Thiosugars. I. Synthesis of Derivatives of 2-Amino-2-deoxy-1-thio-D-glucose[1]

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A range of derivatives of 2-amino-2-deoxy-1-thio-D-glucose, with removable blocking substituents at the amino and thiol groups, has been synthesized by condensation of amino sugar glycosyl halides with thiourea, with potassium thiolacetate, or with potassium ethylxanthate.

The known effectiveness of β- and γ-aminothiol systems in protecting living tissue from damage by ionizing radiation[2] suggested that a carbohydrate molecule containing these functional groups might also have radiation protective ability, and at the same time be more physiologically acceptable than noncarbohydrate analogs, most of which are fairly toxic. Derivatives containing the 3-amino-3-deoxy-2-thio-D-allose[3] and 3-amino-3-deoxy-2-thio-D-altrose[4] systems have been described. The present work is concerned with the synthesis of derivatives of 2-amino-2-deoxy-1-thio-D-glucose with removable blocking groups at the amino and thiol functions. Thioglycosides of the 2-amino-2-deoxy sugars have been known for several years[5-7] but only very recently[8,9] have the established preparative methods of 1-thiosugars with removable *S*-blocking groups[10] been extended to the amino sugar field. Our studies were made on three types of *S*-blocked 1-thiosugars, prepared by condensing amino sugar glycosyl halides with thiourea, potassium ethylxanthate, or potassium thiolacetate. The first two reactions, leading to 2-(glycosyl)-2-thiopseudourea and glycosyl ethylxanthate derivatives, respectively, have been described several times for nonnitrogenous sugars,[11,12] but the third reaction has been reported only briefly,[13] and a preliminary study was made on the condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with potassium thiolacetate, as a model for the amino sugar systems. Conditions were established which gave 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose in 88% yield.

Three amino sugar glycosyl halides were used, 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (II),[14] 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide (VII),[15] and 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide (X).[16] Compound II gave the best results in the condensation reactions, but its preparation by published methods[14] was found to be tedious and unreliable. Reaction of 2-acetamido-2-deoxy-D-glucose with acetyl chloride *at room temperature* was found to give compound II in high purity without further recrystallization of the once-crystallized product. A similar simplified preparative procedure was developed for VII by treatment of 2-deoxy-2-(2,4-dinitroanilino)-D-glucose[15,17] with acetyl bromide.

The sequences of condensation reactions are summarized in the accompanying diagrams. 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (II) condensed smoothly with thiourea in boiling acetone and 2-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-thiopseudo-

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TABLE I
OPTICAL ROTATORY DATA

Compound	α-D-Anomer Reference	α-D-Anomer [α]D	α-D-Anomer [M]D	β-D-Anomer Reference	β-D-Anomer [α]D	β-D-Anomer [M]D	Solvent	Partial Mol. Rot.[a] A	Partial Mol. Rot.[a] B
1,2,3,4,6-Penta-*O*-acetyl-D-glucopyranose	[a]	+101.6°	+39,600	[b]	+3.8°	+1500	$CHCl_3$	19,000	20,500
2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-glucopyranose	[b]	+93.5°	+36,400	[c]	+1.2°	+500	$CHCl_3$	18,000	18,400
2-Acetamido-3,4,6-tri-*O*-acetyl-1-*S*-acetyl-2-deoxy-1-thio-D-glucopyranose (III)	...	...	...	...	−2°	−800	$CHCl_3$	...	...
2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl ethylxanthate	...	...	...	[d]	+30.8°	+13,900	$(CHCl_2)_2$	...	...
2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranosyl ethylxanthate (V)	...	...	...	...	+33°	+14,900	$CHCl_3$	...	...
2-(2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl)-2-thiopseudourea hydrobromide	...	...	...	[e]	−18.8°	−9200	C_2H_5OH	...	...
2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranosyl)-2-thiopseudourea hydrochloride (I)	...	...	...	...	−29.3	−12,900	C_2H_5OH	...	...

[a] See ref. 20. [b] See ref. 21. [c] See ref. 22. [d] See ref. 12. [e] See ref. 11b.

urea hydrochloride (I) crystallized directly from the hot solution in high purity. The condensation of compound II with potassium ethylxanthate in ethanol solution to give 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl ethylxanthate (V) has recently been described,[8,9b] with a reported yield of 50%.[8] In our work it was found that condensation of the reactants in a nonhydroxylic solvent, with an intermediate acetylation stage gave a good yield (82%) of compound V. Omission of the acetylation stage diminished the yield of crystalline product, suggesting that partial saponification occurred during the condensation. Desulfurization of compounds I and V with Raney nickel in boiling ethanol,[18] followed by acetylation, gave in each case crystalline 2-acetamido-3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-glucitol (IV),[6] affording direct evidence for ring size and attachment of sulfur in the two compounds and confirming previous work[9b] in the case of V. The β-D anomeric configuration was assigned to compounds I and V on the basis of the similarity of their molecular rotations with those of 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiopseudourea hydrobromide[11] and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl ethylxanthate[12] (Table I), which differ from compounds I and V essentially only by exchange of the —NHAc group at C-2 by —OAc. Such a substitution at C-2 exerts only a small effect on the rotatory power of the molecule, as can be seen by comparison of the molecular rotations of the anomeric 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α- and β-D-glucopyranoses with the anomeric 1,2,3,4,6-penta-*O*-acetyl-α- and β-D-glucopyranoses (Table I). The configurational correlation of compound V with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl ethylxanthate was further confirmed by comparison of the optical rotatory dispersion curves of the two compounds (Fig. 1); both derivatives showed similar complex.

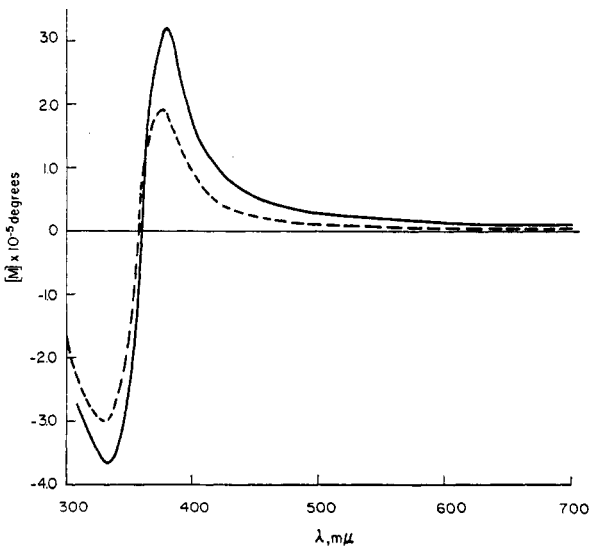

Fig. 1.—Optical rotatory dispersion: ——— 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl ethylxanthate, (V) - - - - 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl ethylxanthate

Cotton effect curves, with a change in sign of rotation at the weak absorption band near 360 mμ. The xanthates showed a strong absorption band

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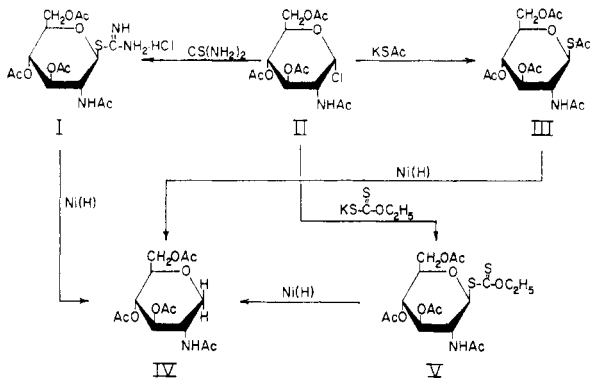

Figure 2

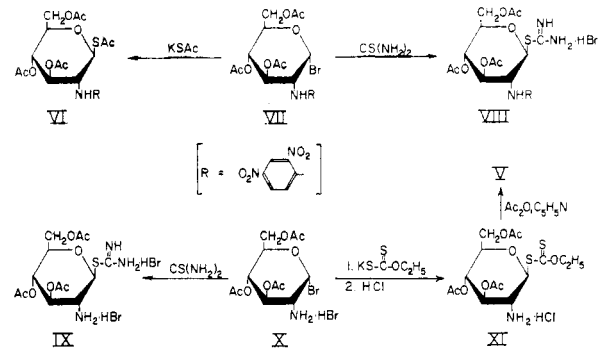

Figure 3

near 270 mμ which prevented observation of the rotatory dispersion curve to wave lengths below 300 mμ. The ultraviolet absorption and rotatory dispersion behavior of the glycosyl ethylxanthates (GlS—CS—OEt) closely resemble that of the *O*-bornyl *S*-alkyldithiocarbonates ($C_{10}H_{17}O$—CS—SR) and the *O*-menthyl analogs[19]: the latter show absorption maxima at 276–285 mμ (strong, C=S) and 353–366 mμ (weak, —S—CS—) with molar absorptivities of the same order of magnitude as those of the carbohydrate xanthates. The rotatory dispersion curves of the *O*-bornyl and *O*-menthyl *S*-alkyldithiocarbonates show a reversal of sign at the weak 353–366-mμ absorption band; high absorptivity at shorter wave lengths prevented observations close to the strong absorption band.[19]

Compound II condensed readily with potassium thiolacetate in acetone solution, and at short reaction times the principal product III had a melting point of 200° and specific rotation −2° in chloroform. Molecular rotatory data (Table I) suggest that it was configurationally related to 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose, and the absence of the infrared absorption peak at 11.9 μ, characteristic of the α-D-glucopyranose structure,[23] supports the assignment of the structure 2-acetamido-3,4,6-tri-*O*-acetyl-1-*S*-acetyl-2-deoxy-1-thio-β-D-glucopyranose (III) to this compound. Raney nickel desulfurization of compound III gave the known anhydro-D-glucitol derivative IV in good yield, affording evidence for the pyranose structure of III. When the duration of the condensation reaction was extended the yield of III was lowered, and a second sulfur-containing acetylated amino sugar derivative was obtained, m.p. 136°, $[\alpha]_D$ +84° (chloroform), together with 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose, m.p. 139°, $[\alpha]_D$ +90° (chloroform). It is probable that the product with m.p. 136° is the α-D-anomer of III, and the formation of 2-acetamido-3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-glucitol (IV) when the compound was treated with Raney nickel supports this view, but the yield of crystalline product in the desulfurization reaction was low, and analytical values were not of acceptable accuracy even after repeated recrystallization. In a recent paper[9a] Meyer zu Reckendorf and Bonner describe a synthesis of III from II and potassium thiolacetate in a solution containing acetone, thiolacetic acid, and "dilute ethanol," and report m.p. 196–197°, $[\alpha]^{25}_D$ +14.1° (*c* 2.16, chloroform). Desulfurization of this product[9b] gave IV in unstated yield. It is probable that their preparation was an anomeric mixture, since the product isolated in our work, prepared in a nonhydroxylic solvent, had a specific rotation 16° lower than their reported value.

The formation of the *N*-(2,4-dinitrophenyl) analogs of compounds I and III was studied since this *N*-substituent can be removed under considerably milder conditions[15a] than those needed for de-*N*-acetylation. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide (VII) condensed with thiourea giving 2-[3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranosyl]-2-thiopseudourea hydrobromide (VIII) as a well crystallized salt, but 3,4,6-tri-*O*-acetyl-1-*S*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-1-thio-β-D-glucopyranose (VI), prepared from compound VII and potassium thiolacetate, crystallized with difficulty, and could only be satisfactorily purified by chromatography. An isomeric side product, possibly the anomeric form of VI, was isolated in this preparation, but direct configurational correlation by Hudson's isorotation rules[20] is not possible[15b] with the chromophoric 2,4-dinitroanilino group present, and the aromatic ring absorptions in the range 11–13 μ make anomeric assignments from infrared data unreliable.

Two direct syntheses of 2-amino-2-deoxy-1-thio-D-glucose derivatives with no covalent *N*-blocking

(19) T. M. Lowry and H. Hudson, *Phil. Trans. Roy. Soc. London, Ser. A*, **232**, 117 (1933); T. M. Lowry, "Optical Rotatory Power," Longmans, Green and Co., London, 1935, p. 324.

(20) C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909).

(21) C. S. Hudson and J. K. Dale, *J. Am. Chem. Soc.*, **37**, 1264 (1915).

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(23) S. A. Barker, E. J. Bourne, M. Stacey, and D. H. Whiffen, *J. Chem. Soc.*, 171 (1954); S. A. Barker, E. J. Bourne, R. Stephens, and D. H. Whiffen, *J. Chem. Soc.*, 3468 (1954).

groups were achieved, first by condensing 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide (X) with thiourea, but the product, 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea dihydrobromide (IX), crystallized with difficulty, and was difficult to purify. A more satisfactory synthesis from the preparative standpoint was achieved by condensation of the glycosyl halide X with an excess of potassium ethylxanthate to give 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl ethylxanthate, isolated as the hydrochloride salt (XI). The structure assigned to XI was confirmed by acetylation, which gave the *N*-acetyl analog V, identical to the product isolated previously in this work. Both XI and V showed similar optical rotatory dispersion curves. The synthesis of XI by a different route has been described by Meyer zu Reckendorf and Bonner.[9b]

Infrared spectral analysis permits ready differentiation of esters and amides[24] in carbohydrate derivatives.[25] Ester carbonyl groups absorb in the region 5.7–5.8 μ, while amide groups show carbonyl absorption at 6.0–6.2 μ (Amide I band) and N—H absorption at 6.45–6.6 μ (Amide II band). In an attempt to discover whether the carbonyl absorption of thiolesters could be distinguished from that of esters and amides in carbohydrates, a simple model compound, 2,3-di-*O*-acetyl-1-*S*-acetyl-1-thio-DL-glycerol was studied. Two infrared peaks in the carbonyl absorption region were observed, a normal acetate ester absorption at 5.74 μ, and a second peak at 5.89 μ. Oxidation of 1-thio-DL-glycerol with hydrogen peroxide and acetylation of the product gave bis-(DL-2,3-diacetoxypropyl) disulfide, which showed only *O*-acetate ester absorption at 5.74 μ, suggesting that the 5.89-μ absorption in the acetylated monomer could be assigned to the *S*-acetate carbonyl absorption. This absorption is close to the 5.97-μ absorption assigned[26] to simple thiolesters. The carbonyl absorption peaks in 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (at 5.78 μ) and in 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose (at 5.76 μ and 5.88 μ) supported this assignment. In 2-acetamido-3,4,6-tri-*O*-acetyl-1-*S*-acetyl-2-deoxy-1-thio-β-D-glucopyranose (III) it was possible to distinguish the *O*-acetyl absorption at 5.75 μ, the *S*-acetyl absorption at 5.88 μ, and the Amide I absorption at 6.01 μ; the corresponding sulfur-free derivative 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose showed the absorptions at 5.75 μ (*O*-acetyl) and 6.10 μ (Amide I), but no absorption in the region 5.85–6.0 μ. Similarly, 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranose and the low melting point product from the preparation of compound III both showed *O*-acetyl and *N*-acetyl carbonyl absorptions, the latter additionally showed the *S*-acetyl absorption at 5.90 μ. It was also possible to distinguish the *O*-acetyl carbonyl absorption (at 5.75 μ) from the absorption at 5.86 μ (*S*-acetyl) in 3,4,6-tri-*O*-acetyl-1-*S*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-1-thio-β-D-glucopyranose (VI).

(24) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., Methuen and Co. Ltd., London, 1958; A. Weissberger, ed., "Chemical Applications of Spectroscopy" (Techniques of Organic Chemistry, Vol. IX), Interscience Publishers Inc., New York, 1956.

(25) S. A. Barker, E. J. Bourne, and D. H. Whiffen, *Methods of Biochem. Anal.*, **3**, 213 (1956); W. Otting, *Ann.*, **612**, 68 (1958).

(26) R. S. Rasmussen, *Fortschr. Chem. org. Naturstoffe*, **5**, 331 (1948).

Experimental[27]

2,3,4,6-Tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose.—The direct method described has been reported briefly in a German patent.[13] A mixture of tetra-*O*-acetyl-α-D-glucopyranosyl bromide[28] (5.51 g., 1 equiv.), potassium thiolacetate[29] (1.53 g., 1 equiv.), and dry acetone (25 ml.) was shaken for 18 hr., filtered, and the filtrate and acetone washings were concentrated to a sirup, which was crystallized as fine needles from ethanol–ether; yield 4.8 g. (88%), m.p. 119–120° $[\alpha]^{23}D$ +10.5 ± 0.5° (*c* 0.6, chloroform), $\lambda^{KBr}_{max\ (\mu)}$ 5.76 (OAc), 5.88 (SAc), 11.17 (axial hydrogen at C-1).

The following constants have been reported for this compound as prepared by a three-step method[12]: m.p. 120°, $[\alpha]D$ +10° (1,1,2,2-tetrachloroethane). A sample of penta-*O*-acetyl-β-D-glucopyranose[21] showed $\lambda^{KBr}_{max\ (\mu)}$ 5.78 (OAc), 11.17 (axial hydrogen at C-1), no absorption in the region 5.85–5.95 mμ (SAc).

2-Acetamido-2-deoxy-α-D-glucose.—2-Amino-2-deoxy-α-D-glucose hydrochloride was *N*-acetylated in 43-g. lots by the method of Inouye and co-workers[30]; yields 41.5–42.5 g. (94–96%), m.p. 203–205° dec.

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl Chloride (II).—The procedure of Micheel and co-workers[14d] was modified. A mixture of 2-acetamido-2-deoxy-D-glucose (50 g.) and acetyl chloride (100 ml.) was stirred overnight under reflux without external heating, 400 ml. of U.S.P. chloroform was added and the solution was poured onto 1 kg. of cracked ice. The mixture was rapidly shaken, the organic layer was run into saturated sodium bicarbonate solution containing cracked ice, and the mixture was stirred at first, then shaken until the acid was neutralized. The chloroform layer was separated and dried over anhydrous magnesium sulfate. The extraction operation was completed in less than 15 min. The solution was filtered, the filter was washed with *dry, alcohol-free* chloroform, and the solution was evaporated to 75 ml. at 50°. Dry ether (500 ml.) was rapidly added, and crystallization, which began after a few minutes, was complete after 12 hr. at room temperature. The product was filtered, washed with 200 ml. of dry ether, and dried, to give dense white prismatic aggregates; yield 60 g. (73%), m.p. 127–128°. The mother liquors yielded a further amount; yield 4 g. (77% total), m.p. 125–127°. The product had

(27) Melting points were taken on a Fisher-Johns apparatus. The $[\alpha]D$ values were measured in a 4-dm. polarimeter tube. Infrared spectra were determined with a Model 21 Perkin-Elmer infrared spectrophotometer. The potassium bromide pellets were pressed from a finely ground mixture of the dried sample with dried analytical reagent grade potassium bromide. Ultraviolet absorption spectra were determined with a Carey Model 10 recording spectrophotometer. Optical rotatory dispersion measurements were made with a Rudolph Model 260/655/850/810-614 recording photoelectric spectropolarimeter.

(28) C. E. Redemann and C. Niemann, *Org. Syntheses*, **22**, 1 (1942).

(29) C. Ulrich, *Ann.*, **109**, 272 (1859).

(30) Y. Inouye, K. Onodera, S. Kitaoka, and S. Hirano, *J. Am. Chem. Soc.*, **78**, 4722 (1956).

$\lambda_{max\ (\mu)}^{KBr}$ 3.06 (NH), 5.74 (OAc), 6.09, 6.49 (NHAc); X-ray powder diffraction data[31]: 11.38 w, 8.91 vw, 7.97 m, 7.20 vs (1), 6.07 m, 5.68 vw, 4.86 vw, 4.63 s (2), 4.28 m (3, 3), 4.00 m (3, 3), 3.70 m.

Micheel and co-workers[14d] quote m.p. 126–127° for this compound, but attempted preparation by their procedure, by *heating* 2-acetamido-2-deoxy-D-glucose with acetyl chloride, gave dark sirups from which only low yields of the desired compound, in an impure state, could be isolated.

The product was stable for at least 6 months when stored in a desiccator over sodium hydroxide.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl Bromide (VII).—This substance was prepared by a more direct method than that described by Lloyd and Stacey.[15a] Acetyl bromide (30 ml.) was added slowly to a stirred suspension of 2-deoxy-2-(2,4-dinitroanilino)-D-glucose[15a] (10 g.) in U.S.P. chloroform (50 ml.), and the solution was stirred under reflux without heating for 5 hr. The solution was then diluted with U.S.P. chloroform (200 ml.), washed at 0° with water and saturated sodium bicarbonate solution, dried (magnesium sulfate), and evaporated at 50°. The crystalline residue was dissolved in dry, alcohol-free chloroform, (100 ml.), petroleum ether (b.p. 30–60°, 200 ml.) was added, and the product, which crystallized rapidly, was filtered, washed with 2:1 petroleum ether–chloroform, then with petroleum ether, and dried; yield 9.5 g. (62%) m.p. 155.5–157° dec., $[\alpha]^{25}D$ +45 ± 3° (*c* 1.2, chloroform); $\lambda_{max(\mu)}^{KBr}$ 3.03 (NH), 5.77 (OAc), 6.18, 6.28, 6.67 (aryl C = C), 6.55 (NO_2, NH), 7.42 (NO_2), 13.50, 13.90 (substituted benzene), X-ray powder diffraction data[31]: 12.25 s, 8.07 vs (1), 7.23 vw, 6.18 w, 5.10 m, 4.86 w, 4.64 w, 4.24 vw, 4.04 m, 3.80 vs (2), 3.65 s (3), 3.46 w.

Lloyd and Stacey[15a] record m.p. 162–164° and $[\alpha]D$ +46.0° (chloroform) for this compound prepared by a different route. The product showed no change in melting point after storage for 8 months in a desiccator over sodium hydroxide.

2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea Hydrochloride (I).—2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (II), (6 g.) and powdered thiourea (6 g.) were refluxed for 30 min. with dry acetone (100 ml.). The solution, clear initially, crystallized during the heating period. The solution was cooled to 0°, filtered, and the product was washed with acetone; yield 5.93 g. (82%). Recrystallization, as fine white needles, was effected with little loss from methanol–acetone; m.p. 179–181° (dec., browning 170°), $[\alpha]^{22}D$ −29.2 ± 0.3° (*c* 1.1, methanol), specific optical rotatory dispersion (complex) (*c* 0.46, ethanol, 20°): −22 (700), −29 (589), −95 (395), −184 (307), −65 (287), −61° (285); $\lambda_{max(\mu)}^{KBr}$ 5.70 (OAc), 6.01, 6.70 (NHAc), 6.20, 6.35 (C=N, $-NH_3^+$); $\lambda_{max}^{C_2H_5OH}$ 210 mμ (ε 23,000); X-ray powder diffraction data[31]: 10.08 m, 9.07 s (3), 8.13 vw, 6.66 w, 5.74 s, 5.34 vs (1), 5.17 m, 4.91 m, 4.71 vw, 4.39 m, 4.04 s (2), 3.84 m, 3.69 w, 3.53 m.

Anal. Calcd. for $C_{15}H_{24}ClN_3O_8S$: C, 40.75; H, 5.48; N, 9.51; S, 7.25; Cl, 8.03. Found: C, 40.71; H, 5.43; N, 9.57; S, 7.45; Cl, 8.65.

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl Ethylxanthate (V).—The following preparative procedure for this compound[8,9b] was found satisfactory. A mixture of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (II) (13.7 g.), potassium ethylxanthate (6.1 g.), and benzene (100 ml.) was shaken for 4 days, filtered, the filtrate evaporated, and the resulting sirup treated with pyridine (50 ml.) and acetic anhydride (20 ml.). After 12 hr. the solution was poured onto 500 g. of ice and water, and the precipitated crystalline product was filtered after 10 min.; yield 11.6 g. (68.5%). Concentration of the filtrate gave further product; yield 2.3 g. (82% total). The dried crude product was dissolved in ethanol (100 ml.), petroleum ether (b.p. 30–60°, 700 ml.) was added, and the pure product crystallized with little loss during 1 day at room temperature as colorless needles; m.p. 144–146°, $[\alpha]^{24}D$ +33° (*c* 1.1, chloroform); optical rotatory dispersion in Fig. 1.; $\lambda_{max(\mu)}^{KBr}$ 3.00 (NH), 5.74 (OAc), 6.01, 6.55 (NHAc), 7.32 (C=S?); $\lambda_{max}^{C_2H_5OH}$ 274 mμ (ε 28,000), 359 mμ (ε 200); X-ray powder diffraction data[31]: 13.95 s, 11.45 s (2, 2), 8.52 s (2, 2), 7.23 w, 5.73 vw, 5.21 m, 4.80 vs (1), 4.35 w, 4.04 vw, 3.85 m, 3.61 s (3).

Anal. Calcd. for $C_{17}H_{25}NO_9S_2$: C, 45.22; H, 5.59; N, 3.10; S, 14.20. Found: C, 45.04; H, 5.89; N, 3.02; S, 14.20.

The following constants have been reported for this compound: m.p. 143–144°, $[\alpha]^{25}D$ +36° (*c* 1.56, chloroform)[9b]; m.p. 142–143°, $[\alpha]^{15}D$ +36° (*c* 1.2, chloroform).[8]

2-Acetamido-3,4,6-tri-*O*-acetyl-1-*S*-acetyl-2-deoxy-1-thio-β-D-glucopyranose (III).—A mixture of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (10 g.), potassium thiolacetate[29] (3 g.), and dry acetone (100 ml.) was shaken for 4 hr., the solution was filtered from inorganic material (1.75 g.), and the filtrate and acetone washings were evaporated to a sirup, which was treated with chloroform (200 ml.). A small hygroscopic residue (0.3 g.) remained undissolved. Recrystallization of this residue from methanol–ether gave hygroscopic needles of an unidentified sulfur-containing product; yield 180 mg., m.p. 206–215° dec., $\lambda_{max(\mu)}^{KBr}$ 2.94 (OH), 6.15, 6.50 (NHAc), X-ray powder diffraction data[31]: 7.28 s (2), 5.96 vw, 5.76 w, 4.94 vw, 3.92 vw, 3.63 m, 3.57 s (3), 3.13 w, 3.02 vs (1), 2.76 m, 2.46 m.

The chloroform extract was evaporated at 40° and the residue crystallized as pink needles from methanol–ether; yield 5.9 g. (53%), m.p. 194–197° dec. Recrystallization from methanol–ether gave white needles; m.p. 199–200° dec., $[\alpha]^{23}D$ −2 ± 0.2° (*c* 1.29, chloroform), $\lambda_{max(\mu)}^{KBr}$ 2.99 (NH), 5.75 (OAc), 5.88 (SAc), 6.01, 6.55 (NHAc), $\lambda_{max}^{C_2H_5OH}$ 227 mμ (ε 20,000), X-ray powder diffraction data[31]: 13.26 vw, 9.85 w, 8.84 s (3), 8.02 m, 5.46 vw, 5.28 vs (1), 5.12 s (2), 4.71 m, 4.30 m.

Anal. Calcd. for $C_{16}H_{23}NO_9S$: C, 47.40; H, 5.72; N, 3.46; S, 7.90. Found: C, 47.58; H, 5.41; N, 3.45; S, 7.45.

Meyer zu Reckendorf and Bonner[9a] quote m.p. 196–197°, $[\alpha]^{25}D$ +14.1° (*c* 2.16, chloroform) for a product prepared in a hydroxylic solvent medium containing thiolacetic acid.

The pure product appeared to be stable indefinitely, but samples of the crude pink product became insoluble in chloroform after a 6-month exposure to the atmosphere.

The mother liquors from the above preparation were acetylated with pyridine (20 ml.) and acetic anhydride (10 ml.), and the product chromatographed on a 20 × 100 mm. column of silicic acid.[32] Elution with benzene (500 ml.) gave a small amount of dark sirup; elution with 1:1 benzene–ether gave a colorless product which crystallized from methanol–ether as needles; yield 0.54 g. (5%), m.p. 136–137.5°, $[\alpha]^{23}D$ +84 ±1° (*c* 0.4, chloroform), $\lambda_{max(\mu)}^{KBr}$ 5.73 (OAc), 5.90 (SAc), 6.01, 6.60 (NHAc). This product could not be purified to give a definitive substance of calculated analysis.

Desulfurization of Derivatives of 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-D-glucopyranose.—A solution of 2-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea hydrochloride (I) (5.0 g.) in ethanol (200 ml.) was refixed for 3 hr. with Raney nickel (50 g.), filtered through carbon, and the residue washed with hot ethanol (500 ml.). The solution was evaporated and the residue was acetylated by boiling briefly with acetic anhydride (25 ml.) and anhydrous sodium acetate (5 g.). The cooled solution was poured on ice (250 g.), stirred overnight, and the product extracted with two 75-ml. portions of chloroform. The extract was washed with

(31) Interplanar spacing, Å., CuKα radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very. First few lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

(32) Silica Gel Davison, grade 950, 60–200 mesh, a product of the Davison Division of the W. R. Grace Chemical Co., Baltimore, Md.

water, dried (magnesium sulfate), and evaporated to a crystalline residue; yield 3.1 g. (82%), m.p. 154–158°. Recrystallization from ethanol-ether gave known[6] pure **2-acetamido-3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-glucitol (IV)** in large prisms; m.p. 165–168°, $\lambda_{max(\mu)}^{KBr}$ 5.83 (OAc), 6.18, 6.49 (NHAc); X-ray powder diffraction data[31]: 7.81 m (3), 7.02 m, 6.01 w, 5.43 w, 4.62 vs (1), 4.17 m, 3.93 s (2), 3.60 w.

Anal. Calcd. for $C_{14}H_{21}NO_8$: N, 4.23. Found: N, 4.39.

The following constants have been reported for this compound: m.p.[6] 164°; m.p. 160–161°, $[\alpha]^{25}D \pm 0°$ (*c* 1.1, chloroform).[9b]

Omission of the acetylation stage in the above procedure gave a product which was only partially crystalline and which showed hydroxyl absorption in the 2.9-μ region of the infrared.

The desulfurization and acetylation procedure was repeated on compounds V and III.[9b] 2-Acetamido-3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-glucitol was obtained in 92% and 86% yields, respectively, and identified by mixed melting point and infrared spectrum as identical with the product obtained in the first preparation. The side product, m.p. 136–137.5°, obtained in the preparation of compound III gave the same crystalline product on desulfurization, but the yield was low.

2-[3,4,6-Tri-*O*-acetyl-2-deoxy-2-[2,4-dinitroanilino)-β-D-glucopyranosyl]-2-thiopseudourea Hydrobromide (VIII).—A mixture of 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide (VII) (4.00 g.), powdered thiourea (4.0 g.), and dry acetone (200 ml.) was refluxed for 30 min., 1-propanol (150 ml.) was added, the solution was evaporated to 200 ml. The resultant yellow crystalline product was filtered after 30 min. at room temperature; yield 3.25 g. (72%), m.p. 198–201° dec., $[\alpha]^{23}D$ −77 ± 0.5° (*c* 0.5, methanol), $\lambda_{max(\mu)}^{KBr}$ 2.96 (NH), 5.72 (OAc), 6.06 (C=N), 6.20, 6.27, 6.64 (aryl C=C), 6.56 (NO_2), 7.47 (NO_2), 13.44, 13.88 (substituted benzene), $\lambda_{max}^{C_2H_5OH}$ 336 mμ (ε 45,000), X-ray powder diffraction data[31]: 11.76 s (3), 6.99 vs (1), 6.01 vw, 5.51 vw, 4.98 w, 4.57 w, 4.37 m, 4.10 s, 3.95 s, 3.76 vs (2), 3.60 vw, 3.45 m.

Anal. Calcd. for $C_{19}H_{24}BrN_5O_{11}S$: C, 37.38; H, 3.97; N, 11.48; S, 5.25; Br, 13.09. Found: C, 37.24; H, 4.24; N, 11.27; S, 5.27; Br, 12.78.

3,4,6-Tri-*O*-acetyl-1-*S*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-1-*thio*-β-D-glucopyranose (VI).—A solution of 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide (VII) (2.0 g.) in dry acetone (50) ml.) was shaken for 1 hr. with potassium thiolacetate[29] (0.45 g.), the filtered solution was evaporated and the residue chromatographed on a 35 × 180-mm. column of silicic acid.[32] Elution with 500 ml. of 1:1 benzene–ether gave crystalline material; yield 1.5 g. (76%). This was recrystallized from benzene–ether to give yellow needles; m.p. 163.5–164°, $[\alpha]^{22}D$ −29 ± 1° (*c* 0.5, chloroform), $\lambda_{max(\mu)}^{KBr}$ 3.02 (NH), 5.75 (OAc), 5.86 (SAc), 6.18, 6.26 (aryl C=C), 6.48, 6.57 (aryl C=C, NO_2), 7.42 (NO_2), 13.51, 13.88 (substituted benzene), X-ray powder diffraction data[31]: 10.41 s (2), 8.61 w, 7.52 m, 4.80 vs (1), 3.96 vw, 3.75 s (3), 3.55 vw, 3.34 vw, 2.91 w, 2.29 vw.

Anal. Calcd. for $C_{20}H_{23}N_3O_{12}S$: C, 45.36; H, 4.38; N, 7.94; S, 6.04. Found: C, 45.47; H, 4.65; N, 7.76; S, 6.47.

When the above preparation was repeated, with the shaking time extended to 24 hr., a crystalline product was isolated; yield 0.63 g. (32%), m.p. 143–145°, $[\alpha]^{22}D$ −392° ± 20° (*c* 0.27, chloroform), $\lambda_{max(\mu)}^{KBr}$ 2.95 (NH), 5.70 (OAc), 5.86 (shoulder) (SAc), 6.15, 6.25 (aryl C=C), 6.58 (aryl C=C, NO_2), 7.49 (NO_2), 13.48, 13.92 (substituted benzene).

Anal. Calcd. for $C_{20}H_{23}N_3O_{12}S$: C, 45.36; H, 4.38; N, 7.94; S, 6.04. Found: C, 44.70; H, 4.05; N, 7.78; S, S, 5.87.

2-(2-Amino-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea Dihydrobromide (IX).—A solution of thiourea (1.2 g.) in warm 2-propanol (30 ml.) was mixed with 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide (X)[16] (7 g.), and the mixture was refluxed for 30 min. The cooled solution was decolorized with carbon, concentrated to 25 ml., and ethyl acetate added to incipient turbidity. The product crystallized slowly on refrigeration, and was filtered, washed with ethyl acetate, and dried; yield 5.05 g. (61%), m.p. 179–181° dec., $[\alpha]D$ −12 ± 2° (*c* 1.06, methanol), $\lambda_{max(\mu)}^{KBr}$ 5.70 (OAc), 6.00, 6.20, 6.35, 6.61 (C=N, NH), $\lambda_{max}^{C_2H_5OH}$ 208 mμ (ε 26,000), X-ray powder diffraction data[31]: 12.69 vs (1), 5.67 m, 4.96 m, 4.64 vw, 4.33 s (2, 2), 4.02 s (2, 2), 3.81 w, 3.66 vw, 3.47 s (3), 3.31 w, 3.11 vw, 2.98 m.

Further recrystallization from the same solvents gave a less pure product, m.p. 182–184° dec., and a completely satisfactory solvent system for recrystallization could not be found.

Anal. Calcd. for $C_{18}H_{23}Br_2N_3O_7S$: C, 29.73; H, 4.42; Br, 30.43; N, 8.00; S, 6.10; CH_3CO, 24.58. Found: C, 28.56; H, 4.85; Br, 30.24; N, 8.21; S, 6.44; CH_3CO, 24.52.

3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl Ethylxanthate Hydrochloride (XI).—A solution of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide (X)[16] (1.00 g.) in dry acetone (25 ml.) was mixed with a solution of potassium ethylxanthate (0.72 g., 2 moles) in ethanol (25 ml.). After 45 min. the inorganic precipitate (0.50 g., theoretical) was filtered, the filtrate was evaporated to 10 ml., ether (150 ml.) was added, followed by a solution of 6 *N* hydrochloric acid (0.38 ml., 1 equiv.) in acetone (5 ml.). The crystalline crude product which rapidly formed was filtered after 2 hr. at 0°; yield 0.72 g. (72%). Purification was effected from ethanol–ether; m.p. 177–179° dec., $[\alpha]^{20}D$ +23 ± 1.5° (*c* 0.2, ethanol); specific optical rotatory dispersion (*c* 0.72, ethanol, 20°) (positive Cotton effect curve) +20 (700), +30 (589), +540 (382), −740 (330), −610° (303); $\lambda_{max(\mu)}^{KBr}$ 3.40, 6.20, 6.39 (amine hydrochloride), 5.73 (OAc), 6.56 (NH), 7.31 (C=S?), 11.41 (axial H at C-1); $\lambda_{max}^{C_2H_5OH}$ 216 mμ (ε 13,000), 269 mμ (ε 13,000), 360 mμ (ε 200); X-ray powder diffraction data[31]; 11.27 s (3), 8.24 m, 7.17 vw, 5.70 vw, 5.20 s (2), 4.46 vs (1), 3.95 vw, 3.55 vw, 3.27 vw, 3.11 m.

Anal. Calcd. for $C_{15}H_{24}ClNO_8S_2$: C, 40.40; H, 5.43; Cl, 7.95; N, 3.14; S, 14.38. Found: C, 40.61; H, 5.75; Cl, 7.63; N, 3.42; S, 13.86.

Meyer zu Reckendorf and Bonner[9b] quote m.p. 188–189° dec., $[\alpha]^{25}D$ +21.9° (*c* 0.87, ethanol) for this compound prepared by a different route.

Acetylation of 100 mg. of the compound with pyridine (1 ml.) and acetic anhydride (0.5 ml.) gave 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl ethylxanthate (V) (60 mg.), m.p. 139–143°, identical by infrared spectrum and X-ray powder diffraction pattern to authentic compound V.

2,3-Di-*O*-acetyl-1-*S*-acetyl-1-thio-DL-glycerol.—A mixture of 1-thio-DL-glycerol[33] (20 g.), acetic anhydride (150 g.), and anhydrous sodium acetate (30 g.) was warmed gently until the initial vigorous reaction had subsided, then boiled for 30 min., cooled, and poured onto 1 kg. of ice. The product was extracted with 1,2-dichloroethane, the extract was washed with sodium bicarbonate solution, dried (magnesium sulfate), the solvent evaporated, and the product was distilled as a colorless oil; yield 36 g. (83%), b.p. 120–140° (0.01 mm.), n^{25} 1.4701, $\lambda_{max(\mu)}^{film}$ 5.74 (OAc), 5.89 (SAc).

Anal. Calcd. for $C_9H_{14}O_5S$: C, 46.20; H, 6.03; S, 13.69. Found: C, 46.50; H, 5.86; S, 13.35.

A crude preparation b.p. 130–136° (1.8 mm.) containing the above compound has been prepared[34] by the reaction of

(33) Thiovanol, a product of Evans Chemetics, Inc., New York, N. Y.

(34) B. Sjöberg, *Ber.*, **75**, 13 (1942).

1,2-di-*O*-acetyl-3-bromo-1,2-propanediol with potassium thiolacetate.

Bis(2,3-diacetoxy-DL-propyl) Disulfide.—A solution of 1-thio-DL-glycerol[33] (20 g.) in water (50 ml.) was treated with 10% hydrogen peroxide (45 ml.), the exothermic reaction was moderated by cooling initially, and after 2 hr. excess peroxide was destroyed by adding manganese dioxide (0.1 g.). After 4 hr. effervescence ceased, and the solution was filtered, evaporated, freed from water by codistillation first with 1-propanol then acetic anhydride, and the crystalline residue was acetylated as in the above preparation. The acetylated product distilled as a yellow oil; yield 32.5 g. (92%), b.p. 200–210° (0.01 mm.), $n^{25}D$ 1.4883, $\lambda_{max(\mu)}^{film}$ 5.74 (OAc), no absorption at 5.8–6.0 μ (SAc).

Anal. Calcd. for $C_{14}H_{22}O_8S_2$: C, 43.95; H, 5.80; S, 16.70. Found: C, 43.66; H, 5.70; S, 17.09.

The sirupy unacetylated disulfide has been described as a reaction intermediate in the preparation of 1-thioglycerol,[35] but it was not characterized.

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(35) L. Smith and B. Sjöberg, *Ber.*, **69**, 678 (1936).

The Reaction of Free Carbonyl Sugar Derivatives with Organometallic Reagents. I. 6-Deoxy-L-idose and Derivatives[1,2]

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Glycol cleavage of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (I) with lead tetraacetate produced a stable monomeric form of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (II). Catalytic debenzylation of the latter substance produced initially a monomeric product which has been previously known only as the dimer. Reaction of II with methylmagnesium iodide produced exclusively 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-*ido*(L-*glycero*-α-D-*xylo*-hexo)furanose (VII), the configuration of which was elucidated by conversion to derivatives of established structure. A mechanism is suggested to explain the exclusive production of the L-*ido*- configuration. It is shown that 6-deoxy-L-idose changes to 6-deoxy-L-sorbose (XIII) in the presence of acid.

The use of the Grignard reagent in reactions of acyclic aldoses has been quite limited.[3] The few recorded examples[4] of the application of this reaction have involved the use of *aldehydo*-D-(and L)-arabinose and *aldehydo*-D-xylose derivatives to produce the corresponding alditols. We wish to report herein the application of the Grignard reaction to suitably blocked dialdoses to produce terminal deoxyaldoses. 1,2-*O*-Isopropylidene-D-*xylo*-pentodialdo-1,4-furanose,[5] which appeared to be a suitable subject for the reaction, failed to condense with the Grignard reagent, probably beause the aldehyde group is masked in the dimeric structure[6] in which it is known to exist. It was found that dimerization was prevented by blocking participation of the hydroxyl on C-3 with an *O*-benzyl group, producing a monomeric pentodialdose with one true aldehyde group free to react with a Grignard reagent. Glycol cleavage of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (I)[7,8] produced 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (II) as a colorless sirup in good yield. The substance gave a positive Schiff aldehyde test. The infrared spectrum revealed essentially no hydroxyl peak but gave an intense carbonyl peak in the region of 5.8 μ. It was quite stable in the absence of moisture and formed a crystalline semicarbazone (V). Hydrogenolysis of the blocked pentodialdose (II) with palladium catalyst[9] produced 1,2,*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (III), which yielded a crystalline semicarbazone (VI) with constants identical with those reported by Iwadare[5] for the same derivative. Substance III also exhibited equal carbonyl and hydroxyl absorptions in the infrared spectrum. These diminished slowly with time. *p*-Nitrobenzoylation of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (I) produced a crystalline 5,6-di-*O*-(*p*-nitrobenzoyl) derivative (IV).

Treatment of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (II) with methylmagnesium iodide in ether solution produced a

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