SYNTHESIS OF 4-ACETAMIDO-4-DEOXY-SUGARS

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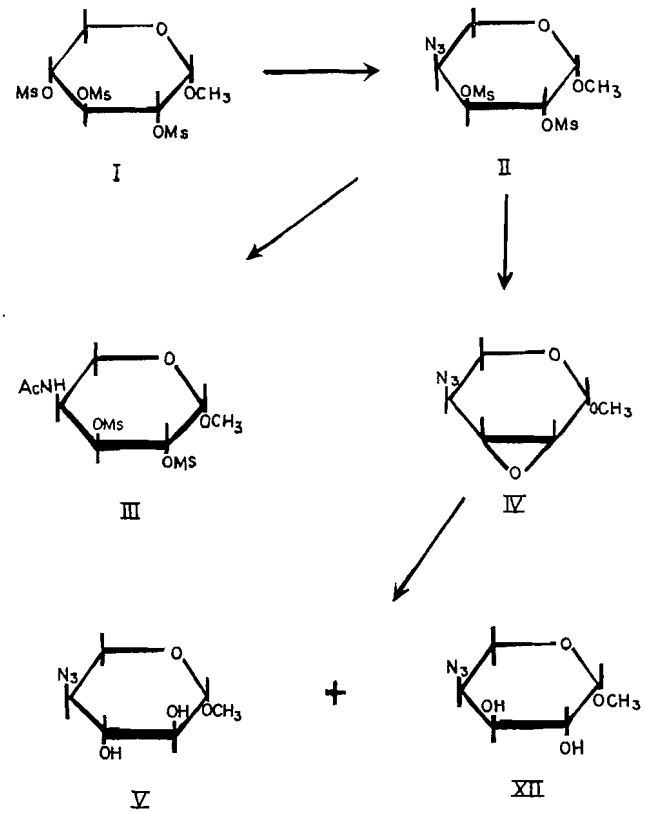
ABSTRACT

The tri-*O*-methanesulfonate derivative (I) of methyl α-D-xylopyranoside has been prepared. This compound when heated with sodium azide in *N*,*N*-dimethylformamide yielded a 4-azido derivative with inversion at C_4. It (I) was thus converted to a methyl 4-azido-4-deoxy-β-L-arabinopyranoside (II) and thence by removal of methanesulfonate residues to a 2,3-anhydro-L-ribopyranoside derivative and further to methyl 4-amino-4-deoxy-β-L-xylopyranoside (V); 4-acetamido-4-deoxy-1,2;3,5-di-*O*-isopropylidene-L-xylose (IX), a sugar with nitrogen in the ring, was prepared from 4-acetamido-4-deoxy-L-xylose. Acetolysis of methyl 4-acetamido-4-deoxy-L-xylopyranoside yielded a pentacetate of unknown ring size (X or XI).

The synthesis of sugar derivatives containing nitrogen as the hetero atom in pyranose rings has been a subject of recent investigation (1). The first synthesis of a sugar derivative with nitrogen as the hetero atom in a five-membered ring, methyl 4-acetamido-4-deoxy-L-erythrofuranoside, was also achieved recently (2). These syntheses all involve replacement of the ring oxygen atom of sugars by the nitrogen atom of an *N*-acetyl group on a primary carbon atom.



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The synthesis of derivatives of 4-amino-sugars with the nitrogen function on a secondary carbon atom is of interest in order to investigate the possible formation of a five-membered furanose ring containing nitrogen as the hetero atom. Methyl 4-amino-4-deoxy-α-D-glucopyranoside has been synthesized (3) via an S_N2 displacement of the 4-*O*-methanesulfonyl group of methyl 2,3,6-tri-*O*-benzoyl-4-*O*-methanesulfonyl-α-D-galactopyranoside by azide. Overend *et al.* (4) have synthesized methyl 4-amino-4-deoxy-α-D-lyxoside by the preferential cleavage of the epoxide ring of methyl 3,4-anhydro-β-L-riboside by ammonia.

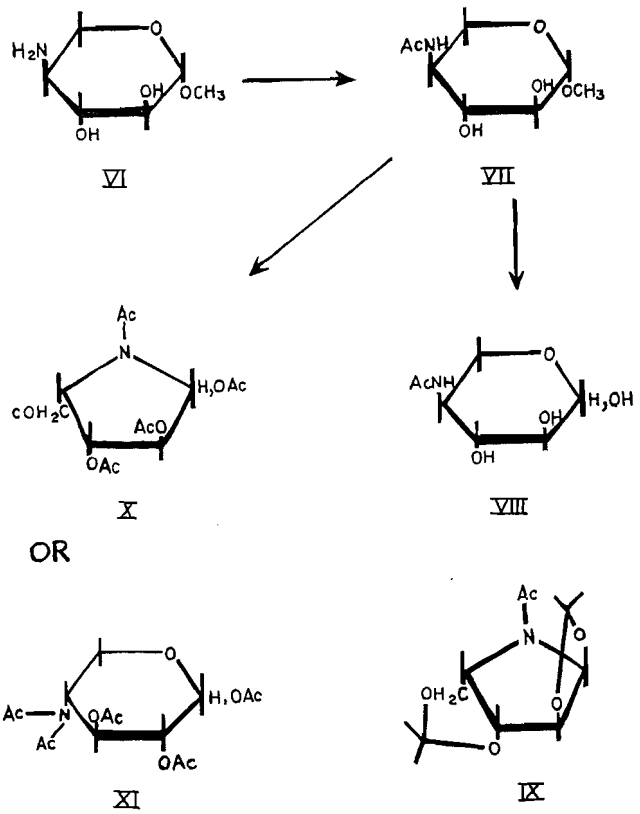
The present communication reports a facile route to the synthesis of derivatives of 4-amino-4-deoxy-pentoses (5). The reaction of sodium azide with the 2,3,4-tri-*O*-methylsulfonyl derivative of methyl α-(I)D-xylopyranoside in dimethylformamide solution gave an azido-deoxy-di-*O*-methylsulfonyl derivative. The azide ion is considered to attack selectively at C-4 in an S_N2 displacement reaction to yield, methyl 2,3-di-*O*-methylsulfonyl-4-azido-4-deoxy-β-L-arabinopyranoside (II). Goodman *et al.* (6) have observed the selective replacement of the 4-*p*-tolysulfonyl group of methyl 2-*O*-benzoyl-3,4-di-*O*-*p*-tolysulfonyl-β-L-arabinopyranoside by azide which led to the synthesis of 4-acetamido-4-deoxy-D-ribose. An analogous situation exists for the reaction of the chlorosulfate ester derivatives of methyl α-D-glucopyranoside, methyl β-D-glucopyranoside, methyl α-D-galactopyranoside, and methyl β-D-galactopyranoside with pyridine hydrochloride. With an excess of pyridine hydrochloride, Jennings and Jones (7) have obtained 4,6-dichloro-dideoxy-substituted derivatives, with inversion of configuration occurring at C-4, in each of these cases, except with methyl 2,3,4,6-tetra-*O*-chlorosulfonyl-β-D-galactopyranoside, which gave a 3,4,6-trichloro-substituted compound as well as other products. It may be noted that reaction of methyl 2,3,4,6-tetra-*O*-methylsulfonyl-α-D-glucopyranoside (V) with an excess of sodium azide in *N*,*N*-dimethylformamide has been shown (8) to give a di-azido-deoxy derivative which is methyl 2,3-di-*O*-methylsulfonyl-4,6-di-azido-4,6-dideoxy-α-D-galactopyranoside.

Reduction of methyl 2,3-di-*O*-methylsulfonyl-4-azido-4-deoxy-β-L-arabinopyranoside (II) with Raney nickel in methanol followed by *N*-acetylation with acetic anhydride in *tert*-butyl alcohol – water gave methyl 2,3-di-*O*-methylsulfonyl-4-acetamido-4-deoxy-β-L-arabinopyranoside (III).

Reaction of methyl 2,3-di-*O*-methylsulfonyl-4-azido-4-deoxy-β-L-arabinopyranoside (II) with methanolic potassium hydroxide gave the 2,3-anhydro derivative (IV). Sorkin and Reichstein (9) report that the reaction of methyl 2,3-di-*O*-*p*-tolysulfonyl-4,6-*O*-benzylidene-α-D-galactopyranoside with sodium methoxide in methanol yields methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-gulopyranoside. By analogy, the anhydro sugar, (XII), is probably methyl 2,3-anhydro-4-azido-4-deoxy-β-L-lyxopyranoside* and (IV) not the corresponding ribopyranoside. Cleavage of this epoxide with aqueous potassium hydroxide gave a mixture containing predominantly methyl 4-azido-4-deoxy-β-L-xylopyranoside (V) with a low positive optical rotation, and in smaller yield methyl 4-azido-4-deoxy-β-L-arabinopyranoside (XII) with a high optical rotation. The mixture could be separated by fractional crystallization from chloroform–petrol.

Reduction of methyl 4-azido-4-deoxy-β-L-xylopyranoside (V) gave methyl 4-amino-4-deoxy-β-L-xylopyranoside (VI), isolated as the crystalline hydrochloride salt, which consumed 2 moles of periodate and liberated 1 mole of formic acid in unbuffered periodate. *N*-Acetylation of VI gave methyl 4-acetamido-4-deoxy-β-L-xylopyranoside (VII) which consumed 1 mole of periodate per mole. Hydrolysis of VII with Amberlite IR 120 cation

**Nuclear magnetic resonance studies and further chemical work have now shown XII to be the* L-*ribopyranoside derivative. Details will be given in a later publication.*



exchange resin (H^+ form) yielded a clear colorless syrup which was strongly reducing to Fehling's solution and which gave absorptions in the infrared corresponding to *OH*, *N—H*, and *N—Ac*. Paper chromatography of the syrup and the purified crystalline material showed only one component. The compound, on periodate oxidation in unbuffered aqueous solution consumed 2 moles of periodate and liberated 1 mole of formic acid; no overoxidation occurred and no formaldehyde was produced. Had the *N*-acetyl group been on C_2, overoxidation would have occurred. These results are consistent with the structure proposed for 4-acetamido-4-deoxy-L-xylopyranose and indicate that the six-membered oxygen ring is the highly favored ring form for the free sugar. The isopropylidene derivative of VIII was a colorless syrup, which crystallized after vacuum distillation. Its infrared spectrum showed absorptions corresponding to *N*—Ac and the isopropylidene group but no absorption attributable to *—OH* or *—NH*. The elemental analysis supports these results and is consistent with the structure 1,2;3,5-di-*O*-isopropylidine-4-acetamido-α-L-xylofuranose (IX). Molecular models indicate that a pyranose type structure is most unlikely.

Acetolysis of methyl 4-acetamido-4-deoxy-β-L-xylopyranoside (VII), gave a syrupy acetate which showed absorptions in the infrared corresponding to *—O—*Ac and *N—*Ac, but no absorption attributable to *—NH*. This compound is thus either 1,2,3,5-tetra-*O*-acetyl-4-acetamido-4-deoxy-L-xylofuranose (X) or 1,2,3-tri-*O*-acetyl-4-diacetamido-4-deoxy-L-xylopyranose (XI). Acetolysis of methyl 4-acetamido-4-deoxy-α-D-ribopyranoside was claimed to give 1,2,3,4-tetra-*O*-acetyl-4-acetamido-4-deoxy-D-ribofuranose (6) but no proof was given.

The investigation of the other monoazido-di-*O*-methylsulfonyl derivatives is being continued.

EXPERIMENTAL

Solutions were concentrated under reduced pressure below 40° with a rotating vacuum-type evaporator. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were measured at 23 ± 3° with a Hilger Standard Polarimeter. Infrared spectra were measured with a Perkin–Elmer Model 21 spectrophotometer. Paper chromatography was carried out by the descending method at room temperature on Whatman No. 1 filter paper for qualitative purposes or on Whatman 3MM filter paper for preparative purposes in butan-1-ol : ethanol : water, 3:1:1. Sugars were detected on paper chromatograms by the following spray reagents: (i) alkaline silver nitrate (10); (ii) *p*-anisidine hydrochloride (11); (iii) sodium metaperiodate – potassium permanganate (12); (iv) sodium iodide and methyl red (epoxide spray (13)). Rates of movement of the sugars on paper chromatograms are given relative to that of rhamnose (R_{rh}).

Methyl 2,3,4-Tri-O-methylsulfonyl-α-D-xylopyranoside (I)

D-Xylose (technical) (100 g) was treated with methanolic hydrogen chloride according to the method of Hudson (14) and yielded crystalline methyl β-D-xylopyranoside (23 g). The residual syrups (75 g), $[\alpha]_D = +98°$ (*c*, 6.60 in water) containing approximately 50 g methyl α-D-xylopyranoside (calculated from the specific rotation) was dried thoroughly, dissolved in dry pyridine (400 ml), and treated with methanesulfonyl chloride (180 g) in the usual manner. The syrupy product was dissolved in hot ethyl acetate and the solution allowed to cool. Methyl 2,3,4-tri-*O*-methylsulfonyl-α-D-xylopyranoside crystallized slowly from this solution; 60 g were obtained from several crops. Three crystallizations from ethyl acetate gave colorless plates which melted at 130.5–131.5° and had $[\alpha]_D = +80°$ (*c*, 2.54 in chloroform).

Anal. Calcd. for $C_9H_{18}O_{11}S_3$: C, 27.1; H, 4.5; S, 24.1. Found: C, 27.0; H, 4.3; S, 24.3.

Reaction of Methanesulfonyl Derivatives with Sodium Azide

(*a*) Methyl 2,3,4-tri-*O*-methylsulfonyl-α-D-xylopyranoside (I) (12.0 g) was dissolved in *N*,*N*-dimethylformamide (150 ml) and a solution of sodium azide (2.35 g, 1.2 mole) and urea (0.4 g) in water (15 ml) was added. This solution was heated at 115° under a stream of nitrogen for 36 h. The black reaction mixture, containing precipitated sodium methanesulfonate, was cooled and poured into ice water (200 ml). The crystalline precipitate which formed was filtered off and the filtrate partitioned between chloroform and water. The chloroform layer was dried (Na_2SO_4), decolorized with charcoal, and filtered, and the filtrate evaporated to dryness. The residue crystallized on standing and was recrystallized from methanol to give methyl 2,3-di-*O*-methylsulfonyl-4-azido-4-deoxy-β-L-arabinopyranoside (II) as large, colorless needles (9.6 g, 92%) which melted at 128–128.5° and had $[\alpha]_D = +140°$ (*c*, 1.96 in chloroform).

Anal. Calcd. for $C_8H_{15}N_3O_8S_2$: C, 27.8; H, 4.35; N, 12.2; S, 18.5. Found: C, 27.6; H, 4.2; N, 12.2; S, 18.8.

When this reaction was carried out with I (4.0 g) dissolved in *N*,*N*-dimethylformamide (100 ml) containing excess sodium azide (2.3 g, 3.5 mole) and urea (0.15 g) in water (5 ml), under the same conditions as described above, the monoazido-deoxy-derivative (II) was again isolated in 50% yield. No other products were isolable.

The infrared spectrum of II in chloroform showed strong absorption at 2 140 cm^{-1} attributable to azide, and strong absorption at 1 370 cm^{-1} and 1 182 cm^{-1} attributable to sulfonate.

Methyl 2,3-Di-O-methylsulfonyl-4-acetamido-4-deoxy-β-L-arabinopyranoside (III)

Methyl 2,3-di-*O*-methanesulfonyl-4-azido-4-deoxy-β-L-arabinopyranoside (4.0 g) was reduced with Raney nickel in methanol. The Raney nickel was filtered off, the filtrate was evaporated to a pale-yellow syrup which was *N*-acetylated in *tert*-butyl alcohol – water (10.1) solution (100 ml) with acetic anhydride (2.0 ml). Evaporation of the solvent gave a glass which on crystallization from methanol gave XI (3.4 g, 81%) as colorless crystals which melted at 158–159° and had $[\alpha]_D = +117°$ (*c*, 2.06 in methanol). The infrared spectrum in chloroform showed absorption at 3 450 cm^{-1} and 1 513 cm^{-1} attributable to *N*—H, strong absorption at 1 683 cm^{-1} attributable to *N*—Ac, and strong absorption owing to the sulfonate groups.

Anal. Calcd. for $C_{10}H_{19}NO_9S_2$: C, 33.2; H, 5.3; N, 3.9; S, 17.7. Found: C, 33.0; H, 5.0; N, 4.2; S, 18.0.

Reaction of Methyl 2,3-Di-O-methylsulfonyl-4-azido-4-deoxy-β-L-arabinopyranoside (II) with Methanolic Potassium Hydroxide

To a solution of potassium hydroxide (10 g) in methanol–water (4:1) (200 ml) (II) (10.0 g) was added. This mixture was heated to boiling point which caused II to dissolve. The solution was refluxed for 2 h. The dark-brown reaction solution was diluted to 400 ml with water, concentrated to 200 ml, and extracted with ether (200 ml). The ether extract was washed with water, dried (Na_2SO_4), and filtered, and the filtrate was concentrated to a clear syrup (4.5 g) which crystallized on standing. Recrystallization of this material from petrol (35–60°) gave long, fine needles which melted at 54–55° and had $R_{rh} = 2.2$ (spray iv) and $[\alpha]_D = -14°$ (*c*, 1.54 in chloroform). This substance analyzed for the anhydro sugar, methyl 2,3-anhydro-4-azido-4-deoxy-β-L-ribopyranoside.

Anal. Calcd. for $C_6H_9O_3N_3$: C, 42.1; H, 5.3; N, 24.6. Found: C, 41.8; H, 5.5; N, 24.2.

The infrared spectrum in chloroform showed absorption at 2 120 cm^{-1} attributable to the azido groups and absorption at 1 270 cm^{-1} attributable to the epoxide ring.

Reaction of Methyl 2,3-Anhydro-4-azido-4-deoxy-β-L-ribopyranoside with Aqueous Potassium Hydroxide

To an aqueous solution (150 ml) of potassium hydroxide (5 g) IV (4.5 g) was added and the mixture was heated under reflux for 4 h. The dark-brown reaction solution was cooled and de-ionized by passing it through Amberlite IR 120 cation exchange resin (H^+ form). The elute was evaporated to a mobile syrup (3.8 g) which crystallized on standing. This material was dissolved in chloroform, and petrol (b.p. 60–80°) was added to incipient turbidity. Fine needles (0.55 g) were obtained which, after two recrystallizations from chloroform–petrol, melted at 108–108.5° and had R_{rh} = 2.2 (spray iii) and $[\alpha]_D$ = 141° (*c*, 0.56 in chloroform).

Anal. Calcd. for methyl 4-azido-4-deoxy-β-L-arabinopyranoside (XII), $C_6H_{11}O_4N_3$: C, 38.1; H, 5.8; N, 22.2. Found: C, 38.1; H, 6.1; N, 21.9.

The mother liquors were concentrated to a syrup which crystallized on standing. Recrystallization from chloroform–petrol (35–60°) gave fine needles (2.7 g) which melted at 81–83° and had R_{rh} = 1.7 (spray iii) and $[\alpha]_D$ = +31.3° (*c*, 1.64 in chloroform).

Anal. Calcd. for methyl 4-azido-4-deoxy-β-L-xylopyranoside (V), $C_6H_{11}O_4N_3$: C, 38.1; H, 5.8; N, 22.2. Found: C, 38.4; H, 6.0; N, 22.4.

Reduction of Methyl 4-Azido-4-deoxy-β-L-xylopyranoside (V)

The above compound V (1.1 g) was reduced with Raney nickel in methanol to yield a clear colorless syrup (0.84 g). The crystalline hydrochloride salt of VI was prepared by dissolving the crude amino sugar in acetone and adding concentrated hydrochloric acid. The hydrochloride salt was recrystallized from methanol–acetone and melted at 136–137° (decomp.) and had R_{rh} = 0.94 and $[\alpha]_D$ = +53° (*c*, 0.225 in water). Periodate oxidation of VI in unbuffered aqueous solution resulted in the consumption of 2 moles of periodate and the liberation of 1 mole of acid.

Anal. Calcd. for $C_6H_{14}O_4NCl$: C, 36.1; H, 7.0; N, 7.0; Cl, 17.8. Found: C, 36.0; H, 7.0; N, 7.2; Cl, 18.1.

Methyl 4-Acetamido-4-deoxy-β-L-xylopyranoside (VII)

Syrupy 4-amino-4-deoxy-β-L-xylopyranoside (VI, 0.84 g) was dissolved in water (20 ml) and acetic anhydride (2 ml) was added. This mixture was allowed to stand at room temperature with occasional shaking for 20 min. The solution was concentrated to a clear colorless syrup (1.05 g) which crystallized on standing. This material was crystallized from chloroform–petrol (60–80°) to give white needles of VII which melted at 157–158° and had R_{rh} = 1.48 (spray iii) and $[\alpha]_D$ = +52.7° (*c*, 2.22 in methanol). When oxidized in unbuffered aqueous solution, VII consumed 1 mole of periodate.

Anal. Calcd. for $C_8H_{15}O_5N$: C, 46.8; H, 7.3; N, 6.8. Found: C, 46.3; H, 7.7; N, 6.9.

Hydrolysis of Methyl 4-Acetamido-4-deoxy-β-L-xylopyranoside (VII)

Amberlite IR cation exchange resin (H^+ form) (2 g) was added to a solution of VII (0.65 g) in water (50 ml). This mixture was heated at a bath temperature of 90° with stirring for 4 h. The mixture was then cooled, the resin filtered off, and the filtrate concentrated to a colorless syrup (0.48 g) which was strongly reducing to Fehling's solution and which showed one spot on a paper chromatogram at R_{rh} = 0.81 (sprays i, ii, iii). The infrared spectrum (smear on NaCl) showed a broad absorption band at 3 550 – 3 220 cm^{-1} attributable to *OH* and *NH*, absorption at 1 640 cm^{-1} attributable to *N*—Ac, and strong absorption at 1 560 cm^{-1} attributable to *NH*. The syrup was caused to crystallize by treatment with ethyl acetate and was recrystallized from methanol–ether to give 4-acetamido-4-deoxy-L-xylopyranose (VIII), which melted at 157–158° and had $[\alpha]_D$ = −22°, mutarotating to −16° (*c*, 1.00 in water). When oxidized in unbuffered aqueous solution, VIII consumed 2 moles of periodate and liberated 1 mole of acid. No overoxidation occurred and no formaldehyde was produced.

Anal. Calcd. for $C_7H_{13}O_5N$: C, 43.93; H, 6.8; N, 7.3. Found: C, 44.0; H, 7.0; N, 7.2.

1,2;3,5-Di-O-isopropylidene-4-acetamido-4-deoxy-α-L-xylofuranose (IX)

Dry acetone (50 ml), anhydrous $CuSO_4$ (0.5 g), and a drop of concentrated sulfuric acid was added to syrupy VII (0.12 g). The mixture was shaken at room temperature for 40 h and was then filtered, the filtrate was neutralized with barium hydroxide and filtered, and the filtrate was concentrated. The syrupy residue was partitioned between ether and water and the ether layer dried (Na_2SO_4) and filtered, and the filtrate concentrated to a colorless syrup (0.055 g). The syrup was distilled under reduced pressure and the resultant syrup crystallized to give IX, m.p. 66–80°; $[\alpha]_D$ = +131 ± 3° (*c*, 2.30 in chloroform) and R_{rh} = 2.47 (spray ii). The infrared spectrum (smears on NaCl) showed strong absorption at 1 677 cm^{-1} attributable to *N*—Ac and a doublet at 1 392, 1 384 cm^{-1} attributable to the ispropylidene group but no absorption attributable to *OH* or *NH*.

Anal. Calcd. for $C_{13}H_{21}O_5N$: C, 57.6; H, 7.8; N, 5.2. Found: C, 57.8; H, 7.9; N, 5.33.

Acetolysis of Methyl 4-Acetamido-4-deoxy-β-L-xylopyranoside (VII)

The above compound VII (0.18 g) was acetolyzed according to the method of Hudson (14) in 10 ml

acetolysis solution. The reaction was followed polarimetrically and the optical rotation had become constant after 24 h. The solution was then poured into an excess of sodium bicarbonate in water and this solution was extracted with carbon tetrachloride. The carbon tetrachloride extract was washed with water and concentrated to a colorless syrup (0.065 g) which was distilled under vacuum. This material was homogeneous on thin-layer chromatography. The infrared spectrum (smear on NaCl) showed strong absorption at 1 755 cm^{-1} for *O*—Ac and at 1 686 cm^{-1} for *N*—Ac but no absorption owing to *N*—*H*. 1,2,3-Tri-*O*-acetyl-4-diacetamido-4-deoxy-L-xylopyranose (XI) (1,2,3,5-tetra-*O*-acetyl-4-acetamido-4-deoxy-L-xylofuranose (X)) had $[\alpha]_D = -23°$ (*c*, 0.95 in chloroform).

Anal. Calcd. for $C_{16}H_{21}O_9N$: C, 50.1; H, 5.9; N, 3.9; *O*-acetyl, 47.9; total acetyl (*O* + *N*), 59.9. Found: C, 48.8; H, 5.9; N, 4.0; *O*-acetyl, 54.4, 57.2; total acetyl (*O* + *N*), 61.1.

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