A New Synthesis of 2,3-Diamino-2,3-dideoxy-D-glucose

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The introduction of an amino function in position 2 of derivatives of 3-deoxy-3-nitro-D-glucose is described. Action of ammonia in aqueous tetrahydrofuran upon methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**1**) readily gave a mixture of two stereoisomeric nitroamines (**3** and **4**). The same products were formed by ammonia addition to the nitro olefin, methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hexopyranos-2-enide (**2**). The preponderant isomer (**3**) proved to be methyl 2-amino-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside. Its *N*-acetylation (or alternatively, *N*-ethoxycarbonylation), followed by debenzylidenation, catalytic hydrogenation, and acid hydrolysis furnished with good yields 2,3-diamino-2,3-dideoxy-α-D-glucose dihydrochloride (**12**). Also prepared were the di-*N*-acetyl (**13**) and di-*N*-benzoyl (**14**) derivatives of **12**, as well as some additional acyl derivatives on the nitroamino and diamino glycoside stages.

Much attention is currently being focused on the chemistry of diamino sugars. The discovery of 2,6-diamino-2,6-dideoxy-D-glucose and -L-idose as components of the neomycin and paromomycin families of antibiotics,[1] and the occurrence of 2,4-diamino-2,4,6-trideoxy-L-altrose (bacillosamine)[2] in a bacterial polysaccharide have emphasized a desirability in this field, of synthetic work that would benefit future structural elucidations and would provide stepping stones for eventual, total syntheses of various products of biological or medicinal interest. Considerable efforts in several laboratories have quite recently resulted in syntheses of a number of diamino sugars including the ones just mentioned. In addition to 2,6-diamino-2,6-dideoxy-D-glucose[3-5] and 2,6-diamino-2,6-dideoxy-L-idose,[6] their stereoisomers with D-*gulo*,[7] D-*galacto*,[8,9] D-*allo*,[10,11] and D-*manno*[12-14] configurations have been made. In the kanamycin group of antibiotics, 2-, 3-, and 6-aminodeoxy glucose moieties are known to form building units.[1] In view of the capability of microorganisms, manifested here and in many other antibiotics,[15] to place an amino group in the 3 position of sugar molecules it is tempting to speculate that 3,6- and 2,3-diamino hexoses may exist in nature. Of the former class, derivatives with D-*ido*,[16,17a,b] D-*gulo*,[17a] D-*allo*,[17c] and D-*altro*[18] configurations and of the latter, derivatives with D-*allo*,[10,19] D-*altro*,[20] D-*manno*,[21,22] and D-*gluco*[10,20] configurations have thus far been synthesized.

The 2,3-diamino sugars described to date have all been obtained through displacement reactions carried out on suitably substituted sugar sulfonates, with or without neighboring group participation and with or without intermediary production of epimino derivatives. The present paper describes a different approach. The starting point is a suitable nitro sugar derivative and use is made of the activating effect of the nitro group which permits a facile introduction of an amino group in vicinal position. It is known that *vic*-nitroamines are obtainable by the addition of amines or ammonia to α-nitroalkenes which may be used as such[23,24] or generated *in situ*[24,25] by elimination of acetic acid from acetylated β-nitro alcohols. This principle had been previously applied to carbohydrates bearing a terminal nitro group and had led in these cases to a number of derivatives of 2-amino-1,2-dideoxy-1-nitroalditols[26] and 5-amino-5,6-dideoxy-6-nitro-D-glucose.[27] As sugars possessing a nonterminal nitro group are now readily available by way of the nitromethane cyclization,[28] it was of interest to examine their utility for the synthesis of vicinal nitroamino and diamino compounds.

Treatment of methyl 2-O-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**1**)[29] in tetrahydrofuran with concentrated aqueous ammonia afforded with great ease and in over 90% yield a mixture of stereoisomeric methyl 2-amino-4,6-*O*-benzylidene-2,-3-dideoxy-3-nitro-β-D-hexopyranosides. By fractional crystallization a major isomer (**3**), with $[\alpha]_D$ −48°, and a minor isomer (**4**), with $[\alpha]_D$ −96°, were isolated

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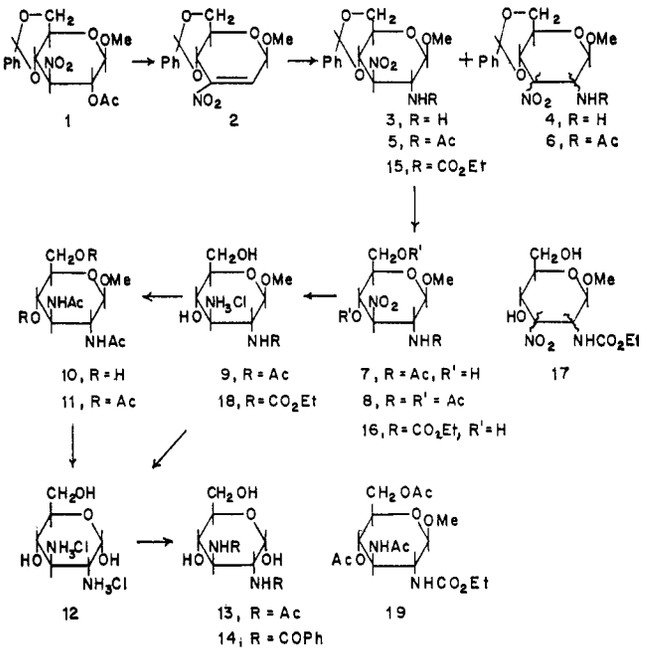
in a ratio of about 10:1. The reaction doubtless proceeded *via* the intermediate nitro olefin (**2**) which arose from **1** by elimination of acetic acid and rapidly added ammonia across the double bond. Indeed, when crystalline methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hexopyranos-2-enide (**2**)[29] was similarly treated with ammonia, the same two nitroamines (**3** and **4**) arose in a similar ratio. As will be shown below, the preponderant isomer (**3**) possesses the D-*gluco* configuration. No assignment has yet been made for the minor isomer (**4**).

Acetylation of **3** and **4** gave the corresponding *N*-acetyl derivatives (**5** and **6**) in excellent yields. Methyl 2-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (**5**) was debenzylidenated by treatment with 70% acetic acid or with a cation-exchange resin, to furnish methyl 2-acetamido-2,3-dideoxy-3-nitro-β-D-glucopyranoside (**7**).[30] Boron trifluoride catalyzed acetylation of **7** produced methyl 2-acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-3-nitro-β-D-glucopyranoside (**8**).[31] Catalytic hydrogenation of **7** using Adams catalyst in the presence of 1 equiv of dilute hydrochloric acid led to an amine hydrochloride, presumably **9**. The latter was amorphous[32] but could be characterized by *N*-acetylation which gave crystalline methyl 2,3-diacetamido-2,3-dideoxy-β-D-glucopyranoside (**10**). A tetraacetate (**11**) was also prepared but was difficult to crystallize because of a tendency to form gels with the common solvents.

Hydrochloric acid hydrolysis of **9** or, better, of the *N,N'*-diacetyl derivative (**10**) afforded reducing 2,3-diamino-2,3-dideoxy-D-glucose dihydrochloride (**12**) in yields of 70%. The sugar was obtained in beautiful, diamond-shaped crystals which exhibited downward mutarotation and therefore represented the α anomer. For further characterization the dihydrochloride was *N*-acetylated giving crystalline 2,3-diacetamido-2,3-dideoxy-α-D-glucose (**13**). A *N,N'*-dibenzoyl derivative (**14**) was likewise prepared. The dihydrochloride (**12**) and the *N,N'*-diacetyl derivative (**13**) proved identical with authentic specimens of these compounds that had been obtained in a stereospecific synthesis by Meyer zu Reckendorf.[10,33] Additional support for the D-*gluco* configuration of the series of compounds derived from **3** came from some nmr spectra which are discussed later in the paper.

The diamino glucose (**12**) was obtained from the glucoside (**3**) also *via* a second series of derivatives. *N*-Ethoxycarbonylation of **3** gave the urethan (**15**) which was debenzylidenated to methyl 2-ethoxycarbonamido-2,3-dideoxy-3-nitro-β-D-glucopyranoside (**16**). This product, which was dextrorotatory ([α]D +16.7°), was also isolated when the *crude* mixture of stereoisomers arising in the addition of ammonia to the nitro olefin **2** was ethoxycarbonylated and subsequently debenzylidenated. In that case, however, a levorotatory product ([α]D −55.5°) crystallized from the mother liquor. Analysis proved this product (**17**) to be an isomer of **16**. It is likely that its precursor was **4**, but owing to lack of material, this has not been established. Catalytic hydrogenation of **16** quantitatively gave the corresponding methyl 2-ethoxycarbonamido-3-amino glucoside hydrochloride (**18**) in crystalline condition, whereas similar hydrogenation of **17** produced a colorless oil. Acetylation of **18** furnished a triacetate (**19**) and hydrolysis of **18** with hydrochloric acid gave reducing diamino glucose dihydrochloride that was identical with the product (**12**) of the previous series. (See Scheme I.)

SCHEME I



The analysis of the 60-Mc nmr spectra of a number of the new compounds was attended with some difficulties because of inadequate solubilities in suitable solvents, and of poor resolutions especially of the ring proton signals. Nevertheless, confirmatory evidence for the *gluco* configuration of the compounds that were derived from **3** accumulated from the spectra of **8**, **15**, and **19**. The acetamidodi-*O*-acetylnitro compound **8** in deuteriochloroform showed three, sharp resonances of equal intensities, each corresponding to three protons, at τ 8.03, 7.96, and 7.92. These could readily be attributed to the methyl groups in equatorial NHCOCH$_3$, equatorial CH$_2$OCOCH$_3$, and equatorial OCOCH$_3$ at C-2, C-5, and C-4, respectively. The resonance of the glycosidic methyl group occurred at τ 6.49, and the signal for the C-6 methylene group (2 H) was centered at 5.79. Two of the five ring protons gave signals bunched together in the region τ 4.4–4.7 and two others at 6.0–6.4. There was, however, a clearly resolved doublet with a spacing of 8 cps centered near τ 5.0 which must be due to the anomeric proton. The magnitude of the spacing indicated that this axial proton signal was split by an axial proton at C-2, thus supporting the assumption of an equatorial acetamido group. The spectrum of the benzylideneth-

(30) Compound **7** could be conveniently prepared, in nearly quantitative yield, directly from **3** by successive *N*-acetylation and debenzylidenation without purification of intermediate **5**.

(31) It was recently reported that certain aliphatic nitro compounds on treatment with acetic anhydride and boron trifluoride suffer a replacement of the nitro by an acetoxyl group; see P. K. Bhattacharyya, A. C. Ghosh, V. M. Sathe, N. L. Dutta, and M. Ram in "Nitro Compounds," T. Urbański, Ed., Pergamon Press Ltd., London, 1964, p 275. Apparently such a replacement does not occur in nitro sugar derivatives, several of which were found in our laboratory to be smoothly acetylated under the conditions to give the expected nitro sugar acetates (unpublished results).

(32) The possibility of N-2 → N-3 acyl migration, though remote, has not been ruled out.

(33) We are obliged to Dr. W. Meyer zu Reckendorf, Münster, Germany, for providing samples for comparison.

oxycarbonamidonitro compound (**15**), taken in pyridine because of poor solubility in chloroform, also exhibited a low-field doublet, centered at τ 4.83, with a splitting of 8.5 cps; the methoxyl resonance appeared at 6.49. The acetamidoethoxycarbonamidodi-*O*-acetyl compound (**19**) in deuteriochloroform showed a signal (3 H) at τ 8.09 and one at 7.96 (6 H), which was in line with an equatorial acetamido group and the two equatorial acetoxy groups. The OCH_3 signal was at τ 6.53, and the ethyl CH_3 gave a triplet centered at τ 8.80.

Experimental Section

Melting points were taken in capillaries in an electrically heated aluminum block apparatus using a calibrated thermometer. Infrared spectra were obtained by the Nujol mull technique on a Beckman spectrometer, Model IR-8. Unless otherwise indicated evaporations were done *in vacuo* with a rotatory evaporator at an outside bath temperature of 35–40°.

Methyl 2-Amino-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (3) and Isomer 4. A. By Addition of Ammonia to Nitro Olefin 2.—To a solution of 500 mg of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hexopyranos-2-enide (**2**)[29] in ethyl acetate (25 ml) was added 25 ml of concentrated aqueous ammonia. The mixture was refluxed gently for 1 hr. Removal of the ethyl acetate *in vacuo* caused the separation of a crystalline solid from the aqueous solution. Recrystallization from ethanol gave 350 mg (66%) of *platelets* showing $[\alpha]^{23}D$ −48.6° (*c* 0.9, DMF). The product sintered or melted (dependent upon the speed of heating) between 190 and 200°, resolidified with rising temperature and then decomposed without melting above 250°. It was methyl 2-amino-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (**3**).

Anal. Calcd for $C_{14}H_{18}N_2O_6$ (310.3): C, 54.19; H, 5.85; N, 9.03. Found: C, 54.15; H, 5.87; N, 8.86.

Evaporation of the ethanol mother liquor of **3** and recrystallization of the residue, first from ethyl acetate–petroleum ether (bp 30–60°) and then from a small amount of ethanol gave *needles* (11 mg, mp 155°) representing isomer **4**.

The infrared spectra obtained from Nujol mulls of **3** and **4** exhibited characteristic differences. The NH stretch frequency of **3** occurred as a sharp singlet at 3390, with that of **4** as a weaker doublet at 3320 and 3385 cm^{-1}. The asymmetric NO_2 vibration of **3** was at 1555 with that of **4** at 1545 cm^{-1}. Especially significant were differences in the fingerprint region which could serve to distinguish the two isomers and to detect small admixtures of one in the other. The following peaks[34] were shown by **3**, but not by **4**: 1220–1200 (doublet, w), 1075 s, 1020 m, 980 ms, 825 m, 745 ms. The following peaks were shown by **4**, but not by **3**: 1215 m, 1095–1085 (doublet, s), 1000 s, 960 ms, 915–895 (doublet, m), 845 m, 785 m, 765 ms.

B. By Reaction of Ammonia with *O*-Acetate 1.—To a solution of 3.0 g of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**1**)[29] in 30 ml of tetrahydrofuran was added 10 ml of concentrated, aqueous ammonia. The mixture was vigorously agitated for 20 min in a loosely stoppered, conical flask by means of a magnetic stirrer, and was then evaporated in a flask large enough to minimize the effect of foaming. The solid that separated was triturated thoroughly with some water, and evaporation was continued to remove residual ammonia and tetrahydrofuran. The moist residue was again triturated carefully with fresh water and finally filtered with suction and washed with water. Recrystallization of the moist material from 50 ml of hot ethanol furnished three crystal fractions. The first crop consisted of platelets that began to deposit quickly; it was isolated and washed with ethanol after being kept at 4° overnight. This crop (2.20 g) was mainly glucoside **3**, but according to its infrared spectrum and specific rotation ($[\alpha]^{25}D$ −63° in DMF) it contained an appreciable amount of isomer **4**. It decomposed on heating at 250–270°, with prior sintering (or melting) and resolidification at 160–165°. Concentration of the mother liquor and washing alcohol to a volume of 20–25 ml followed by cooling for a few hours in a refrigerator gave a crop (225 mg) of fine needles which were washed with a little ice-cold ethanol, mp 151–152° with sintering from 147°, $[\alpha]^{25}D$ −85.5° (*c* 1, DMF). Infrared spectroscopy revealed this crop to be chiefly **4**, with a small admixture of **3**. A third crop of crystals (115 mg) was obtained when water was added to the mother liquor to incipient cloudiness. It was a mixture of platelets and needles, *i.e.*, **3** and **4**, which was also borne out by the infrared spectrum. The combined yield of the isomeric nitroamines **3** and **4** was 96% of the theory.

In similar runs the weights and isomer distributions of the crystal fractions obtained differed slightly from those just described. For instance, on one occasion the first crop weighed 2.05 g and showed $[\alpha]^{23}D$ −55° (*c* 1.04, DMF), and the second crop was 213 mg with $[\alpha]^{23}D$ −93° (*c* 1, DMF), which indicated a somewhat better separation of the isomers, although either was contaminated with the other. The third (mixed) crop weighed 170 mg in this case.

Recrystallization from ethanol of the crops with low levorotation (−55°, −63°) furnished **3** (1.34 g, 1.23 g) that was virtually free from isomer **4**: $[\alpha]^{23}D$ −48.0°, −49.0° (*c* 1.15, DMF). The behavior on determination of the melting point was as described under A and remained unchanged upon admixture of **3** prepared from **2**. Concentration of the mother liquor of recrystallization afforded fractions varyingly composed of **3** and **4** as indicated by their infrared spectra, crystal shapes, and melting behavior.

Recrystallization from a small amount of ethanol of a crop with high levorotation (−85.5°) gave 1-cm-long needles of isomer **4**: mp 153–154, $[\alpha]^{25}D$ −96° (*c* 1, DMF). A mixture melting point with **4** obtained from **2** was undepressed, and the infrared spectra were identical.

Anal. Calcd for $C_{14}H_{18}N_2O_6$ (310.3): C, 54.19; H, 5.85; N, 9.03. Found: C, 54.17; H, 5.72; N, 9.26.

When a nearly pure sample of **4** (from another experiment, mp 151–152°, $[\alpha]^{23}D$ −93°) was recrystallized further from ethanol, it seemed to deteriorate rather than to increase in purity.[35]

Methyl 2-Acetamido-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (5) and Isomer 6.—Nitroamine **3** (1.25 g) was dissolved by gentle warming in 125 ml of methanol. Upon cooling of the slightly turbid solution with tap water, acetic anhydride (4 ml) was added dropwise and the acetylation was allowed to proceed with magnetic stirring at 25–28° for 1 hr. Crystals of **5** began to separate within a few minutes. The reaction mixture was concentrated to a volume of about 20 ml and the colorless product (mp 309–310° dec) was isolated and washed with 20 ml of methanol. The filtrate on further concentration gave a second (smaller) crop (mp 310–311° dec). The combined yield was 1.323 g (93.5%). One sample was recrystallized from nitromethane giving fine needles of mp 309–310° and $[\alpha]^{23}D$ −40.5° (*c* 1.06, DMF). Another sample gave long, thin needles from much methanol: mp 310–311° dec, $[\alpha]^{23}D$ −40.3° (*c* 1.07, DMF).

Acetylation of **3** (200 mg) with acetic anhydride (0.5 ml) in pyridine (2 ml) at room temperature during 15 hr afforded 180 mg (79%) of **5** melting at 310–312° dec. Its infrared spectrum was identical with that of the material obtained by acetylation in methanol solution.

Anal. Calcd for $C_{16}H_{20}N_2O_7$ (352.3): C, 54.54; H, 5.72; N, 7.95. Found: C, 54.81; H, 5.78; N, 7.94.

Nitroamine **4** (87 mg) was similarly acetylated with acetic anhydride (0.2 ml) in methanol (4 ml). After 45 min another milliliter of methanol and 0.1 ml of acetic anhydride were added, and the reaction solution was evaporated in an open beaker in an air stream. The *N*-acetate (**6**) was obtained as a white, solid mass that was dried in a desiccator over potassium hydroxide, mp 223–224° dec. The infrared spectrum showed absence of the bands at 845 and 785 cm^{-1} which are diagnostic of the starting material, and therefore proved complete acetylation.

The infrared spectra of the isomeric *N*-acetates (**4** and **6**) exhibited the expected amide NH and C=O stretching vibrations and showed overlap of amide II and asymmetric nitro bands. The fingerprint patterns were sufficiently distinct in band positions and intensity ratios to permit ready differentiation.

Methyl 2-Acetamido-2,3-dideoxy-3-nitro-β-D-glucopyranoside (7).—Benzylidene derivative **5** (1.15 g) in 120 ml of acetic acid–water (7:3, v/v) was heated in a steam bath for 20 min. The

(34) Relative intensities are indicated as w (weak), m (medium), ms (medium strong), and s (strong). Peaks less suitable for identification are not listed.

(35) This might indicate that partial epimerization was caused in hot ethanol. An investigation is contemplated.

temperature of the solution rose to 90° during the first and to 95–97° during the second quarter of that period. The yellowish solution was cooled with running water, diluted with 50 ml of water, treated with activated charcoal, and filtered. The faintly yellow filtrate upon evaporation to dryness gave a residue that was once more evaporated with added water, then taken up in 50 ml of water. Another charcoal treatment followed by evaporation gave a white solid that was dried in a desiccator: mp 187–189° dec, 805 mg (93.3%). Recrystallization from ethanol–toluene gave 703 mg of **7** in two batches: mp 189–190° dec, $[\alpha]^{23}D$ −24.2° (*c* 0.9, water); and mp 188–189° dec, $[\alpha]^{23}D$ −25.2° (*c* 1.3, water).

It was found that compound **7** can exist in two distinctly different modifications. Although no significant change in melting point occurred, the product prior to recrystallization showed four sharp absorption bands in the region 3525 to 3250 and an amide I band at 1680 cm^{-1} (modification A), whereas the second batch from the recrystallization had a broad absorption centered at 3350 and an amide I band at 1645 cm^{-1} (modification B). The first batch of recrystallization clearly was a mixture of the two forms which also showed slight differences in the fingerprint region. Considerable efforts were made to clear up this phenomenon. Recrystallization of either form using ethanol or aqueous ethanol or mixtures of ethanol and ethyl acetate with or without addition of petroleum ether or toluene erratically gave either modification or mixtures of both. Melting points of 195–197° dec were observed and the crystal shapes varied from prismatic or lancet-like needles to plates or stout prisms. Both modifications gave elemental analyses that suggested the presence of approximately $^1/_3$ mole of water of crystallization. Drying of a mixture of A and B under high vacuum at 110° over phosphorus pentoxide for 4 hr caused no spectral change whatsoever. It seemed that concentration and speed of crystal formation were factors influencing the result of the operation.

Anal. Calcd for $C_9H_{16}N_2O_7$ (264.2): C, 40.91; H, 6.10; N, 10.60. Calcd for $C_9H_{16}N_2O_7 \cdot {}^1/_3H_2O$: C, 40.00; H, 6.22; N, 10.37. Found for A: C, 40.30; H, 6.07; N, 10.57. Found for B: C, 40.29; H, 6.22; N, 10.41.

The debenzylidenation of **5** could conveniently be carried out using a crude starting material. A methanolic solution in which 2.30 g of nitroamine **3** had been *N*-acetylated was brought to dryness, and the total residue so obtained was hydrolyzed with 200 ml of 70% acetic acid as described above. The yield of crude **7**, mp 181–184° dec, was 1.92 g (98% based on **3**). Recrystallization from ethanol–benzene gave 1.29 g of a material with mp 195° and $[\alpha]^{23}D$ −25° (*c* 1, water).

Debenzylidenation of **5** (500 mg) by refluxing for 4 hr in methanol–water (4:1, v/v) in the presence of 2.5 g of Dowex 50W-X12 (H^+) afforded, upon removal of the solvent and recrystallization from ethanol, 260 mg (69%) of **7** melting at 195–196°.

Methyl 2-Acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-3-nitro-β-D-glucopyranoside (8).—A suspension of compound **7** (500 mg) in acetic anhydride (4 ml) was chilled with ice–water, and 5 drops of boron trifluoride etherate was added with swirling. The mixture was kept at 0° for 45 min. and then taken up in 50 ml of methanol and evaporated three times with excess methanol. The crystalline residue was recrystallized from ethyl acetate–petroleum ether (bp 30–60°) to yield 475 mg (72%) of triacetate **8** as plates with mp 166–167°. Infrared bands were at 3350 (NH), 1740 (ester CO), 1680 (amide-I), and 1550–1530 cm^{-1} (amide II and NO_2).

Anal. Calcd for $C_{13}H_{20}N_2O_9$ (348.3): C, 44.83; H, 5.79; N, 8.05. Found: C, 45.00; H, 5.95; N, 8.28.

Methyl 2-Acetamido-3-amino-2,3-dideoxy-β-D-glucopyranoside Hydrochloride (9).—Platinum dioxide (250 mg) was prehydrogenated in 27 ml of 0.1 *N* hydrochloric acid. A solution of **7** (690 mg) in water (70 ml) was added to the acidic suspension of the catalyst and hydrogenated with efficient shaking at 23° and atmospheric pressure. After 6 hr there had been consumed 180 ml of hydrogen (calcd for 3 moles, 175 ml at STP), and uptake had ceased. The catalyst was filtered off, and evaporation of the solution, followed by two evaporations with added ethanol and benzene, furnished a colorless pulverizable foam that appeared slightly hygroscopic and was dried in an oil pump vacuum: 700 mg, $[\alpha]^{23}D$ −42.5° (*c* 2, water). Attempted crystallization from a variety of common solvents proved fruitless. The microanalytical data were satisfactory if the presence in the sample of 3% of water was assumed.

Anal. Calcd for $C_9H_{19}ClN_2O_5 \cdot 0.5\ H_2O$ (279.7): C, 38.55; H, 7.20; Cl, 12.65. Found: C, 38.16; H, 7.49; Cl, 12.78.

Methyl 2,3-Diacetamido-2,3-dideoxy-β-D-glucopyranoside (10).—*N*-Acetylation of hydrochloride **9** (100 mg) was performed with acetic anhydride (0.06 ml) in water (6 ml) containing methanol (0.3 ml) and about 2 ml of Dowex-1-X8 (CO_3^{2-}); the reaction mixture was stirred for 90 min in an ice–water bath. Filtration, brief treatment with a small amount of Dowex-50 (H^+), and evaporation gave a colorless residue that was twice evaporated with ethanol (74 mg). For crystallization, the material was triturated with boiling acetone (about 5 ml) containing 5 drops of water. Gel formation was overcome by allowing the solution to cool slowly in a bath of warm water. The compound formed microscopic needles which melted at 262–263° dec when heated slowly in the bottom of a capillary, but at 287–288° dec on rapid heating in the mouth of an inverted capillary. Another recrystallization did not change this behavior: $[\alpha]^{23}D$ −105.2° (*c* 1.15, water); infrared hands, hydroxyl, 3280 with shoulder at 3400; amide I, 1645; amide II, 1545 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}N_2O_6$ (276.3): C, 47.82; H, 7.30; N, 10.14. Found: C, 47.63; H, 7.43; N, 10.26.

Preparation of the di-*N*-acetate **10** on a larger scale was conveniently done by using hydrochloride **9** in solution directly as obtained from the hydrogenation of nitroamine **7**.

Methyl 2,3-Diacetamido-4,6-di-*O*-acetyl-2,3-dideoxy-β-D-glucopyranoside (11).—Hydrochloride **9** (200 mg) was acetylated with acetic anhydride (1 ml) and pyridine (2 ml) during 15 hr at room temperature. Exhaustive evaporation with ethanol gave a yellowish residue. Attempted crystallization from a number of common solvents and solvent combinations resulted in the formation of jellies. A gel which separated from ethanol was filtered with suction, pressed between filter paper, and dried in a desiccator before its infrared and nmr spectra were taken. Infrared bands showed ester carbonyl, 1735; amide I, 1640; amide II, 1545 cm^{-1}. There were three peaks in the 3500–3100-cm^{-1} region and the fingerprint pattern showed considerable detail.

2,3-Diamino-2,3-dideoxy-α-D-glucose Dihydrochloride (12).—A solution of glycoside hydrochloride **9** (600 mg) in 20 ml of concentrated hydrochloric acid and 40 ml of water was refluxed gently for 90 min. The yellow solution was evaporated at 45° giving a froth which was evaporated five times with excess water to remove most of the acid. The residue was taken up in water, decolorized with charcoal, and again brought to syrup consistency. The syrup was transferred with a few milliliters of water into a 5-cm Petri dish, and glacial acetic acid was added dropwise with swirling to incipient, but not permanent, cloudiness. When the solution was fanned with a stream of warm air, beautiful rhombohedra crystallized within 1 hr. The crystals were isolated, washed with water (containing acetic acid), and dried in a vacuum desiccator over potassium hydroxide (291 mg). On heating the product decomposed without melting at 180–185°, $[\alpha]^{23}D$ +52.5° (10 min) → +46° (2 hr, final, *c* 1.05, water). The mother liquor was rehydrolyzed for 1 hr in 30 ml of half-concentrated hydrochloric acid on a steam bath. Work-up as described afforded another 55 mg of **12** with the same rotation and range of decomposition. The noncrystallizable residue then remaining was acetylated with 5 ml of acetic anhydride and some anhydrous sodium acetate, for 30 min at 100°. Removal of the excess anhydride by evaporation with methanol and of sodium ion by treatment with cation exchange resin, led to an acetylated material which, upon hydrochloric acid hydrolysis as described, furnished another 51 mg of **12**. Thus, the total yield was 71%.

Anal. Calcd for $C_6H_{16}Cl_2N_2O_4$ (251.1): C, 28.70; H, 6.42; N, 11.16; Cl, 28.24. Found: C, 28.82; H, 6.46; N, 11.03; Cl, 27.90.

Dihydrochloride **12** was also obtained, in like yield (71.5%) and in a less cumbersome manner, by hydrolyzing for 2 hr the diacetamido glycoside **10** (700 mg) in 70 ml of gently refluxing 1 *N* hydrochloric acid. Work-up and crystallization from water–acetic acid as described furnished 455 mg of **12**. The rotation was $[\alpha]^{23}D$ +66° (initial, extrapolated) → +62.1° (12 min) → +46.8° (2 hr, constant) (*c* 0.98, water), in good agreement with values found[36] by Meyer zu Reckendorf. An authentic sample,[10,33] which under our conditions decomposed at 180–185°, did not depress the decomposition range of **12** in admixture,

(36) Dr. W. Meyer zu Reckendorf has kindly informed us, with an authorization to communicate, that his published[10] data for the specific rotations of **12** and **13** were in error and that upon redetermination he has found, for **12**, $[\alpha]D$ +66.5° → +50.0°, and for **13**, $[\alpha]D$ −19.0° → −46.0°.

and gave an identical infrared spectrum and X-ray powder diagram.

2,3-Diacetamido-2,3-dideoxy-α-D-glucose (13).—Dihydrochloride **12** (100 mg) was *N*-acetylated at 0–3° in water (4 ml) and methanol (0.4 ml) by stirring with acetic anhydride (0.2 ml) and 3 ml of Dowex-1-X8 (CO_3^{2-}). After 90 min the reaction mixture was removed from the ice bath, another 2 ml of resin and 0.05 ml of acetic anhydride were added, and stirring was continued for 30 min. The resin was filtered off and washed with 100 ml of water, and the filtrate upon short treatment with a small amount of Dowex-50 (H^+) was evaporated to a colorless syrup which solidified on evaporation with ethanol. The residue crystallized as fine needles from ethanol by careful addition of ethyl acetate and slow evaporation in the air: 76 mg (73%) of **13**, mp 237–238°. Recrystallization from the same solvents raised the melting point to 253–254°. An authentic sample of 2,3-diacetamido-2,3-dideoxy-α-D-glucose[10,33] was found to melt at the same temperature under our conditions, and a mixed melting point was underpressed (lit.[10] mp 249–250° dec). The infrared spectra were identical. The rotation was $[\alpha]^{23}D$ −10° (initial, extrapolated) → −15.3° (3 min) → −41.7° (1 hr) → −46.1° (16 hr, final, *c* 0.91, water), in good agreement with values found[36] by Meyer zu Reckendorf.

Anal. Calcd for $C_{10}H_{18}N_2O_6$ (262.3): C, 45.79; H, 6.92; N, 10.68. Found: C, 45.64; H, 7.19; N, 10.46.

2,3-Dibenzamido-2,3-dideoxy-D-glucose (14).—Dihydrochloride **12** (400 mg) and sodium bicarbonate (550 mg, slightly more than 4 equiv) were dissolved in water (15 ml), and a solution of freshly distilled benzoyl chloride (468 mg, 2 molar equiv) in tetrahydrofuran (5 ml) was added dropwise with magnetic stirring at room temperature. Stirring was continued for 1 hr during which time a white precipitate appeared. The pH was frequently checked, and the medium remained neutral to slightly alkaline throughout. The crystalline precipitate was isolated (with ice cooling prior to filtration), washed with chilled water, and dried in a desiccator. It weighed 291 mg and melted at 261–262° dec. The mother liquor was diluted with water, deionized by stirring with 10 ml each of Dowex 50 (H^+) and Amberlite IR-45 (OH^-), extracted three times with ether to remove traces of benzoic acid, and finally brought to dryness. The near-colorless residue (82 mg) melted with decomposition at about 200°, but the melting point rose to 262° dec upon one recrystallization. This was done by dissolving the material in the minimum amount (about 5 ml) of boiling methanol, adding two volumes of nitromethane, and allowing partial evaporation to take place on a steam bath to incipient crystallization. Slow cooling then afforded microscopic needles that melted sharply.

The rotation was determined using the main crop without recrystallization, $[\alpha]^{23}D$ +83° and +81.5° (two different preparations, *c* 1, 90% methanol, which requires gentle warming for dissolution).

Anal. Calcd for $C_{20}H_{22}N_2O_6$ (386.4): C, 62.16; H, 5.74; N, 7.25. Found: C, 62.04; H, 5.90; N, 7.40.

Methyl 4,6-*O*-Benzyliden-2-ethoxycarbonamido-2,3-dideoxy-3-nitro-β-D-glucopyranoside (15).—Pure methyl 2-amino-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (**3**, 220 mg) was dissolved in pyridine (4 ml) at 0°. Ethyl chloroformate (0.5 ml) was added dropwise which caused a red coloration that gradually changed to light yellow overnight. Addition of water (15 ml) precipitated the crude acylated product (200 mg) which on crystallization from ethanol gave needles (180 mg, 67%): mp 266–267°; $[\alpha]^{23}D$ −49.5° (*c* 1.01, DMF); infrared peaks at 3310 (NH), 1687 (amide I), 1543 (amide II and NO_2), and 752 and 698 cm^{-1} (phenyl).

Anal. Calcd for $C_{17}H_{22}N_2O_8$ (382.4): C, 53.40; H, 5.80; N, 7.33. Found: C, 53.60; H, 5.81; N, 7.27.

Methyl 2-Ethoxycarbonamido-2,3-dideoxy-3-nitro-β-D-glucopyranoside (16) and Isomer 17.—Pure benzylidene derivative **15** (500 mg) in a mixture of methanol (80 ml) and water (20 ml) was stirred and heated under reflux for 4 hr with 2.5 g of Dowex-50W-X12 (H^+). Removal of resin and solvent gave a crystalline residue which upon recrystallization from ethanol afforded 310 mg (93%) of debenzylidenated product (**16**) as needles: mp 183–184°; $[\alpha]^{23}D$ +16.7° (*c* 1.2, DMF); infrared bands at 3320 with shoulders at 3390 and 3200 (NH and OH), 1688 (amide I), 1540 (amide II and NO_2), and 1090, 1079, 1058, 1028, and 988 cm^{-1} (COC).

Anal. Calcd for $C_{10}H_{18}N_2O_8$ (294.3): C, 40.81; H, 6.17; N, 9.52. Found: C, 40.98; H, 6.32; N, 9.38.

When debenzylidenation was performed on a *crude* benzylidene product (120 mg) which in turn had been prepared by *N*-ethoxycarbonylation of a mixture of nitroamines **3** and **4** as arising from ammonia addition to **2**, there was obtained, from the ethanolic mother liquor of the crystallization of **16**, a second kind of needles (20 mg): mp 133–134°, $[\alpha]^{23}D$ −55.5° (*c* 1.1, DMF). Analysis and infrared spectrum indicated that this product (**17**) was an isomer of **16**. Infrared bands were at 3455 and 3340 with shoulder at 3250 (NH and OH), 1715 (amide I), 1555 (NO_2), 1522 (amide II), and 1075, 1050, and 989 cm^{-1} (COC).

Anal. Calcd for $C_{10}H_{18}N_2O_8$ (294.3): C, 40.81; H, 6.17; N, 9.52. Found: C, 40.72; H, 6.31; N, 9.36.

Methyl 3-Amino-2-ethoxycarbonamido-2,3-dideoxy-β-D-glucopyranoside Hydrochloride (18).—Nitro glycoside **16** (200 mg) in water (10 ml) was added to a suspension of a platinum catalyst (50 mg of PtO_2, prereduced) in 7 ml of 1 *N* hydrochloric acid. Hydrogenation at ordinary temperature and pressure led to an uptake of 60 ml of hydrogen within 4 hr. Removal of the catalyst and evaporation yielded a colorless, crystalline residue (200 mg). Recrystallization from ethanol furnished **18** as needles: mp 233–234° dec; infrared peaks at 3330 with shoulder at 3460 (NH and OH), 2510, 2010, 1575 and 1540 (NH_3^+), 1695 (amide I), 1525 (amide II), and 1087, 1070, and 1040 cm^{-1} (COC).

Anal. Calcd for $C_{10}H_{21}ClN_2O_6$ (300.7): Cl, 11.79. Found: Cl, 11.85.

Similar hydrogenation of the isomer **17** gave a colorless oil that was not investigated further.

A sample of **18** was refluxed gently for 2 hr in about 100 parts of half-concentrated hydrochloric acid. Removal of the acid by several evaporations with water gave a yellow residue which upon treatment with charcoal in water crystallized from aqueous ethanol. An off-white product was obtained, in about 50% yield, showing positive ninhydrin and Fehling reactions; it decomposed at about 190° and, according to its infrared spectrum and chromatographic mobility, was identical with **12**.

Methyl 3-Acetamido-2-ethoxycarbonamido-4,6-di-*O*-acetyl-2,3-dideoxy-β-D-glucopyranoside (19).—Hydrochloride **18** (200 mg) was treated overnight at room temperature with acetic anhydride (1 ml) and pyridine (4 ml). Addition of water (20 ml) precipitated crude triacetate **19** which was recrystallized from ethyl acetate–petroleum ether (bp 30–60°). The yield was 140 mg (53%) of needles with mp 225–226° and $[\alpha]^{23}D$ +16° (*c* 1.02, DMF).

The infrared spectrum showed bands at 3290 (NH), 1738 (ester CO), 1683 (urethan CO), 1642 (amide I), 1539 (amide II), 1250 and 1220 (acetate COC), and 1091, 1053, and 1022 cm^{-1} (ether COC).

Anal. Calcd for $C_{16}H_{26}N_2O_9$ (390.4): C, 49.22; H, 6.72; N, 7.18. Found: C, 49.11; H, 6.76; N, 7.22.

Registry No.—2,3-Diamino-2,3-dideoxy-α-D-glucose, 7687-95-8; **3**, 7687-96-9; **4**, 7687-97-0; **5**, 7687-98-1; **6**, 7687-99-2; **7**, 7695-33-2; **8**, 7688-00-8; **9**, 7695-39-8; **10**, 7688-01-9; **11**, 7721-85-9; **12**, 7695-34-3; **13**, 7703-49-3; **14**, 7703-48-2; **15**, 7695-35-4; **16**, 7695-36-5; **17**, 7695-37-6; **19**, 7695-38-7.

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