butanol–water, 86:14). The mother liquor from this solid was saved for later examination. Crude XV was then absorbed on Dowex 50 (H^+), washed with water, and then eluted with 1 *N* ammonium hydroxide. The basic eluates were combined and concentrated to dryness. Ethanol was added and removed several times. The colorless sirup was treated with a few milliliters of ethanol and allowed to remain at room temperature overnight. XV was obtained as colorless needle clusters, 200 mg. (40% from XII), m.p. 229–230° with yellowing at 217°, $[\alpha]^{23}D$ +47° (*c* 0.35, water). Ultraviolet properties follow: in 0.1 *N* hydrochloric acid, maximum at 285 mμ (ϵ_{max} 11,900), minimum at 243.5 mμ (ϵ_{min} 1200); at pH 7.53, maximum at 276 mμ (ϵ_{max} 8300), minimum at 254 mμ (ϵ_{min} 5100), shoulder at 240 mμ (ϵ 6700); in 0.1 *N* sodium hydroxide, maximum at 277.5 mμ (ϵ_{max} 8200), minimum at 254 mμ (ϵ_{min} 4600), shoulder at 240 mμ (ϵ_{sh} 6300).

Anal. Calcd. for $C_{10}H_{16}N_4O_3$: C, 49.98; H, 6.71; N, 23.32. Found: C, 50.43; H, 6.86; N, 22.90.

The methanolic mother liquor from crude XV was examined chromatographically in two solvent systems (ascending method, Whatman No. 1 paper, 1-butanol–water, 86:14, and 1-butanol–ammonium hydroxide (1 *N*), 86:14), each of which showed two ultraviolet absorbing spots along with some fluorescence. The lower spot corresponded to XV. The upper spot (assumed to be the 4-*N*-*n*-butyl derivative, XVI) was excised and showed a cytidine-like spectrum. A crystalline sample of XVI could not be isolated.

Picrate of 4-*N*-*n*-Butyl-2′-deoxycytidine (XVIII) from 2′-Deoxycytidine (XVII).—The hydrochloride salt of 2′-deoxycytidine (XVII, 1.0 g.) and 12 ml. of *n*-butylamine in 60 ml. of methanol was heated in a sealed tube at 105° for 20 hr. The tube was cooled and opened, and the contents were evaporated to dryness. The residue was partitioned between water and chloroform, the organic layer was discarded, and the aqueous layer was concentrated to dryness. The residue was examined by paper chromatography (1-butanol–water, 86:14, ascending system, Whatman No. 1 paper). The major spot (R_f 0.83) corresponded to that for *N*-*n*-butyl-2′-deoxycytidine (see below). A trace spot corresponding to 2′-deoxycytidine (R_f 0.25) was also present. The residue was then dried azeotropically with benzene. The residue was dissolved in ethanol and treated with a saturated solution of picric acid in methanol. Concentration of the solution to a small volume and addition of water yielded the crystalline picrate (1.65 g.) which was filtered and washed with water, cold alcohol, and ether. One recrystallization from 95% ethanol gave pure material, m.p. 165–166° dec., which was not depressed when admixed with an authentic sample of picrate of XVIII.

When 2′-deoxycytidine was treated with *n*-butylamine in a manner similar to that described above, only a faint trace spot of the *N*-*n*-butyl derivative (XVIII) was detected chromatographically.

Treatment of 2′-deoxycytidine with *n*-butylamine in methanol plus 1 equiv. of ammonium acetate in a sealed tube at 105° for 20 hr. yielded a mixture of products which by chromatographic examination showed two spots corresponding to starting material XVII and product XVIII in the proportion of 2:1, respectively.

Picrate of 4-*N*-*n*-Butyl-2′-deoxycytidine (XVIII) from XIX.—XIX[11] (0.8 g.) was refluxed in 40 ml. of methanol containing 6 ml. of *n*-butylamine for 1 day. The solution was concentrated to dryness and fractionated between chloroform and water. The almost colorless aqueous layer was concentrated to dryness and the residue azeotroped with benzene. The residue was dissolved in ethanol and treated with alcoholic picric acid. The picrate salt crystallized (0.4 g.), m.p. 157–159°. After recrystallization from ethanol, needle clusters were obtained, m.p. 165–166° dec.

Anal. Calcd. for $C_{19}H_{24}N_6O_{11}$: C, 44.54; H, 4.72; N, 16.39. Found: C, 44.90; H, 4.69; N, 16.38.

Acknowledgment.—The authors are indebted to Dr. George B. Brown for his warm and continued interest.

The Anomeric 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-D-glucopyranoses

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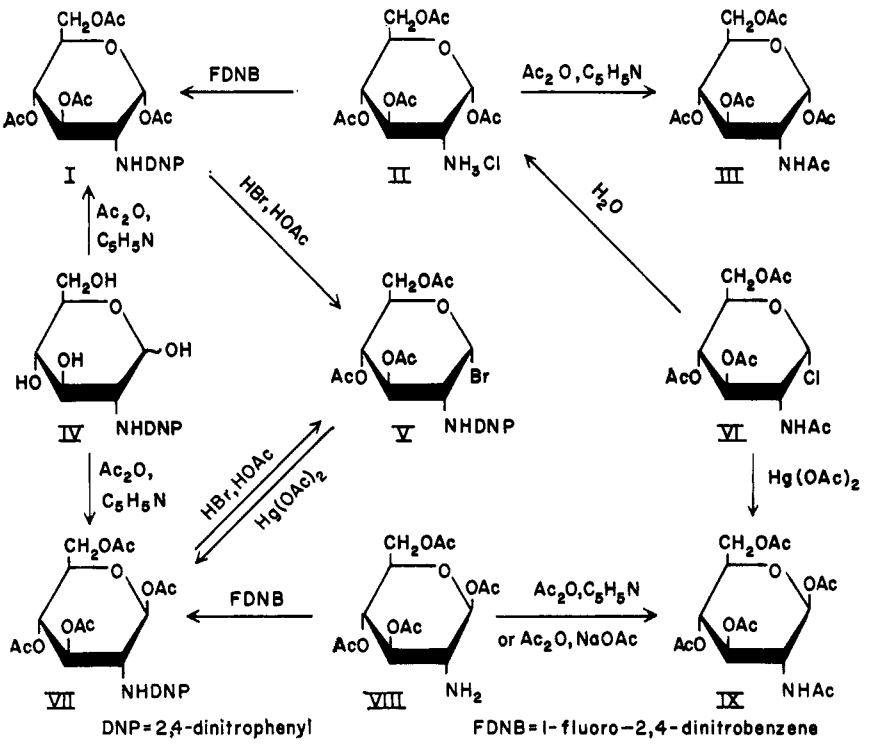
1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α- and -β-D-glucopyranose (I and VII) were prepared by several different procedures. The evidence of nuclear magnetic resonance, as well as route of synthesis, indicate that the isomer having m.p. 218–219° and $[\alpha]D$ +9.1° (chloroform) is the α-D anomer (I), and the isomer having m.p. 167.0–167.5° and $[\alpha]D$ +50° (chloroform) is the β-D anomer (VII), contrary to predictions based on the Hudson rules of rotation. The relative difference between the specific rotations of I and VII increases at shorter wave lengths. The corresponding 2-acetamido analogs (III and IX) of I and VII give plain rotatory dispersion curves in agreement with the Hudson rules at all wave lengths between 300 and 700 mμ.

Conflicting reports exist in the literature for the physical constants of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranose (I) and its β-D anomer (VII). A compound of unspecified anomeric configuration was reported by Kent[1,2] to have m.p. 159–160° and $[\alpha]D$ +73° (chloroform), while Lloyd and associates[3,4] give m.p. 166–167°, $[\alpha]D$ +47.9° (chloroform) for a compound described as I. It has been suggested by Wang and Tai[5] that Lloyd's product[3] is in fact the β-D anomer (VII), and the Chinese workers describe a product, m.p. 214–215°, $[\alpha]D$ +12° (chloroform), which they consider to have the structure I; this assignment would involve a violation of Hudson's empirical rule[6] that the more dextrorotatory isomer of a pair of anomeric D sugar derivatives has the α-D-configuration.

This work describes the preparation of compounds I and VII by various independent routes (Chart I). The homogeneity of the product has been rigorously established with a thin layer chromatographic technique by which the anomers are well differentiated. The structures of the products are defined by the route of synthesis and are supported by nuclear magnetic resonance data. All evidence indicates that 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranose (I) has m.p. 218–219° and $[\alpha]D$ +9.1° (chloroform), and the β-D anomer (VII) has m.p. 167.0–167.5° and $[\alpha]D$ +50° (chloroform). This direct contradiction[5] of Hudson's rule[6] holds true over a range of observed wave lengths.

(1) P. W. Kent, *Research* (London), **3**, 427 (1950).
(2) P. W. Kent, G. Lawson, and A. Senior, *Science*, **113**, 354 (1951).
(3) P. F. Lloyd and M. Stacey, *Tetrahedron*, **9**, 116 (1960).
(4) P. F. Lloyd and G. P. Roberts, *J. Chem. Soc.*, 2962 (1963); *cf.* related work on disaccharide derivatives, P. F. Lloyd and G. P. Roberts, *Proc. Chem. Soc.*, 250 (1960).
(5) Y. Wang and H.-I. Tai, *Acta Chim. Sinica*, **24**, 368 (1958).
(6) C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909); *Advan. Carbohydrate Chem.*, **3**, 15 (1948).

CHART I



A definitive synthesis of I was made starting from the very stable 1-halo sugar, 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (VI).[7,8] A synthesis of I by Wang and Tai[5] had utilized the labile bromide analog[9] of VI. Treatment of VI in wet chloroform with a trace of acid[10] gave 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride (II) in high yield; the reaction presumably involves an *ortho*-acetyl amide intermediate[10] and results in stereospecific formation of the α-D anomer. The anomeric configuration of the free base of II has been proved[11] to be α-D by acetylation under nonequilibrating conditions to give the known[12,13] 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (III). The hydrochloride salt II used in this work could likewise be converted into III by acetylation with acetic anhydride in excess pyridine. *N*-Arylation of II with 1-fluoro-2,4-dinitrobenzene in the presence of sodium bicarbonate gave I in approximately 70% yield. This product could be obtained in two dimorphous forms, m.p. 218–219° and m.p. 191°, having different X-ray powder diffraction patterns. The low melting point form spontaneously recrystallized a few degrees above its melting point to give the high melting point form. The two forms had identical specific rotations and chromatographic mobilities, and gave very closely similar infrared spectra. On thin layer chromatography the compound I gave a single, fast-moving yellow zone, which was well resolved from the slower moving β-D anomer (VII), and from minor side products formed in the reaction.

(7) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).
(8) D. Horton and M. L. Wolfrom, *ibid.*, **27**, 1794 (1962).
(9) F. Micheel and H. Petersen, *Ber.*, **92**, 298 (1959).
(10) F. Micheel, F.-P. van de Kamp, and H. Petersen, *ibid.*, **90**, 521 (1957).
(11) F. Micheel, F.-P. van de Kamp, and H. Wulff, *ibid.*, **88**, 2011 (1955).
(12) C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Rec. trav. chim.*, **18**, 77 (1899).
(13) C. S. Hudson and J. K. Dale, *J. Am. Chem. Soc.*, **38**, 1431 (1916).

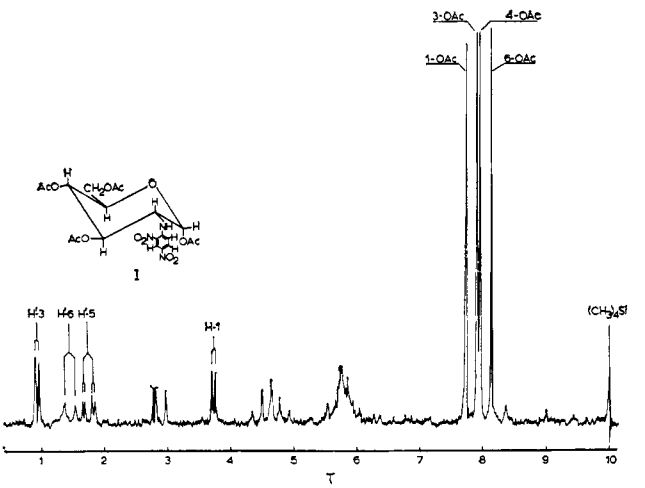
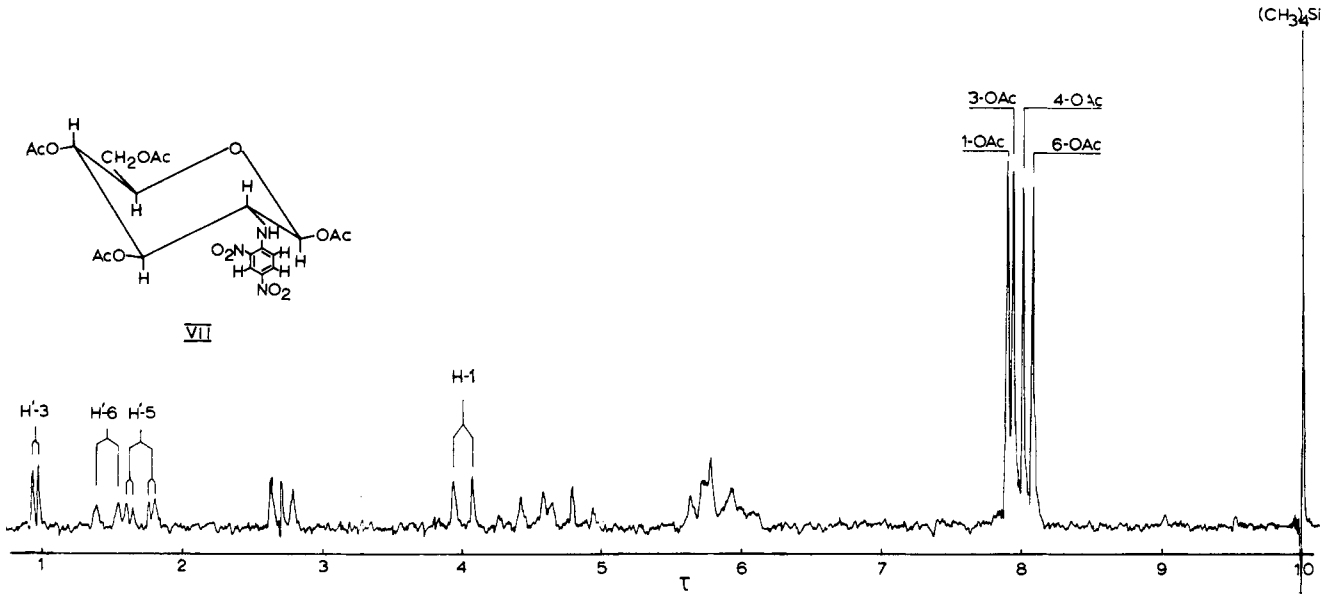


Fig. 1.—Nuclear magnetic resonance spectrum of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranose (I) in $CHCl_3$–$CDCl_3$, Varian HR-60 n.m.r. spectrometer. The solvent peak at τ 2.72 has been omitted.

Direct acetylation of carefully purified 2-deoxy-2-(2,4-dinitroanilino)-D-glucose[14] (IV) with acetic anhydride in excess pyridine gave I in high yield,[5] indicating that IV has the α-D-configuration. Preparation of IV from 2-amino-2-deoxy-D-glucose[3] gives a nearly quantitative yield of crude product, but after purification it was seldom found possible to obtain the product in more than 35% yield, as observed by others.[3] Acetylation of the dried crude product, however, gave I in good yield by direct crystallization; the mother liquors contained three additional yellow substances migrating more slowly than I on thin layer chromatograms. The four components in the crude acetylated product could be readily separated by silicate extrusion chro-

(14) K. H. Meyer and D. E. Schwartz, *Helv. Chim. Acta*, **33**, 1651 (1950); E. F. Annison, A. T. James, and W. T. J. Morgan, *Biochem. J.*, **48**, 477 (1951).



VII

Fig. 2.—Nuclear magnetic resonance spectrum of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranose (VII) in $CDCl_3$, Varian A-60 n.m.r. spectrometer.

matography, and were all obtained crystalline. The fastest migrating component had m.p. 217–219°, and was identical with I prepared by the definitive route. The component which followed I had m.p. 166°, and was shown to be identical with the anomer of I (VII), which had been prepared by a definitive route (see below). The other two slow-moving components, m.p. 200° and 188°, were apparently tri-*O*-acetyl derivatives of IV, and were not further investigated.

The reaction of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose[15] (VIII), or its hydrochloride salt, with 1-fluoro-2,4-dinitrobenzene provided a definitive route to 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranose (VII). Either the free base or the salt underwent *N*-arylation to give VII, having m.p. 167–167.5°, $[\alpha]_D$ +50° (chloroform). A product having similar constants, and prepared similarly from the hydrochloride (VIII-HCl) of the compound of Bergmann and Zervas[15] had been described[3] as the α-D anomer. Acetylation of either of the starting materials (VIII or VIII-HCl) used in the present work, under nonequilibrating conditions (acetic anhydride and excess pyridine in the cold) gave the known[12,13] 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (IX) in high yield; this establishes the anomeric configuration of the tetra-*O*-acetyl derivatives used, and confirms the observation of Bergmann and Zervas[15] on the free base VIII.

The highest yield of VII, essentially quantitative, was obtainable by treatment of 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide[3,8] (V) with mercuric acetate[16] in acetic acid, and no side products were detectable by thin layer chromatography. The glycosyl bromide derivative V[3] could be prepared, in almost quantitative yield from I, VII, or the crude mixture from acetylation of IV, by treatment with hydrogen bromide in acetic acid.

A facile preparative route to 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (IX) was found in the reaction of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[7,8] (VI) with mercuric acetate[16] in acetic acid. This route gives IX in high yield in three stages,[8] and provides a useful alternative to the four-step procedure of Bergmann and Zervas.[15]

The nuclear magnetic resonance (n.m.r.) spectra of I and VII (Fig. 1 and 2) provide independent physical proof of the structures assigned on the basis of synthesis. The anomeric proton of I appeared as a doublet at τ 3.72 with a coupling constant ($J_{1,2}$ = 3.5 c.p.s.) that was indicative[17,18] of an equatorially oriented C-1 proton having a projected valence angle[19] of 60° with the C-2 proton. In contrast, the anomeric proton of VII appeared at higher field, τ 4.01, characteristic[17,18] of the axial orientation, and this structure is supported by the large coupling constant, $J_{1,2}$ = 8.3 c.p.s., which is in agreement with a projected valence angle of 180° between the C-1 and C-2 protons. The corresponding 2-acetamido analogs (III and IX) of I and VII, whose n.m.r. spectra are recorded in Fig. 3, give closely comparable data for the anomeric protons. In the α-D anomer (III) the equatorial anomeric proton appears at τ 3.82 with a coupling constant, $J_{1,2}$ = 3.5 c.p.s., while for the β-D anomer (IX) the corresponding values are τ 4.27 and $J_{1,2}$ = 8.5 c.p.s. The coupling constants recorded are the directly observed doublet spacings, and may be considered to be minimum values of the absolute coupling constant $J_{1,2}$. It is recognized that the observed spacings may be somewhat smaller than the absolute value of $J_{1,2}$ owing to second-order effects[20] which depend on the relative chemical shift of the 2- and 3-protons and the $J_{2,3}$ coupling constant.

Further supporting data may be deduced from the chemical shifts of the C-1 acetoxy groups.[17] In I the acetoxy singlet at lowest field, τ 7.71, may be assigned

(15) M. Bergmann and L. Zervas, *Ber.*, **64**, 975 (1931).
(16) B. Lindberg, *Acta Chem. Scand.*, **3**, 1355 (1949).
(17) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958); J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 395.
(18) L. D. Hall, *Advan. Carbohydrate Chem.*, **19**, in press.
(19) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLaughlan, *J. Chem. Soc.*, 3699 (1962); R. U. Lemieux, J. D. Stevens, and R. R. Fraser, *Can. J. Chem.*, **40**, 1955 (1962).
(20) R. U. Lemieux and J. W. Lown, *ibid.*, **41**, 889 (1963).

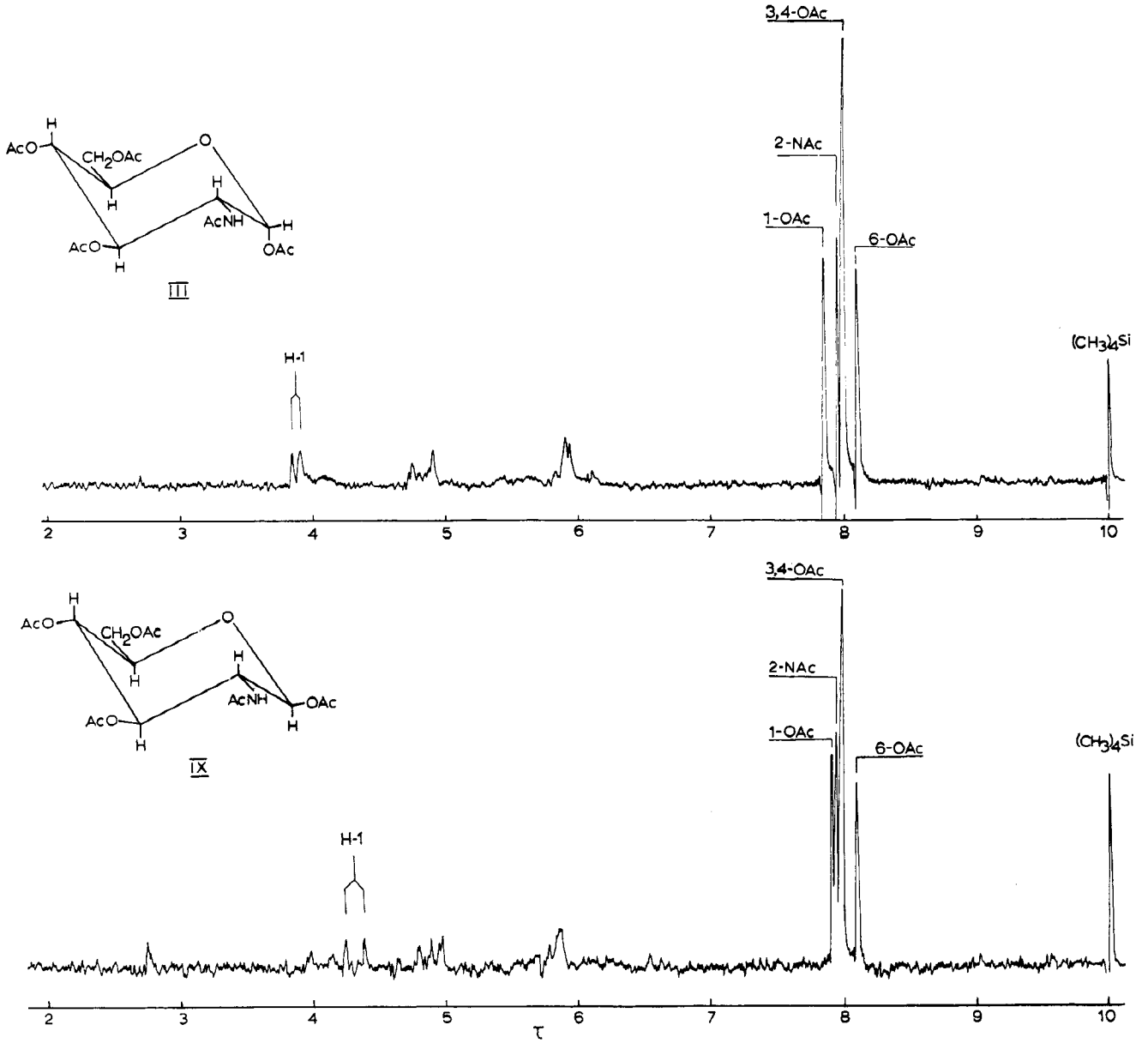


Fig. 3.—Nuclear magnetic resonance spectra of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α- and -β-D-glucopyranose (III and IX) in $CDCl_3$, Varian A-60 n.m.r. spectrometer.

to the axial C-1 acetoxy group, while in VII the group is equatorial and appears at higher field as a singlet, τ 7.89. In like manner, the singlet at τ 7.81 in the spectrum of III may be assigned to the axial C-1 acetoxy group, and the corresponding equatorial C-1 acetoxy group in IX appears as a singlet at higher field, τ 7.89. The integrated peak intensities of the anomeric protons and C-1 acetoxy groups in all four compounds were in the expected ratios. The anomeric proton resonances in I and VII were shifted to lower field in comparison with those of III and IX and other sugars,[18] presumably because of the extra deshielding effect of the 2,4-dinitroanilino sustituent. All of the foregoing n.m.r. data fully support the anomeric configurations assigned to I and VII.

Further empirical analysis of the n.m.r. spectra is possible. All four compounds show at highest field an acetyl singlet in the region τ 8.09–8.12 which may reasonably be assigned[18] to the primary C-6 acetoxy group. Compounds III and IX each show a singlet at τ 7.98 corresponding to two acetyl groups, attributable to the C-3 and C-4 acetoxy groups, and additionally a singlet at τ 7.93 corresponding to one acetyl group, presumably that of the acetamido function. In the 2,4-dinitroanilino derivatives I and VII, the C-3 and C-4 acetoxy groups gave singlets resolved from each other, lying in the region between the singlets for the C-1 acetoxy group (at lowest field) and the C-6 acetoxy group (at higher field). Since the deshielding effect of the C-2 substituent would be expected to influence the adjacent C-3 acetoxy group but probably not the C-4 substituent, the lower of the C-3, C-4 acetoxy resonances is assigned to the C-3 substituent. The low field doublet at τ 2.81 (in I) and 2.72 (in VII), of unit proton intensity, is very probably due to the proton on the nitrogen atom, but the resonance is partially obscured by the peak due to chloroform in the solvent. The three aryl protons in I and VII appeared at different fields; an empirical first-order analysis would indicate the 3-proton at τ 0.97 as a doublet, $J_{3,5}$ = 2.7 c.p.s.;

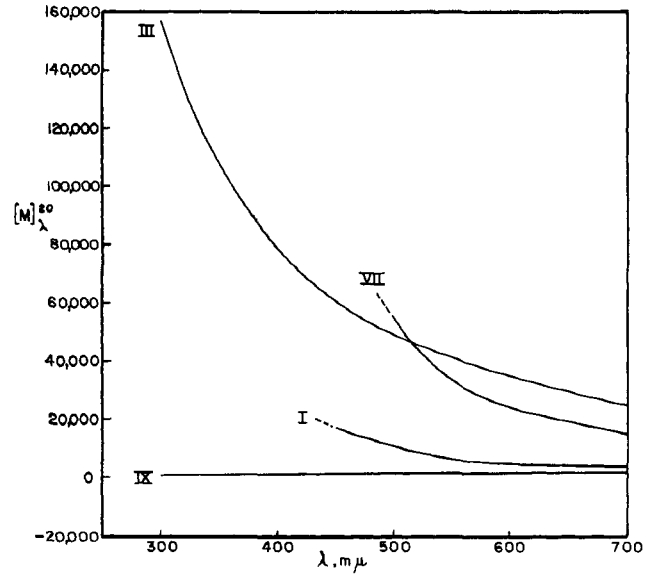


Fig. 4.—Optical rotatory dispersion spectra of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α- and -β-D-glucopyranose (I and VII) and 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α- and -β-D-glucopyranose (III and IX).

the 5-proton at τ 1.71 as a quartet, $J_{5,3}$ = 2.7 and $J_{5,6}$ = 9.5 c.p.s., and the 6-proton at τ 1.47 as a doublet, $J_{6,5}$ = 9.5 c.p.s.

The n.m.r. data for the bromo derivative V (see Experimental) are consistent with the assigned α-D anomeric configuration.

Optical rotatory dispersion curves for the two pairs of anomers I and VII, and III and IX (Fig. 4) show that the specific rotation of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranose (VII) is higher than that of its α-D anomer (I) at all observed wave lengths, and the difference increases at shorter wave lengths. Both derivatives show plain[21] positive curves from 700 to 450–500 mμ; absorption bands prevented observations below this limit. In contrast, 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (III) shows a plain positive curve from 700 to 300 mμ, and its specific rotation is at all wave lengths greater than that of its β-D anomer (IX), which shows little change in specific rotation over this range of wave lengths.

Discussion

The foregoing data establish beyond reasonable doubt that the specific rotations of the anomeric pair of compounds I and VII do not accord with the Hudson rule[6] that "in the D series the more dextrorotatory member of an α,β-pair of anomers is to be named α-D, the other being β-D." The Hudson rule for assignment of anomeric configuration is based "on the hypothesis that optical superposition holds for [anomeric pairs of sugar derivatives] in an approximation that is at least sufficient to exclude a complete reversal of relative rotations for an α,β-pair of anomers."[6] This rule holds true for many thousands of anomeric pairs, although exceptions have been noted[22] with the anomeric 1-(2-deoxy-D-*erythro*-pentofuranosyl) derivatives of 5-methyl (and 5-fluoro) uracil and other 2′-deoxynucleosides; in these examples the carbon atom vicinal to the anomeric carbon is not asymmetric.

The present example demonstrates a case of the complete reversal of the normal relative rotations of an α,β-pair of anomers, in a pyranose ring sugar having an asymmetric center at C-2, when the 2,4-dinitroanilino group is introduced at C-2. It would appear probable[5] that the methyl (and ethyl) 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α(and β)-D-glucopyranoses[3,4] also show a similar reversal of the normal relative rotations, although there is lack of agreement[3-5] on the specific rotations of these glycoside derivatives. The present observations indicate that assignment of anomeric configuration[4] should not be based solely on optical rotatory data when the 2,4-dinitroanilino group, and possibly other groups of high polarizability, are present.

The Hudson rules are based on the Van't Hoff principle of optical superposition,[23] and on the assumption that vicinal effects do not greatly influence the magnitude of the rotatory contribution of C-1 in relation to the rotatory contribution of the rest of the molecule. The relatively large magnitude of the C-1 contribution normally outweighs the small-magnitude effect of vicinal action, and ensures the general applicability of the rules. More recent views[24-26] of optical activity regard an optically active center as an asymmetric screw pattern of polarizability arising from (a) the difference in polarizability of groups attached to an asymmetric carbon atom (atom asymmetry), and (b) the spatial arrangement of groups in the molecule (conformational asymmetry); the latter effect usually provides the larger rotatory contribution. Calculations of molecular rotation of cyclic sugars, in good agreement with experimental values, have been made[24] from considerations of conformational asymmetry, by algebraic summation of a series of empirical rotation parameters, along each bond of the ring in its favored conformation. Rotation parameters have been calculated[25] from the polarizabilities of the substituent groups. The conformational rotatory power of the amino group is approximately the same as that of the hydroxyl group[26]; hence, the 2-amino sugars and their derivatives in general obey the isorotation rules well,[27] but *N*-substitution with the 2,4-dinitrophenyl group would appear to produce a large change in the group polarizability and, by the consequent large change in conformational rotatory power, gives rise to a large vicinal effect which overrides the rotatory contribution of the anomeric center in its effect on the net rotation.

Further studies are in progress to determine the effect of temperature changes on the specific rotations of I, VII, and related derivatives.

(21) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(22) R. U. Lemieux and M. Hoffer, *Can. J. Chem.*, **39**, 110 (1961); R. U. Lemieux, *ibid.*, **39**, 116 (1961); J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 340 (1959).

(23) J. H. Van't Hoff, "Die Lagerung der Atome in Raume," Vieweg-Verlag, Brunswick, Germany, 1893, p. 119.

(24) D. H. Whiffen, *Chem. Ind.* (London), 964 (1956).

(25) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475, 5483 (1959).

(26) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 14.

(27) A. B. Foster and M. Stacey, *Advan. Carbohydrate Chem.*, **7**, 247 (1952).

Experimental[28]

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranose (I). A. From 1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose Hydrochloride (II).—A related procedure from the hydrobromide analog of II has been described,[5] but the yield was very low, and there was no chromatographic verification of product homogeneity. A solution of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride (II,[10] 2.00 g.) in water (10 ml.) and acetone (30 ml.) was stirred overnight at room temperature with sodium bicarbonate (0.44 g.) and 1-fluoro-2,4-dinitrobenzene (1.00 g.). The solution was evaporated, the residue was washed with petroleum ether (b.p. 30–60°), and the washings were discarded; then the product was extracted with chloroform (50 ml.), and inorganic material was removed by filtration. The extract was evaporated to 10 ml., and ethanol (50 ml.) was added, whereupon the product I crystallized rapidly, yielding 1.10 g. (41%), m.p. 218–219°. Recrystallization from chloroform–ethanol was effected with little loss to give pure material as very fine lemon yellow needles, m.p. 218–219°, $[\alpha]^{21}D$ +9.1 ± 0.2° (*c* 1.5, chloroform); λ_{max}^{KBr} 3.00 (NH), 3.17 (aryl CH), 5.66, 5.75 (OAc), 6.18, 6.29, 6.65 (aryl C=C, 6.50 (NH, NO_2), 7.42 (NO_2), 13.48, 13.90 μ (substituted benzene); λ_{max}^{EtOH} 208 mμ (ε 6400), 264 (5000), 333 (7800); n.m.r. data[28]: τ 8.02 (6-OAc), 7.94 (4-OAc), 7.89 (3-OAc), 7.71 (1-OAc), 3.72 (doublet, H-1, $J_{1,2}$ 3.5 c.p.s.); X-ray powder diffraction data[28]: 13.19 w, 11.95 s (3), 7.76 vs (1,1), 6.15 s (2,2), 5.50 w, 5.19 m, 4.87 vs (1,1), 4.46 m, 4.35 w, 4.15 w, 3.97 s, 3.75 s (2,2), 3.53 vs (1,1) 3.38 s (2).

Anal. Calcd. for $C_{20}H_{23}N_3O_{13}$: C, 46.78; H, 4.52; N, 8.19. Found: C, 46.68; H, 4.49; N, 8.29.

The product gave a homogeneous yellow zone, R_f 0.60 (R_x 1.00), on thin layer chromatography. The mother liquors contained approximately 50% of the same component, which could be isolated by column chromatography (see below) to raise the total yield to approximately 70%. Smaller proportions of two other yellow components, R_x 0.5 and 0.3, were present, together with a colorless component, R_x 0.1, which appeared after spraying with sulfuric acid.

One preparation of this material crystallized in a second form having m.p. 191°, which on further heating resolidified at about 195° and finally melted at 218–219°. The mixture melting point of the two forms was 218–219°. The second form had X-ray powder diffraction data[28]: 10.78 m, 9.31 vs (1), 7.25 m, 5.87 w, 5.54 s, 5.31 vw, 4.96 s (2,2), 4.80 m, 4.42 s (3), 4.00 s (2,2), 3.74 s (3), 3.56 s, 3.39 s (2,2), 3.10 w, 2.90 m. The specific rotations and chromatographic mobilities of the two forms were identical. A supersaturated solution of I gave either dimorph by appropriate nucleation.

B. From 2-Deoxy-2-(2,4-dinitroanilino)-D-glucose (IV).—Crude IV was prepared[14] in almost quantitative yield from 2-amino-2-deoxy-D-glucose hydrochloride, and was not recrystallized. Dried IV (27 g.) in pyridine (160 ml.) was treated at 0° with acetic anhydride (65 ml.). After 3 days at 0° the solution was poured on ice (1.5 kg.), stirred for 3 hr., then filtered to give the crude acetylated product in a 35-g. (88%) yield. Thin layer chromatography revealed the presence of four yellow components in this mixture, R_x 1.0, 0.9, 0.5, and 0.3, in the relative intensity ratios 10:2:3:1. Recrystallization of a 5-g. sample of the crude product from ethanol gave yellow needles of I in a 3.5-g. yield (corresponding to 62% in the over-all reaction), m.p. 217–219°. The product was identical by mixture melting point and by thin layer chromatography with the product isolated in A above.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranose (VII). A. From 1,3,4,6,-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose Hydrochloride (VIII-HCl).—A solution of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose hydrochloride (VIII-HCl)[15] (2.00 g.) in water (10 ml.) containing sodium bicarbonate (0.44 g.) was treated with a solution of 1-fluoro-2,4-dinitrobenzene (0.98 g.) in acetone (30 ml.); the mixture was stirred overnight, and then evaporated. The residue was partitioned between chloroform (30 ml.) and water (20 ml.); the chloroform extract was dried over magnesium sulfate and evaporated. Crystallization of the product from ethanol gave canary yellow needles, 1.30-g. yield, m.p. 167°. Concentration of the mother liquors gave a further 0.32 g. of product, m.p. 164–166°, to give a total yield of 61%. Recrystallization from ethanol gave pure product with little loss, m.p. 167.0–167.5°, $[\alpha]^{21}D$ +50.0 ± 0.1° (*c* 1.1, chloroform); λ_{max}^{KBr} 3.02 (NH), 3.22 (aryl CH), 5.75 (OAc), 6.18, 6.24 (aryl C=C), 6.48 6.58, 6.69 (NH, aryl C=C, NO_2), 7.40 (NO_2), 13.50, 13.90 μ (substituted benzene); λ_{max}^{EtOH} 208 mμ (ε 7250), 261 (ε 5250), 336 (ε 8300); n.m.r. data[28]: τ 8.09 (6-OAc), 8.00 (4-OAc), 7.93 (3-OAc), 7.81 (1-OAc), 4.01 (doublet, H-1, $J_{1,2}$ = 8.3 c.p.s.); X-ray powder diffraction data[28]: 10.16 s (2), 8.51 w, 7.56 w, 5.19 vw, 4.75 m (3,3), 4.53 w, 4.37 vw, 4.17 w, 4.00 m (3,3), 3.75 s (1).

Anal. Calcd. for $C_{20}H_{23}N_3O_{13}$: C, 46.78; H, 4.52; N, 8.19. Found: C, 46.69; H, 4.71; N, 8.39.

The product was chromatographically homogeneous, R_x 0.9, on thin layer chromatography. The noncrystalline mother liquor contained an estimated 40% of this component, together with traces of yellow components R_x 1.0 and 0.5, and a moderately intense yellow component R_x 0.3. A colorless zone of weak intensity appeared near the origin after spraying with sulfuric acid.

The reaction was repeated, but with 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose (VIII)[15] as starting material, in place of the hydrochloride salt. The product VII was isolated in 51% yield, and the mother liquors contained a similar distribution of components to those in the preceding preparation.

B. From 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl Bromide (V).—A solution of the bromo sugar (V,[8] 0.25 g.) and mercuric acetate (0.20 g.) in acetic acid (10 ml.) was stirred for 2 hr. at room temperature. Chloroform (50 ml.) was added; the solution was washed with three 30-ml. portions of water, dried over magnesium sulfate, and evaporated; the residue crystallized from ethanol to give canary yellow needles of the product VII in a 0.22-g. (92%) yield, m.p. 166.5–167.0°. The product was identical with that obtained in A above by mixture melting point and thin layer chromatography.

C. From 2-Deoxy-2-(2,4-dinitroanilino)-D-glucose (IV).—A 3-g. amount of the crude product obtained by acetylation of 2-deoxy-2-(2,4-dinitroanilino)-D-glucose (IV), as described for preparation of I by procedure B, was resolved by chromatography on a 27 × 8 cm. Magnesol[29] Celite column,[30] using 200:1 benzene–*t*-butyl alcohol (5 l.) as eluent. Four yellow zones were observed, centered at 15, 11, 5, and 0 cm. from the top of the column. The zones were sectioned from the extruded column and extracted with acetone, and the products crystallized from chloroform–petroleum ether. The fastest moving zone gave a crystalline product in an 0.86-g. yield, m.p. 217–219°, indistinguishable from I, while the zone which had moved 11 cm. gave fine needles in a 0.10-g. yield, m.p. 166–166.5°, indistinguishable from VII by mixture melting point, infrared spectrum, and the X-ray powder diffraction pattern. The 5-cm. zone gave an unidentified product in a 0.13-g. yield, m.p. 200°, and the stationary zone gave a second unidentified product in an 0.08-g. yield, m.p. 188°.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl Bromide (V).—Treatment of either 1,3,4,6-tetra-*O*-acetyl-2-(2,4-dinitroanilino)-α-D-glucopyranose (I) or its β-D anomer (VII), or the crude mixture of both, with hydrogen

(28) Melting points were determined with a Hershberg-type apparatus and are corrected. Specific rotations were determined at the D line in a 4-dm. tube, optical rotatory dispersion measurements were made with a Rudolph Model 260/655/850/810-614 recording photoelectric spectropolarimeter. Microanalyses were performed by W. N. Rond. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord spectrophotometer, with potassium bromide pellets pressed from a finely ground mixture of the sample with dried analytical reagent grade potassium bromide. Ultraviolet absorption spectra were measured by L. D. Sannes with a Cary Model 10 recording spectrophotometer. The proton magnetic resonance spectra were measured at 60 Mc./sec. in deuteriochloroform or deuteriochloroform–chloroform, with tetramethylsilane as internal standard. Thin layer chromatography was performed with Desaga equipment (Brinkmann Instruments, Great Neck, N. Y.) using the ascending technique with a 250-μ layer of silica gel G (E. Merck, Darmstadt, Germany) activated for 2 hr. at 100°. The developing solvent was 3:1 chloroform–ether, and zones were detected visually and after spraying with sulfuric acid. R_x values denote mobility relative to 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranose (I). X-Ray powder diffraction data give interplanar spacings, Å., for Cu Kα radiation. Relative intensity was estimated visually: s, strong; m, moderate; w, weak; v, very. First three strongest lines are numbered (1, strongest), double numbers indicate approximately equal intensities.

(29) A product of the Westvaco Chemical Division of Food Machinery and Chemical Corp., South Charleston, W. Va.

(30) A. Thompson, *Methods Carbohydrate Chem.*, **1**, 36 (1962). This separation was carried out by Mr. L. D. Sannes.

bromide in acetic acid according to the conditions of Lloyd and Stacey[3] for a compound described as I, gave V in almost quantitative yield, with physical constants in agreement with those reported[3]; n.m.r. data[28]: τ 8.15 (6-OAc), 7.93 (4-OAc), 7.89 (3-OAc), 3.40 (doublet, H-1, $J_{1,2}$ = 3.5 c.p.s.).

2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (III).—This compound[12,13] was prepared in 56% yield by direct acetylation of 2-amino-2-deoxy-D-glucose hydrochloride by the acetic anhydride–sodium acetate procedure.[12] It could also be obtained by acetylation of II with acetic anhydride in an excess of pyridine.[11] The pure material had m.p. 139.5–140.5°, $[\alpha]_D$ +93° (*c* 1.0, chloroform); λ_{max}^{KBr} 2.92 (NH), 5.74 (OAc), 6.00, 6.57 (NHAc), and 11.82 μ (equatorial H at C-1); n.m.r. data[28]: τ 8.09 (6-OAc), 7.98 (3,4-OAc), 7.93 (2-NAc), 7.81 (1-OAc), 3.82 (doublet, H-1, $J_{1,2}$ = 3.5 c.p.s.); X-ray powder diffraction data[28]: 12.28 m, 9.31 vs (1), 7.03 w, 6.28 w, 5.99 vw, 5.44 s, 5.13 m, 4.80 m, 4.58 vw, 4.37 m, 4.17 s (2), 4.00 m, 3.63 s (3), 3.52 m, 3.35 m, 3.13 m.

2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (IX).—The following procedure provided a facile route to this compound. 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (VI)[8] (3.47 g.) was dissolved in acetic acid (30 ml.), mercuric acetate (3.18 g.) was added, and the mixture was stirred for 2 hr. at room temperature. Chloroform (150 ml.) was added to the clear solution followed by water (10 ml.), the mixture was shaken, and the organic layer was separated and dried over magnesium sulfate. After evaporation of the chloroform, the product was crystallized from methanol–ether yielding 3.20 g. (86%), m.p. 186–186.5°. A second recrystallization gave small prisms, m.p. 186.0–186.5°, $[\alpha]_D$ +1.5 ± 0.5° (*c* 1, chloroform); λ_{max}^{KBr} 3.10 (NH), 5.73 (OAc), 6.02, and 6.50 μ (NHAc); n.m.r. data[28]: τ 8.09 (6-OAc), 7.97 (3,4-OAc), 7.93 (2-NAc), 7.89 (1-OAc), 4.27 (doublet, H-1, $J_{1,2}$ 8.5 c.p.s.); X-ray powder diffraction data[28]: 9.31 m, 7.08 s, (2,2), 6.66 w, 6.24 m, 5.19 w, 4.85 vs (1), 4.60 w, 4.21 m, 3.79 s (2,2), 3.55 s (3), 3.25 w. The product was only moderately soluble in chloroform, almost insoluble in water, and readily soluble in methanol. The above route provides a synthesis of IX from 2-amino-2-deoxy-D-glucose hydrochloride, in 67% over-all yield, by way of 2-acetamido-2-deoxy-D-glucose and VI.[7,8]

A sample of VIII (347 mg.), as used in the conversion to VII, was acetylated with acetic anhydride in excess pyridine solution, and after conventional processing crystalline IX was obtained in 290-mg. (75%) yield, m.p. 185–186°. A repeat preparation with the hydrochloride salt of VIII (383 mg.) also gave IX in 310-mg. (80%) yield. Similar results were obtained when VIII·HCl was acetylated by the acetic anhydride–sodium acetate procedure.[15] In all cases the product was identical with that prepared by the first procedure.

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Aryl Thioglycopyranosides, Aryl Glycopyranosyl Sulfones, and the Novel Oxidation–Acetylation of Aryl 1-Thio-β-D-glucopyranosides to 6-*O*-Acetyl-β-D-glucopyranosyl Aryl Sulfones[1]

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When *p*-tolyl 1-thio-β-D-glucopyranoside in a mixture of glacial acetic acid and 30% hydrogen peroxide is allowed to stand for several days at room temperature, the product, obtained in nearly quantitative yield, is not the expected β-D-glucopyranosyl *p*-tolyl sulfone but the 6-*O*-acetyl derivative of the sulfone. Experiments indicate that this novel acetylation reaction may occur at the intermediate sulfoxide stage. A number of other aryl thioglycosides and aryl glycosyl sulfones are described, and some of their reactions and their infrared and nuclear magnetic resonance spectra are discussed.

In an attempt to find new antimalarials, Montgomery, Richtmyer, and Hudson[3] prepared a series of substituted phenyl 1-thio-β-D-glucopyranosides. In 1947, one of these compounds, the *p*-tolyl 1-thio-β-D-glucopyranoside (IV), was dissolved in glacial acetic acid and oxidized with an excess of 30% hydrogen peroxide for several days at room temperature. The product, obtained in nearly quantitative yield, was expected to be the β-D-glucopyranosyl *p*-tolyl sulfone (III),[4] but carbon and hydrogen analyses corresponded almost exactly to the values required for a 1:1 double compound between the sulfone and the sulfoxide.[5] This seemed quite plausible in view of a paper entitled "Mixed Crystals of Sulfoxides and Sulfones" that had been published shortly before.[6] Ten years later, however, when an infrared spectrum of our compound revealed what appeared to be strong carbonyl absorption at 1695 cm.$^{-1}$, the problem seemed to warrant further study.

A survey of the literature showed that the oxidation products of thioglycosides included both sulfones and sulfoxides. Wrede and Zimmermann[7] prepared the first sulfones; these were mainly of the bis(β-D-glycopyranosyl) sulfone type and were made by oxidation of the acetylated bis(β-D-glycopyranosyl) sulfides with potassium permanganate in acetic acid and then deacetylating the crystalline products. Micheel and Schmitz[8] described the first sulfoxide, ethyl α-D-glucopyranosyl sulfoxide; this was obtained by the oxidation of ethyl 1-thio-α-D-glucopyranoside with dilute aqueous hydrogen peroxide. Bonner and Drisko[9] oxidized five acetylated thioglycosides to their respective sulfones by heating either with aqueous potassium

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(2) Associate in the Visiting Program of the National Institutes of Health, Oct., 1961, to Sept., 1963.

(3) E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *J. Org. Chem.*, **11**, 301 (1946).

(4) It was thus listed, under Survey No. 15418* and N.I.H. No. 2873 by G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg in "Survey of Antimalarial Agents," Public Health Monograph No. 9, U. S. Government Printing Office, 1953, p. 214.

(5) *Anal.* Calcd. for $C_{26}H_{36}O_{13}S_2$: C, 50.31; H, 5.85. Found: C, 50.30; H, 5.80.

(6) H. Rheinboldt and E. Giesbrecht, *J. Am. Chem. Soc.*, **68**, 973 (1946).

(7) F. Wrede and W. Zimmermann, *Z. physiol. Chem.*, **148**, 65 (1925).

(8) F. Micheel and H. Schmitz, *Ber.*, **72**, 992 (1939).

(9) W. A. Bonner and R. W. Drisko, *J. Am. Chem. Soc.*, **70**, 2435 (1948).