tities of catalyst as before, to give on work-up 1.31 g. (75%) of mustard XXIV hydrochloride as a yellow sirup: $\lambda_{max}^{film}$ 3.0 (OH), 9.18, 9.32, and 9.55 (C–O–C) $\mu$. There was no absorption at 14.3 $\mu$ due to $C_6H_5CH_2$.

*Anal.* Calcd. for $C_{11}H_{21}Cl_2NO_5 \cdot HCl \cdot 0.25H_2O$: C, 36.8; H, 6.28; Cl, 29.6; N, 3.90. Found: C, 36.4; H, 6.36; Cl, 29.8; N, 3.70.

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# Syntheses with Partially Benzylated Sugars. IV.[1] A Route to Some 1-O-Acyl-2-acylamido-2-deoxy-D-glucopyranoses and -D-galactopyranoses

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2-Acylamido-2-deoxyhexoses of the D-glucose and D-galactose series can be benzylated to give benzyl 2-acylamido-3,4,6-tri-O-benzyl-2-deoxyhexopyranosides. When such glycosides are successively hydrolyzed by acid, acylated, and O-deacylated, they afford 2-acylamido-3,4,6-tri-O-benzyl-2-deoxyhexopyranoses. Through a sequence, involving acylation and debenzylation, these latter substances serve as precursors of the 1-O-acyl-2-acylamido-2-deoxyhexopyranoses.

It has been suggested that some of the 2-acetamido-2-deoxy-D-galactosyl moieties in ovine submaxillary gland mucoprotein (OSM) are bound by a C-1 ester linkage to the nonpeptide-bonded carboxyl groups of aspartic and glutamic acids.[3] For this reason, the properties of 1-O-acyl derivatives of the 2-acetamido-2-deoxyhexoses become of interest and we wish to report here a study of the synthesis of some representatives of this class of substance.

Aldoses, fully etherified with benzyl groups except at C-1 and C-4 (aldofuranoses) or C-5 (aldopyranoses), can be obtained through the hydrolysis of fully benzylated aldopyranosides[4–6] or aldofuranosides.[6,7] By esterification of such ethers at C-1 and subsequent removal of the benzyl groups by catalytic hydrogenolysis, C-1 esters of the aldoses can be prepared; by this route Schmidt and Schmadel[8] were able to synthesize the two anomeric 1-O-galloyl-D-glucopyranoses while Tejima and Fletcher[6] similarly prepared the anomeric 1-O-benzoyl-L-arabinopyranoses as well as the anomeric 1-O-benzoyl-L-arabinofuranoses. The application of this type of process to the synthesis of 1-O-acyl-2-acylamido-2-deoxyaldopyranoses requires 2-acylamido-2-deoxyaldopyranoses etherified with benzyl groups except at C-1 and C-5. For the synthesis of such an intermediate, attention was first turned to *t*-butyl 3,4,6-tri-O-acetyl-2-benzamido-2-deoxy-β-D-glucopyranoside (I), a substance reported by Micheel and Köchling[9]; the glycosidic linkage in such a compound should be relatively labile to acid while the benzamido group should be more stable than the acetamido group. Treatment of I with benzyl chloride and potassium hydroxide in boiling tetrahydrofuran caused replacement of the acetyl groups by benzyl groups, giving the tribenzyl ether II (Scheme I); hydrolysis of II in a mixture of tetrahydrofuran and hydrochloric acid afforded 2-benzamido-3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranose (III) in 61% yield.[10] It is evident, therefore, that the *t*-butyl group may be removed from C-1 without substantial loss of the benzoyl group from the nitrogen. However, the synthesis of I is both laborious and time consuming and a more direct route to III was sought.

Kuhn and Trischmann[11] have shown that cautious methylation of 2-acetamido-2-deoxy-D-glucopyranose in N,N-dimethylformamide with methyl iodide, barium oxide, and barium hydroxide octahydrate affords a very high yield of methyl 2-acetamido-2-deoxy-3,4,6-tri-O-methyl-β-D-glucopyranoside. This procedure was adapted to the benzylation of 2-benzamido-2-deoxy-D-glucopyranose (IV), using benzyl bromide, and a crystalline benzyl 2-benzamido-3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranoside (V) was obtained. By analogy with the findings of Kuhn and Trischmann,[11] one might expect this glycoside to have the β configuration; the n.m.r. spectrum of the substance confirmed this expectation. Hydrolysis of this glycoside V afforded 2-benzamido-3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranose (III) in 62% yield, demonstrating that a benzyl glycoside is as suitable as a *t*-butyl glycoside for the preparation of this substance.

Since the 2-amino-2-deoxyaldoses most frequently occur in nature as *N*-acetyl derivatives, we studied next the synthesis of 2-acetamido-3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranose (VIII). Direct benzylation of 2-acetamido-2-deoxy-D-glucopyranose (VI) readily gave benzyl 2-acetamido-3,4,6-tri-O-benzyl-2-deoxy-β-D-glucopyranoside (VII) in 76% yield. However, in contrast to the conversion of V to III, the hydrolysis of benzyl 2-acetamido-3,4,6-tri-O-benzyl-2-deoxy-β-D-

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(2) Fellow in the Visiting Progam, 1963–1964.

(3) E. R. B. Graham, W. H. Murphy, and A. Gottschalk, *Biochim. Biophys. Acta*, **74**, 222 (1963); K. Tanaka, M. Bertolini, and W. Pigman, *Biochem. Biophys. Res. Commun.*, **16**, 404 (1964); S. Harbon, G. Herman, B. Rossignol, P. Jollès, and H. Clauser, *ibid.*, **17**, 57 (1964); V. P. Bhavanandan, E. Buddecke, R. Carubelli, and A. Gottschalk, *ibid.*, **16**, 353 (1964) *cf.* also B. Anderson, N. Seno, P. Sampson, J. Riley, P. Hoffman, and K. Meyer, *J. Biol. Chem.*, **239**, 2716 (1964).

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(7) R. Barker and H. G. Fletcher, Jr., *ibid.*, **26**, 4605 (1961).

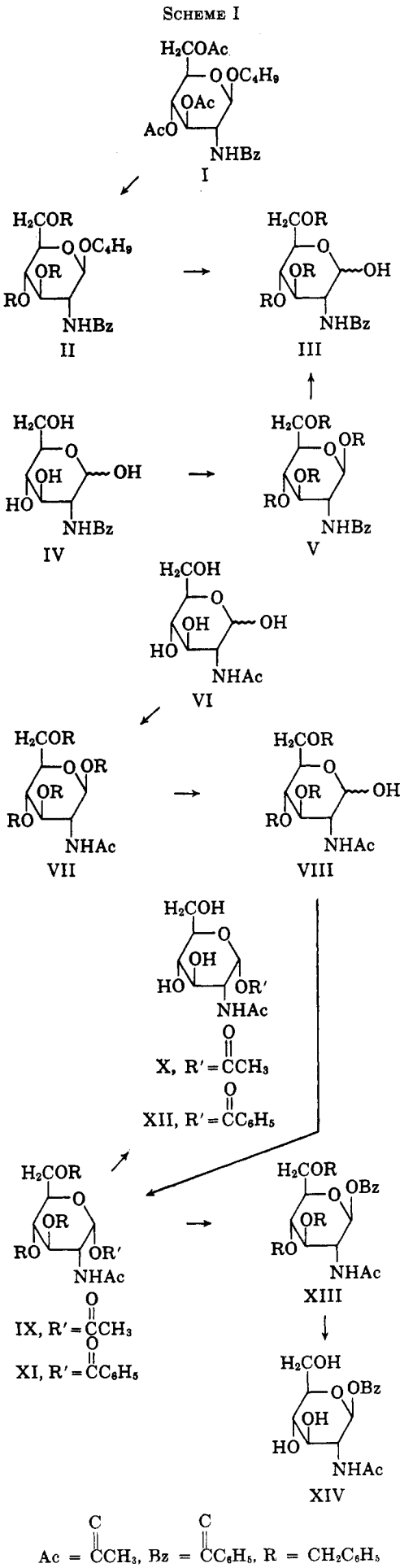
(8) O. T. Schmidt and H. Schmadel, *Ann.*, **649**, 149 (1961).

(9) F. Micheel and H. Köchling, *Ber.*, **91**, 673 (1958).

(10) While this substance is dextrorotatory, $[\alpha]^{20}D$ +89° ($CHCl_3$) and $[\alpha]^{20}D$ +89° (pyridine), it was not observed to mutarotate; assignment of an anomeric configuration to it cannot be made with assurance at this time.

(11) R. Kuhn and H. Trischmann, *Ber.*, **96**, 284 (1963).

SCHEME I




glucopyranoside (VII) with a mixture of hydrochloric acid and tetrahydrofuran gave a sirup from which only a negligible quantity (*ca.* 2%) of the desired 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (VIII) could be obtained after chromatography. The major portion of the product was amorphous and lacked the absorption bands at 1640 and 1510 cm.$^{-1}$ characteristic of a secondary amide. Hydrolysis of VII with a mixture of hydrochloric and acetic acids similarly resulted in loss of the *N*-acetyl group although, in this case, a strong band at 1720 cm.$^{-1}$ showed an ester group to be present. In view of these findings, the entire hydrolysate, obtained from VII through the action of hydrochloric acid in tetrahydrofuran, was acetylated and the product was *O*-deacetylated with sodium methoxide in methanol; the desired 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (VIII) was thus obtained in 65% yield. It showed $[\alpha]^{20}D$ +71.3° in chloroform and $[\alpha]^{20}D$ +63° in pyridine, no mutarotation being observed in this latter solvent, even after the addition of a trace of concentrated hydrochloric acid. The dextrorotation of the substance suggests that it may be the $\alpha$ anomer.

Acetylation of VIII afforded 2-acetamido-1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-$\alpha$-D-glucopyranose (IX), the anomeric configuration being assigned on the basis of its n.m.r. spectrum and its rotation of $[\alpha]^{20}D$ +108° in chloroform. Removal of the benzyl groups from IX by catalytic hydrogenolysis over palladium afforded 2-acetamido-1-*O*-acetyl-2-deoxy-$\alpha$-D-glucopyranose (X), $[\alpha]^{20}D$ +149° in methanol.

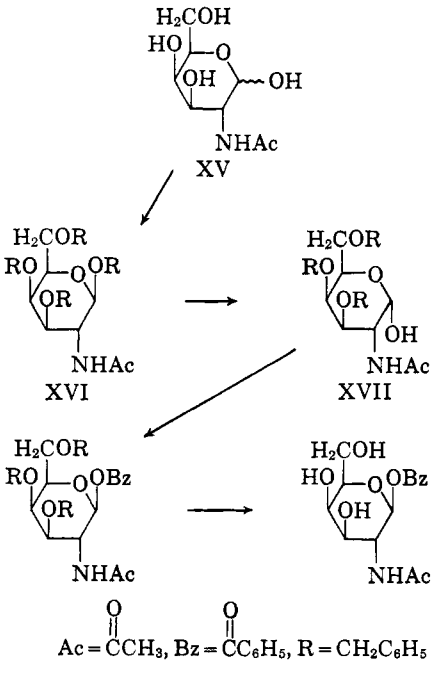
In similar fashion, benzoylation of VIII gave a mixture from which 2-acetamido-1-*O*-benzoyl-3,4,6-tri-*O*-benzyl-2-deoxy-$\alpha$-D-glucopyranose (XI) was isolated; catalytic hydrogenolysis then gave 2-acetamido-1-*O*-benzoyl-2-deoxy-$\alpha$-D-glucopyranose (XII). That XI and XII are actually $\alpha$-D anomers was demonstrated by a stereospecific synthesis of the corresponding $\beta$-D compounds. The diacetyl derivative IX was converted to amorphous 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl bromide which was then condensed with silver benzoate to give 2-acetamido-1-*O*-benzoyl-3,4,6-tri-*O*-benzyl-2-deoxy-$\beta$-D-glucopyranose (XIII), $[\alpha]^{20}D$ −11.1° in chloroform. On catalytic hydrogenolysis, XIII afforded 2-acetamido-1-*O*-benzoyl-2-deoxy-$\beta$-D-glucopyranose (XIV), $[\alpha]^{20}D$ −38° in methanol.

With the experience gained in the 2-amino-2-deoxy-D-glucopyranose series we turned to the less accessible but biochemically more interesting 2-amino-2-deoxy-D-galactopyranose series. The direct benzylation of 2-acetamido-2-deoxy-D-galactose (XV) gave crystalline benzyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranoside (XVI)[12] (Scheme II). Hydrolysis of this glycoside, followed by acetylation and *O*-deacetylation gave a crystalline 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranose, which showed $[\alpha]^{20}D$ +72° in chloroform; since it mutarotated $[\alpha]^{20}D$ +125 → 116° in pyridine, it is presumed to be the $\alpha$ anomer

(12) While the signal for H-1 in the n.m.r. spectrum of V appeared as a well-defined doublet ($J \sim 9$ c.p.s.) at $\delta$ 6.08, the corresponding signals of VII and XVI apparently were shifted upfield into a complex multiplet in which they were not readily distinguishable. However, VII, with $[\alpha]^{20}D$ −12.1° ($CHCl_3$), and XVI, with $[\alpha]^{20}D$ −20° ($CHCl_3$), are both more levorotatory than benzyl 2-benzamido-3,4,6-tri-*O*-benzyl-2-deoxy-$\beta$-D-glucopyranoside (V) and the $\beta$ configuration is, therefore, tentatively assigned to both these glycosides.

XVII. A crystalline benzoate obtained from XVII in 62% yield showed $[\alpha]^{20}D$ +2.5° in chloroform and (after exchange of the amide proton by exposure to deuterium oxide) a doublet at $\delta$ 5.9 with a spacing of 9 c.p.s.; hence the ester is the $\beta$ anomer XVIII. Hydrogenolysis of XVIII gave 2-acetamido-1-O-benzoyl-2-deoxy-$\beta$-D-galactopyranose (XIX) as a well-defined, crystalline product.

SCHEME II




On standing in methanol solution at room temperature for several days the 2-acetamido-1-O-acyl-2-deoxyhexopyranoses proved to be unstable as indicated by thin layer chromatography. This and other properties of these substances are currently under investigation in this laboratory.

## Experimental[13]

**t-Butyl 2-Benzamido-3,4,6-tri-O-benzyl-2-deoxy-$\beta$-D-glucopyranoside (II).**—t-Butyl 3,4,6-tri-O-acetyl-2-benzamido-2-deoxy-$\beta$-D-glucopyranoside[9] (1 g.) was dissolved in 30 ml. of tetrahydrofuran (freshly distilled from lithium aluminum hydride), and the solution was treated with Drierite (0.5 g.) and commercial powdered potassium hydroxide (1.4 g.).[14] With vigorous stirring, benzyl chloride (3 ml., 9.2 molar equiv.) was added dropwise, and the stirred reaction mixture boiled under reflux for 18 hr. The cooled reaction mixture was filtered, the residue being washed thoroughly with tetrahydrofuran and dichloromethane; concentration of the combined mother liquor and washings afforded a semisolid mass which was dissolved in dichloromethane. The solution was washed with water, dried with magnesium sulfate, and concentrated, finally at 100° and 15-mm. pressure, to give a semicrystalline mass. From ethanol solution, II was obtained as colorless needles: 0.5 g. (38%), m.p. 177–178°, $[\alpha]^{20}D$ +24° (*c* 1.22, $CH_2Cl_2$). After recrystallization from ethanol, the product showed m.p. 177–178° and $[\alpha]^{20}D$ +25° (*c* 0.178, $CHCl_3$).

*Anal.* Calcd. for $C_{38}H_{43}NO_6$ (609.77): C, 74.85; H, 7.11; N, 2.30. Found: C, 75.07; H, 7.10; N, 2.39.

**2-Benzamido-3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranose (III) from II.**—Compound II (0.9 g.) was dissolved in a mixture of tetrahydrofuran (70 ml.) and 2 *N* hydrochloric acid (35 ml.), and the solution boiled under reflux for 48 hr. The cooled solution was neutralized with solid sodium bicarbonate and concentrated *in vacuo* to remove the tetrahydrofuran. The product was extracted with dichloromethane, and the extract was washed with water, dried with magnesium sulfate, and concentrated *in vacuo* to give a semisolid mass. Crystallization from ethanol afforded III as colorless needles: 0.5 g. (61%), m.p. 221–222° dec., $[\alpha]^{20}D$ +89° (*c* 0.5, $CHCl_3$). Recrystallization from alcohol failed to change either the melting point or specific rotation of the compound; in anhydrous pyridine (*c* 0.593) the substance showed $[\alpha]^{20}D$ +89°, no mutarotation being observed in the course of 24 hr.

*Anal.* Calcd. for $C_{34}H_{35}NO_6$ (553.66): C, 73.76; H, 6.37; N, 2.53. Found: C, 73.79; H, 6.05; N, 2.64.

**Benzyl 2-Benzamido-3,4,6-tri-O-benzyl-2-deoxy-$\beta$-D-glucopyranoside (V).**—A solution of 2-benzamido-2-deoxy-D-glucopyranose[15] (IV, 1 g.) in *N,N*-dimethylformamide (20 ml.) and benzyl bromide (6 ml., 14 molar equiv.) was cooled to 0° and stirred while barium oxide (5 g.) and barium hydroxide octahydrate (2 g.) were added; stirring was continued at 0° for 5 hr. and then at 22° for 18 hr. The reaction mixture was then diluted with dichloromethane and filtered, the residue being washed with dichloromethane. The combined filtrate and washings were washed with water, dried with magnesium sulfate, and concentrated, finally at 90° and 1-mm. pressure to give a gelatinous material. Crystallization from ethanol afforded a microcrystalline solid: 0.6 g. (26%), m.p. 154–158°, $[\alpha]^{20}D$ +28° (*c* 1.38, $CHCl_3$).

*Anal.* Calcd. for $C_{41}H_{41}NO_6$ (643.79): C, 76.49; H, 6.42; N, 2.18. Found: C, 76.56; H, 6.66; N, 2.25.

Hydrolysis of a sample of this product by the technique described earlier for the hydrolysis of II afforded 2-benzamido-3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranose (III) in 62% yield. Recrystallized from ethyl acetate–ether, the III thus obtained had m.p. 217–218°; on admixture with the III prepared from II, it melted at 217.5–218°.

**Benzyl 2-Acetamido-3,4,6-tri-O-benzyl-2-deoxy-$\beta$-D-glucopyranoside (VII).**—To a well-stirred solution of 10 g. of 2-acetamido-2-deoxy-D-glucopyranose[16] (VI) in a mixture of 200 ml. of *N,N*-dimethylformamide and 70 ml. of benzyl bromide at 0° were added 65 g. of barium oxide and 25 g. of barium hydroxide octahydrate. The stirring was continued at 0° for 5 hr. and then at room temperature for 18 hr. Dichloromethane (200 ml.) was then added, and the reaction mixture was filtered, the residue being washed thoroughly with more dichloromethane. The combined filtrate and washings were washed three times with water, dried over magnesium sulfate, and concentrated, finally at 90° and 1 mm. pressure, to give a hard gel. Crystallization from methanol afforded VII as small, spherical crystalline aggregates: 20 g. (76%), m.p. 160–165°, $[\alpha]^{20}D$ −12.4° ($CHCl_3$). After recrystallization from methanol, the crystalline form of the product was unchanged; it melted at 160–161°, resolidified, and then melted at 170–172°; $[\alpha]^{20}D$ −12.1° (*c* 1.3, $CHCl_3$). Thin layer chromatography on silica gel G, using benzene–methanol (7:1) showed the substance to be homogeneous.

*Anal.* Calcd. for $C_{36}H_{39}NO_6$ (581.72): C, 74.33; H, 6.76; N, 2.41. Found: C, 74.13; H, 6.95; N, 2.49.

**2-Acetamido-3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranose (VIII).**—A mixture of VII (10 g.), tetrahydrofuran (900 ml.), and 3 *N* hydrochloric acid (450 ml.) was heated to the boiling point and more tetrahydrofuran (*ca.* 450 ml.) was added until the solution was homogeneous; boiling under reflux was then continued for 48 hr. The tetrahydrofuran was removed by distillation (40° bath, 15 mm.), and the remaining aqueous solution was stirred rapidly with 500 ml. of dichloromethane. Sodium bicarbonate was added to neutralize the acid, and the dichloromethane layer was separated, washed well with water, and dried with magnesium sulfate. Concentration *in vacuo* afforded a mobile sirup which was dissolved in 150 ml. of dry pyridine and treated with 15 ml. of acetic anhydride. After 24 hr. at room temperature, the reaction mixture was poured into ice–water (1 l.), and the product was extracted with dichloromethane. The extract was washed with aqueous sodium bicarbonate solution, then with water, and finally dried with magnesium sulfate. Concentration gave a thick sirup from which benzyl acetate was largely removed by distillation at 90° and 1 mm. pressure. The residual, semicrystalline gum was dissolved in

(13) Melting points are corrected. N.m.r. spectra were obtained in deuteriochloroform solution using a Varian A-60 spectrometer and tetramethylsilane as an internal standard at 0 p.p.m.

(14) Hooker Chemical Corp., Niagara Falls, N. Y.

(15) S. Konstas, I. Photaki, and L. Zervas, *Ber.*, **92**, 1288 (1959).

(16) Pfanstiehl Laboratories, Inc., Waukegan, Ill.

100 ml. of dry methanol, and the solution treated with 2 ml. of sodium methoxide in methanol. Within 2 min. the reaction mixture solidified through the precipitation of crystalline product; it was left for 1 hr. and the alkali then was neutralized by the addition of carbon dioxide. The solid was removed by filtration, and the filtrate was concentrated *in vacuo* (30° bath) to a solid. The combined solids were dissolved in dichloromethane, and the solution was washed with water. Moisture was removed with magnesium sulfate and the solution was concentrated *in vacuo* to a solid mass. Recrystallization from methanol afforded VIII as long needles: 4.5 g., m.p. 218–219°, $[\alpha]^{20}D$ +71.3° (*c* 1.08, $CHCl_3$), $[\alpha]^{20}D$ +63° (*c* 0.93, pyridine, no change in 20 hr.). A second crop (1.0 g., m.p. 216–218°) raised the total yield to 65%. Recrystallization of the first crop from methanol failed to change its properties.

*Anal.* Calcd. for $C_{29}H_{33}NO_6$ (491.59): C, 70.86; H, 6.77; N, 2.85. Found: C, 70.92; H, 6.77; N, 2.88.

**2-Acetamido-1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranose (IX).**—A mixture of VIII (1.0 g.), dry pyridine (10 ml.), and acetic anhydride (0.2 ml.) was left at room temperature for 18 hr. and then poured into 100 ml. of cold water. After stirring for 0.5 hr., the solid precipitate was removed by filtration, washed thoroughly with water, and dried (1.1 g.); recrystallization from ethyl acetate–petroleum ether gave 2-acetamido-1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranose as long, thick needles: 0.85 g. (78%), m.p. 146–147°, $[\alpha]^{20}D$ +108° (*c* 0.743, $CHCl_3$). Recrystallization from ethyl acetate–petroleum ether failed to change the above values; thin layer chromatography on silica gel G, using benzene–methanol (7:1), showed the product to be homogeneous. A similar examination of the material remaining in the mother liquor revealed IX, together with a faster moving component, presumably the β anomer.

*Anal.* Calcd. for $C_{31}H_{35}NO_7$ (533.63): C, 69.77; H, 6.61; N, 2.62. Found: C, 69.89; H, 6.74; N, 2.59.

**2-Acetamido-1-*O*-acetyl-2-deoxy-α-D-glucopyranose (X).**—A suspension of 100 mg. of palladium chloride in methanol was shaken with hydrogen until reduction was complete. The palladium black thus formed was washed five times by decantation with methanol, and a solution of 0.7 g. of IX in 20 ml. of methanol was added. The solution was then shaken with hydrogen until absorption of the gas had ceased (30 min.), the catalyst was removed by filtration, and the filtrate was concentrated to give a crystalline residue. Recrystallization from ethanol–ethyl acetate afforded needles: 0.2 g. (58%), m.p. 165–167°, $[\alpha]^{20}D$ +148° (*c* 0.38, methanol). Further recrystallization gave the pure ester, m.p. 169–170° and $[\alpha]^{20}D$ +149° (*c* 0.286, methanol); these properties were unchanged by a third recrystallization.

*Anal.* Calcd. for $C_{10}H_{17}NO_7$ (263.25): C, 45.62; H, 6.51; N, 5.32. Found: C, 45.29; H, 6.70; N, 5.14.

**2-Acetamido-1-*O*-benzoyl-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranose (XI).**—A solution of VIII (1.0 g.) in a mixture of dry pyridine (10 ml.) and benzoyl chloride (0.5 ml.) was allowed to stand at room temperature for 48 hr. Three drops of water was then added, and the mixture was stirred for 2 hr. and poured into 100 ml. of ice–water. The product was extracted with dichloromethane and the extract was washed successively with aqueous sodium bicarbonate and water. Moisture was removed with magnesium sulfate, and the solution was concentrated to give a sirup (1.3 g.) which proved to be a mixture of XI and its anomer XIII as shown by thin layer chromatography on silica gel G, using benzene–methanol (7:1). The material could be crystallized from ethanol–petroleum ether to give fractions of varying rotation but purification by crystallization alone proved impracticable. The sirupy mixture of anomers was, therefore, chromatographed on silicic acid (Mallinckrodt, 100 mesh). Elution with mixtures of benzene and ethanol afforded a slower moving component only slightly contaminated with the β anomer XIII: m.p. 113–115°, $[\alpha]^{20}D$ +162° ($CHCl_3$). Careful recrystallization from isopropyl ether gave a mixture of needles and fine crystalline rosettes. The latter, separated from the heavier needles by swilling with petroleum ether, proved to be a mixture of XI and XIII in approximately equal proportions. Recrystallization of the needles from isopropyl ether gave pure XI: 180 mg. (15%), m.p. 118–119°, $[\alpha]^{20}D$ +171° (*c* 0.539, chloroform). Recrystallization failed to change these values and the substance was homogeneous on thin layer chromatography (silica gel G, benzene–methanol, 7:1).

*Anal.* Calcd. for $C_{36}H_{37}NO_7$ (595.70): C, 72.58; H, 6.26; N, 2.35. Found: C, 72.81; H, 6.38; N, 2.39.

**2-Acetamido-1-*O*-benzoyl-2-deoxy-α-D-glucopyranose (XII).**—2-Acetamido-1-*O*-benzoyl-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranose (170 mg.) was reduced in methanolic solution with hydrogen in the presence of palladium black from 50 mg. of palladium chloride. Removal of the catalyst and the solvent gave a hard glass which, from its solution in ethyl acetate–ethanol, gave rosette-shaped crystals of XII: 70 mg. (75%), m.p. 190–192°, $[\alpha]^{20}D$ +190° (*c* 0.26, methanol). Recrystallization from ethyl acetate–ethanol gave needles: m.p. 192–193°, $[\alpha]^{20}D$ +190° (*c* 0.83, methanol).

*Anal.* Calcd. for $C_{15}H_{19}NO_7$ (325.33): C, 55.38; H, 5.89; N, 4.31. Found: C, 55.64; H, 6.16; N, 4.11.

**2-Acetamido-1-*O*-benzoyl-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranose (XIII).**—A solution of IX (0.4 g.) in dry dichloromethane (4 ml.) was treated with a solution of hydrogen bromide in dry dichloromethane (0.4 *N*, 2 ml.), and the rotation of the resulting solution was observed at 20° in a 1-dm. polarimeter tube. From an initial value of +4.98° the observed rotation fell to a constant rotation of *ca.* +0.9° in the course of 8 hr. Concentration *in vacuo* (30° bath) afforded a sirup from which the acetic acid was removed by three codistillations (*in vacuo*) with toluene. Dissolved in 20 ml. of dry toluene, the material was stirred with 1.3 g. of silver benzoate for 18 hr. After filtration, the solution was concentrated *in vacuo* to a sirup which was dissolved in dichloromethane, the resulting solution then being washed with water, dried with magnesium sulfate, and concentrated to a sirup. On the addition of 50 ml. of benzene, 100 mg. of VIII was precipitated. The filtrate was chromatographed on a column of silicic acid (Mallinckrodt, 100 mesh). Elution with mixtures of benzene and ether gave 110 mg. of sirup which was shown by thin layer chromatography (silica gel G, benzene–methanol, 7:1) to correspond with the second product encountered in the benzoylation of VIII. Small quantities of the anomeric XI were shown to be present in the fractions which were later eluted from the column.

Compound XIII was crystallized from ethanol–petroleum ether as long needles: 90 mg. (20%), m.p. 147–148°, $[\alpha]^{20}D$ −11.1° (*c* 0.536, chloroform). Further recrystallization from the same solvent mixture did not change these values.

*Anal.* Calcd. for $C_{36}H_{37}NO_7$ (595.70): C, 72.58; H, 6.26; N, 2.35. Found: C, 72.32; H, 6.42; N, 2.50.

**2-Acetamido-1-*O*-benzoyl-2-deoxy-β-D-glucopyranose (XIV).**—Compound XIII (470 mg.) in 50 ml. of methanol was reduced with hydrogen in the presence of thoroughly washed palladium black which had been prepared by the reduction of 200 mg. of palladium chloride. After removal of the catalyst and solvent, the product was dissolved in water, and the toluene was removed by extraction with benzene. Reconcentration gave a sirup with was crystallized from water as long needles: 100 mg. (39%), m.p. 154–158° dec. The crystals obtained on recrystallization from water became anisotropic at *ca.* 100° and then melted at 154–160°; $[\alpha]^{20}D$ −38° (*c* 0.815, methanol).

*Anal.* Calcd. for $C_{15}H_{19}NO_7$ (325.33): C, 55.38; H, 5.89; N, 4.31. Found: C, 55.57; H, 6.16; N, 4.05.

**Benzyl 2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-galactopyranoside (XVI) from 2-Acetamido-2-deoxy-D-galactopyranose (XV).**—Compound XV[16] (10 g.) was benzylated by the same procedure as that used for its diastereoisomer in the D-glucose series (VI). Crystallization from methanol yielded a jelly-like mass which could be filtered and washed with methanol to give a waxy solid. Recrystallization from methanol again gave a jelly-like material which was removed by filtration and dried *in vacuo* over phosphorus pentoxide. The XVI thus obtained existed as thin sheets of anisotropic microcrystalline material: 10 g. (38%), m.p. 193–194°, $[\alpha]^{20}D$ −20° (*c* 2.12, chloroform).

*Anal.* Calcd. for $C_{36}H_{39}NO_6$ (581.72): C, 74.33; H, 6.76; N, 2.41. Found: C, 74.53; H, 6.57; N, 2.57.

**2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranose (XVII).**—Ten grams of XVI was hydrolyzed as described for the conversion of the diastereoisomeric compound VII to VIII. As was the case with VIII, XVII crystallized spontaneously from the methanolic sodium methoxide. Methanol (100 ml.) was added to the solidified mass, and the mixture was stirred for 1 hr. The suspension was then neutralized through the addition of solid carbon dioxide and the crystalline product was removed by filtration. The filtrate was evaporated *in vacuo* (30° bath) to dryness, and the solid residue was combined with the first

crop. The crude product was dissolved in dichloromethane and washed with water; moisture was removed with magnesium sulfate, and the solution was concentrated *in vacuo* to a dry solid. Recrystallization from methanol gave long needles of XVII: 3.5 g. (41%), m.p. 184–185°, $[\alpha]^{20}D$ +72° (*c* 0.538, chloroform). Further recrystallization failed to change these constants. A second crop (1.0 g.), m.p. 180–182°, raised the total yield to 53%. In anhydrous pyridine (*c* 1.47) the pure compound mutarotated $[\alpha]^{20}D$ +125 → +116° in 10 days.

*Anal.* Calcd. for $C_{29}H_{32}NO_6$ (491.59): C, 70.86; H, 6.77; N, 2.85. Found: C, 70.73; H, 6.54; N, 2.89.

**2-Acetamido-1-*O*-benzoyl-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-galactopyranose (XVIII).**—A solution of XVII (1.0 g.) in dry pyridine (10 ml.) was treated with 0.5 ml. of benzoyl chloride and left at 24° for 24 hr. On pouring into ice–water (100 ml.) and stirring, the reaction mixture gave a solid precipitate as a fine powder, 1.3 g. Recrystallization from ethanol afforded XVIII as a voluminous crystalline mass: 0.75 g. (62%), m.p. 148–149°, $[\alpha]^{20}D$ +2.5° (*c* 0.325, chloroform). Thin layer chromatography on silica gel G, using benzene–methanol (7:1), showed the material to be homogeneous and further recrystallization failed to change its physical constants.

*Anal.* Calcd. for $C_{36}H_{37}NO_7$ (595.70): C, 72.58; H, 6.26; N, 2.35. Found: C, 72.62; H, 6.52; N, 2.26.

The n.m.r. spectrum of the product showed a doublet for the C-1 proton with a spacing of 8 c.p.s. centered at δ 6.06, indicating that this is the β anomer. A doublet at δ 5.9 with a spacing of 9 c.p.s. was removed on shaking the $CDCl_3$ solution of the substance with a drop of $D_2O$, identifying the peaks in question as arising from the amide proton.

Thin layer chromatography of the mother liquor from the first crystallization of XVIII revealed a second component, moving slightly slower than XVIII, presumably the α anomer.

**2-Acetamido-1-*O*-benzoyl-2-deoxy-β-D-galactopyranose (XIX).**—Hydrogenation of XVIII (380 mg.) in methanol and in the presence of washed, freshly prepared palladium black (from 120 mg. of palladium chloride) gave, after removal of the catalyst and solvent, needles which were recrystallized from methanol: 180 mg. (88%), m.p. 203–205°, $[\alpha]^{20}D$ −5.2° (*c* 0.38, methanol). Further recrystallization from methanol failed to change these values.

*Anal.* Calcd. for $C_{15}H_{19}NO_7$ (325.33): C, 55.38; H, 5.89; N, 4.31. Found: C, 55.63; H, 6.17; N, 4.14.

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# Syntheses with Partially Benzylated Sugars. V.[1] Substitution at Carbon 4 in an Aldose. The Synthesis of 4-*O*-Methyl-β-D-arabinopyranose

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The readily accessible 2,3,5-tri-*O*-benzyl-D-arabinofuranose (I) was converted successively to 4-*O*-benzoyl-2,3,5-tri-*O*-benzyl-D-arabinose diethyl dithioacetal (III) and 4-*O*-benzoyl-2,3,5-tri-*O*-benzyl-D-arabinose dibenzyl acetal (VI). Replacement of the benzoyl group in the latter compound by methyl, followed by hydrogenolysis of the five benzyl groups, afforded crystalline 4-*O*-methyl-β-D-arabinopyranose (IX). This synthesis may be regarded as illustrating a possibly general technique whereby C-4 or C-5 in an aldose may be selectively substituted.

The synthesis of aldose derivatives with substituents at C-4 or C-5, the carbon atoms normally participating in hemiacetal ring formation, involves special problems which have been met with many ingenious solutions, each solution, in general, being unique for a specific aldose. The present paper describes a synthetic pathway for the preparation of 4-*O*-substituted derivatives of an aldose, a pathway which is not dependent upon the stereochemistry of the aldose.

The hydroxyl groups of aldopyranosides and aldofuranosides may readily be masked as benzyl ethers; subsequent removal of the aglycon by hydrolysis yields aldoses which are fully benzylated save at C-1 and at the other carbon atom involved in the hemiacetal ring (C-5 or C-4). A number of such aldose ethers have been reported in recent years.[1-7] The conversion of compounds of this class to acyclic derivatives, their dithioacetals, for instance, should unmask for selective substitution the carbon atom originally involved in the hemiacetal ring.[8] Having developed a simple synthesis of 2,3,5-tri-*O*-benzyl-D-arabinofuranose (I)[3,5] and being in need of 4-*O*-methyl-D-arabinopyranose (IX), we have investigated this synthetic approach (see Scheme I).

Treatment of 2,3,5-tri-*O*-benzyl-D-arabinofuranose (I) with ethanethiol and hydrogen chloride afforded an amorphous diethyl dithioacetal (II) which was conveniently isolated as its crystalline 4-*O*-benzoyl derivative (III). The dithioacetal II was further characterized through its 4-*O*-*p*-toluoyl and 4-*O*-*p*-chlorobenzoyl derivatives (IV and V); efforts to obtain a tosyl derivative were unsuccessful, owing, perhaps, to steric hindrance. Attempts to methylate either II or III (under conditions which would eliminate the benzoyl group) gave highly heterogeneous, amorphous mixtures and it seems probable that methylation was accompanied by

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(8) Alternative methods for the unmasking of C-4 or C-5 in partially benzylated aldoses may be envisaged. B. P. Vaterlaus, J. Kiss, and H. Spiegelberg [*Helv. Chim. Acta*, **47**, 381 (1964)], for instance, oxidized 3,5,6-tri-*O*-benzyl-2-*O*-methyl-D-glucofuranose to the corresponding D-glucono γ-lactone and then made the methyl ester as well as the N-methylamide of 2-*O*-methyl-3,5,6-tri-*O*-benzyl-D-gluconic acid, acyclic derivatives which were mesylated at C-4 in the course of an extremely ingenious synthesis of 3-*O*-carbamoylnoviose. Fortunately this synthesis did not involve subsequent reduction of C-1 to the aldehyde stage, since such reductions are difficult to carry out in high yield; the dithioacetal approach adopted here appears to be the method of choice when a substituted aldose is to be regenerated.