated diene. From the rate constants at 2 and 25° the ρ constant of this reaction in dichloromethane solution was tentatively established as $+2.51 \pm 0.04$.

In an effort to gain further insight in the nature of the transition state and to determine electronic factors that activate aromatic nitroso compounds towards a 1,4 cycloaddition reaction we have undertaken a more extensive kinetic study of this reaction involving seven aromatic nitroso derivatives.

The selection of the aromatic nitroso compounds was based on the following criteria. First, the nitroso compounds were to be monomeric in solution. Second, if an alternative reaction path was detected by the formation of more than one reaction product the data were discarded. The sole exception made was for the parent compound nitrosobenzene. Third, essential irreversibility was required of the 1,4 cycloaddition reaction in the temperature range studied.

Results of the kinetic runs of seven aromatic nitroso compounds and 2,3-dimethyl-1,3-butadiene are summarized in Table I at up to five temperatures in dichloromethane solution. The rate constants were obtained spectrophotometrically by methods reported earlier in detail.[2,3] The clear facilitation of the reaction by electron-withdrawing substituents is illustrated in the Hammett plots at 2 and 25° (Figures 1–3). In Figures 1 and 2, ordinary σ values were plotted *vs.* log k_x/k_0, yielding a ρ value at 2 and 25° of +2.53 and +2.50, respectively. In Figure 3, Taft $\sigma°$ values[4] were employed at 25° in order to provide a comparison of Hammett plots. The correlation coefficient is not significantly different and was found to be +2.30. It should be noted that this series is constituted by both *para*- and *meta*-substituted nitrosobenzene derivatives. The simple linearity of the $\sigma\rho$ relationship including *para*- and *meta*-substituted nitrosobenzene derivatives may imply the existence of only a single electronic effect influencing the rate of the 1,4 cycloaddition reaction in the case under study.

TABLE I

RATE CONSTANTS OF THE 1,4 CYCLOADDITION REACTION BETWEEN NITROSOBENZENE OR DERIVATIVES AND 2,3-DIMETHYL-1,3-BUTADIENE IN DICHLOROMETHANE AT VARIOUS TEMPERATURES

		Rate constant, $k \times 10^3$, l./mole × sec[a]				
Substituent	Temp, +0.1°	2	10	18	25	30
None		0.284	···	···	2.10	···
p-Cl		0.810	···	···	5.05	7.11
m-Cl		1.44	2.66	4.49	7.64	8.79
p-Br		1.10	···	3.84	7.60	8.29
m-Br		1.55	2.81	4.58	7.97	9.64
p-I		1.39	2.59	4.39	7.77	8.81
p-CH_3		0.105	0.213	0.389	0.726	0.817

[a] Average value for three to four determinations. Deviation of average value not less than 0.5 but not more than 3%.

A Hammett ρ constant of 2.57 has been reported[5] for the reaction between 1,3-cyclohexadiene and substituted nitrosobenzene derivatives. The following substituents were employed for the determination of the ρ constant: *p*-methoxy, *p*-methyl, *p*-chloro, *m*-nitro, and *p*-nitro. Inclusion of the nitro derivatives in this series creates two complications in the determination of the rate constants, and hence of the ρ constant, which apparently were ignored. The first one is that for *m*-nitro- and *p*-nitronitrosobenzene in solution an equilibrium exists between monomer and dimer which favors the dimer.[6] The second one is that the nitronitroso compounds with another diene, 2,3-dimethyl-1,3-butadiene, were each found to yield two reaction products in approximately equal amounts.[7] Although this may not be the case with 1,3-cyclohexadiene, doubts are raised. Considering these complications and the fact that different conjugated dienes were employed, the close agreement between the value of our ρ constant and the

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