Reaction of Free Carbonyl Sugar Derivatives with Organometallic Reagents. II. 6-Deoxy-L-idose and a Branched-Chain Sugar[1–3]

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A crystalline dicarbonyl sugar derivative, 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (II), was prepared by the chromium trioxide in pyridine oxidation of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-ido(L-*glycero*-α-D-*xylo*-hexo)furanose (I) or 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (V). Reduction of the keto sugar derivative (II) with metal hydrides resulted in a mixture of C-5 epimeric derivatives of 6-deoxy-L-idose and 6-deoxy-D-glucose, with the former predominating. The 6-deoxy-D-glucose derivative (V) was synthesized by an alternative procedure for comparative purposes. The dicarbonyl sugar derivative II gave on reaction with methyl Grignard reagent the crystalline derivative III which on reduction to IV and acid hydrolysis yielded the branched-chain sugar 6-deoxy-5-methyl-D-*xylo*-hexose (VII), obtained as a sirup characterized by its crystalline phenylosazone.

The pyridine–chromium trioxide complex[4] is a useful oxidizing agent for substances containing acid-sensitive blocking groups. It has been applied in the preparation of steroid derivatives[5] and in a few instances in the field of carbohydrates.[6,7]

The Grignard reagents have been applied sparingly to the *aldehydo*-sugar derivatives.[8] Wolfrom and Hanessian[3] treated 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,2-furanose with methylmagnesium iodide to produce stereospecifically 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-ido(L-*glycero*-α-D-*xylo*-hexo)furanose (I).

In early work Paal and co-workers[9] applied Grignard reagents to sugar lactones and esters to obtain 1,1-di-C-substituted sugar derivatives. Later Ohle and associates[10] prepared a number of terminal di-C-alkyl substituted sugars by the action of Grignard reagents on 5-hexosulose derivatives. The Grignard reagent was applied by Folkers and co-workers[7] to methyl 2,3-*O*-isopropylidene-L-*lyxo*-hexofuranosid-5-ulose in the elucidation of the L-lyxose configuration of the branched sugar noviose, a constituent of novobiocin. These workers also prepared the corresponding D-ribose[7] derivative by the action of Grignard reagent on methyl (methyl 2,3-*O*-isopropylidene-D-ribofuranosid)uronate. The use of metal borohydrides[11] in the reduction of aldoses,[12] now well established, has been employed to reduce a keto sugar, D-*xylo*-5-hexulosonic acid to a mixture of D-gluconic and L-idonic acids.[13]

We wish to report herein the extension of the use of the pyridine–chromium trioxide complex[4] to the oxidation of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-ido(L-*glycero*-α-D-*xylo*-hexo)furanose (I) and of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (V) followed by the reduction of the resulting 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (II) with metal hydrides. The resulting mixture of C-5 epimers, 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-gluco- and β-L-idofuranose (V and I), were separated by crystallization of I over a prolonged period. Reductive debenzylation of the mother liquor residue with hydrogen and palladium catalyst followed by acetylation, yielded in relatively small amounts the known crystalline 3,5-di-*O*-acetyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (VI).[14,15] The 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (V) was also synthesized by the reductive cleavage of the *p*-tolylsulfonyloxy function in 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose with lithium aluminum hydride in ether. The product was purified by chromatography on alumina and was a colorless sirup, which upon reductive cleavage of the *O*-benzyl group followed by acetylation, yielded the known diacetate (VI).[14]

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[2] Reported in part in Abstracts Papers Am. Chem. Soc., **138**, 4D (1960).

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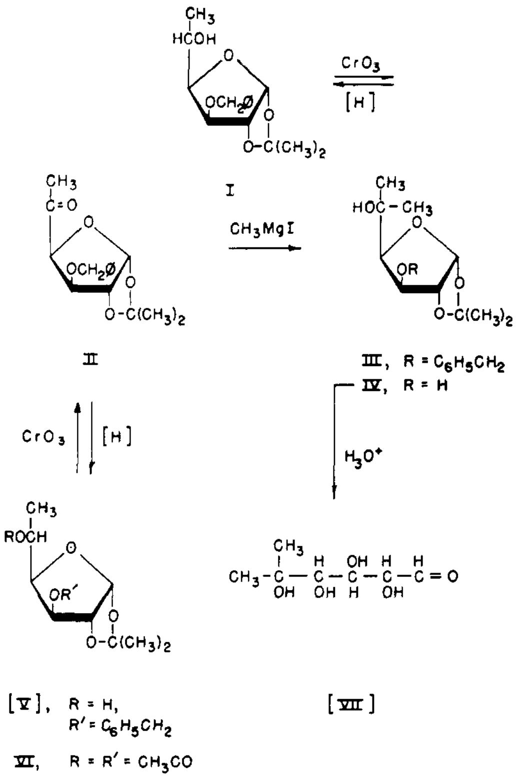

Treatment of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (II) with methylmagnesium iodide produced crystalline 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-5-methyl-α-D-*xylo*-hexofuranose (III). Reductive debenzylation using palladium-on-carbon catalyst yielded crystalline 6-deoxy-1,2-*O*-isopropylidene-5-methyl-α-D-*xylo*-hexofuranose (IV). Removal of the isopropylidene group from IV produced the sirupy branched-chain sugar, 6-deoxy-5-methyl-D-*xylo*-hexose (VII), characterized as a crystalline phenylosazone.

Experimental

3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (II).—Pyridine (75 ml.) was cooled to 10° in a three-necked flask immersed in an ice bath and 7.48 g. of powdered chromium trioxide[4] was added cautiously while stirring under an atmosphere of nitrogen. When the solution became viscous, as the yellow complex formed, the temperature was allowed to rise to 20°. At the end of the addition (20 min.) a thick yellow slurry formed. A solution of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-ido(L-*glycero*-α-D-*xylo*-hexo)furanose (I, 10 g. in 100 ml. of dry pyridine) was added dropwise with stirring. After the addition was complete the solution became dark brown in color. The stirring was maintained for 24 hr. in an atmosphere of dry nitrogen. Most of the pyridine was removed by evaporation under reduced pressure, and the resulting brown residue was suspended in 25 ml. of water and extracted with three 150-ml. portions of ether. The combined ether extract was dried with anhydrous sodium sulfate and evaporated to a yellow sirup which partially crystallized upon standing. The infrared absorption spectrum revealed hydroxyl and carbonyl peaks of about equal magnitude indicating incomplete reaction. The oxidation of the product was repeated twice by the above procedure to produce colorless needles (II); yield 5.08 g. (50%). Three recrystallizations from ether–petroleum ether produced pure material; m.p. 55–56°, $[\alpha]^{25}\text{D}$ −89° (*c* 1.5, chloroform), infrared absorption spectral data: $\lambda_{\max}^{\text{KBr}}$ 5.8 μ (C=O), 9.22, 9.51, 9.8 μ (C—O—C), 13.8, 14.6 μ (unsubstituted phenyl), X-ray powder diffraction data[16]: 10.25 m, 8.5 m, 5.90 m, 5.24 s (1), 4.84 m (3), 4.64 m (2), 4.39 w, 4.04 w, 3.78 vw, 3.45 vw.

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.73; H, 6.89; mol. wt., 292. Found: C, 65.50; H, 6.53; mol. wt. (Rast), 292.

The above oxidation was repeated with 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose to give crystalline II in slightly lower yield.

3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-ido(L-*glycero*-α-D-*xylo*-hexo)- and α-D-glucofuranose (I and V).—To a solution of 0.5 g. of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-*xylo*-hexofuranos-5-ulose (II) in 20 ml. of 50% aqueous methanol was added portionwise 65 mg. of sodium borohydride. The solution was allowed to stand at room temperature 16 hr., when it was diluted with 10 ml. of water and extracted with two 10-ml. portions of chloroform. The colorless sirup obtained on solvent removal was dissolved in 2 ml. of ether and diluted with 4 ml. of petroleum ether. On storing at 10° for 20 days colorless needles formed and were filtered; yield 0.296 g., m.p. 90–91°, mixed melting point unchanged with authentic 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-ido(L-*glycero*-α-D-*xylo*-hexo)furanose (I).[3]

The mother liquor was concentrated to a sirup (87 mg.) which failed to crystallize and exhibited no carbonyl band in its infrared spectrum. A solution containing 87 mg. of sirup from the mother liquor dissolved in 20 ml. of absolute ethanol was hydrogenated with palladium-on-carbon catalyst[3] at 65° and 500 p.s.i. for 4 hr. The solution was filtered and evaporated to a sirup which lacked the characteristic substituted phenyl absorption in its infrared spectrum; yield, 57 mg. Acetylation of 50 mg. of this sirup in 2.5 ml. of acetic anhydride and 2.5 ml. of pyridine at room temperature yielded a sirupy acetate which crystallized on standing; yield, 22 mg., m.p. 80–85°. Recrystallization from methanol–water gave fine needles; m.p. 86–87° undepressed upon admixture with VI as prepared below. No significant change in the yields of the respective products was observed when the solvent composition and temperature of the reaction were varied. The same observations were made using potassium borohydride in methanol.

3,5-Di-*O*-acetyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (VI).—A solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose[15] (13.7 g.) in 120 ml. of anhydrous ether was added dropwise to a suspension of 2.5 g. of lithium aluminum hydride in 100 ml. of anhydrous ether, essentially according to the procedure of Reist, Spencer, and Baker.[17] The mixture was gently refluxed 24 hr. with stirring. The excess hydride was decomposed by the cautious addition of water and the mixture was extracted with ether. The ether solution was dried with magnesium sulfate and concentrated under reduced pressure to a dark yellow sirup. A portion of the sirup (6 g.) was dissolved in ether and placed on a column (300 × 60 mm.) of neutral alumina powder. A yellow band which appeared was eluted and discarded. Subsequent elution with 95% ethanol gave upon evaporation a pale yellow sirup containing no sulfur and exhibiting an infrared absorption spectrum nearly identical to that of I and V; yield 4 g. A portion of the sirup was distilled at 150° and 0.1 mm. pressure to give a colorless sirup of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (V), soluble in ether but insoluble in petroleum ether; $[\alpha]^{25}\text{D}$ −67.5° (*c* 4, chloroform).

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.38; H, 7.64.

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[16] Interplanar spacing, CuKα radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very. First three strongest lines are numbered (1, strongest).

[17] E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **25**, 1753 (1958).

Reductive debenzylation of this material as described above produced a sirup; $[\alpha]^{25}\text{D}$ $-19°$ (*c* 1.5, chloroform). Baker and co-workers[17] record for 6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose; m.p. 92°, $[\alpha]^{20}\text{D}$ $-26.3°$ (chloroform). Acetylation of the sirup with acetic anhydride and pyridine as described above produced crystalline material (VI); m.p. 87–88°, $[\alpha]^{22}\text{D}$ $+20°$ (*c* 2, chloroform). Freudenberg and associates[14] record for 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (VI): m.p. 96°, $[\alpha]^{20}\text{D}$ $+23°$ (chloroform); Meyer and Reichstein[15] report m.p. 88–89°.

3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-5-methyl-α-D-*xylo*-hexofuranose (III).—A solution of 1 g. of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (II) was added dropwise with stirring over a period of 30 min. to 30 ml. of an ether solution of methylmagnesium iodide (0.375 g. of magnesium turnings and 5 ml. of methyl iodide). The mixture was refluxed gently 1.5 hr., cooled, and added dropwise with vigorous stirring to a cold saturated solution of ammonium chloride (50.ml.). The organic layer was separated and washed with water. The aqueous solutions were washed with ether and the combined ether extract was dried with anhydrous sodium sulfate and evaporated under reduced pressure to a sirup which was crystallized from 2 ml. of ether; yield, 0.5 g., m.p. 78–80°. Further processing the mother liquor gave an additional amount; total yield, 0.75 g. Three recrystallizations from petroleum ether produced pure material (III); m.p. 91–92°, $[\alpha]^{25}\text{D}$ $-49°$ (*c* 2, chloroform), infrared absorption spectral data: $\lambda_{\max}^{\text{KBr}}$ 2.9 μ (OH), 13.75, 14.5 μ (substituted phenyl), no carbonyl absorption, X-ray powder diffraction data[16]: 10.62 s (1), 7.46 m, 6.20 m, 5.34 m, 5.12 m, 4.65 m (3), 4.42 m (2), 4.02 w, 3.73 w, 3.60 w, 3.41 vw, 3.24 vw.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.43; H, 7.88.

Attempts to acetylate this compound resulted in recovery of the starting product or very incompletely acetylated material.

6-Deoxy-1,2-*O*-isopropylidene-5-methyl-α-D-*xylo*-hexofuranose (IV).—A solution of 0.4 g. of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-5-methyl-α-D-*xylo*-hexofuranose (III) was reductively debenzylated with hydrogen and palladium catalyst as described above. The solution was filtered and evaporated to dryness under reduced pressure. Trituration with petroleum ether gave colorless needles; yield, 0.22 g., m.p. 113–115°. Recrystallization from ether–petroleum ether gave a pure material (IV); m.p. 115–116°, $[\alpha]^{25}\text{D}$ $-21°$ (*c* 2, water), infrared absorption spectral data: $\lambda_{\max}^{\text{KBr}}$ 2.9 μ (OH), no substituted phenyl absorption in the region 13–15 μ, X-ray powder diffraction data[16]: 11.30 m, 9.60 m, 7.74 m, 7.08 m, 6.18 m, 5.59 m, 5.29 s (1), 4.95 m (2), 4.30 m (3), 3.52 vw, 3.16 vw.

Anal. Calcd. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.06; H, 8.32.

6-Deoxy-5-methyl-D-*threo*-hexose Phenylosazone.—1,2-*O*-Isopropylidene-5-methyl-α-D-*xylo*-hexofuranose (IV, 0.57 g.) was heated 2 hr. at 70° in 1.5 ml. of 0.05% sulfuric acid. The solution was then neutralized with powdered barium carbonate, filtered, and the filtrate evaporated to a sirup (6-deoxy-5-methyl-D-*xylo*-hexose, VII); yield, 45 mg., $[\alpha]^{25}\text{D}$ $-10.5°$ (*c* 0.9, water). The sirup was strongly reducing in warm Fehling solution. It was soluble in water, alcohol, and acetone but was insoluble in ether. It did not restore the color of Schiff reagent and was quite stable at room temperature. On paper chromatograms, using the solvent system 1-butanol–ethanol–water (4:1:5) a single spot having an R_{Rf} value of 1.18 was obtained. Another hydrolyzate of IV, obtained in the same manner and containing about 150 mg. of the sugar, was neutralized with 2 *N* sodium hydroxide and allowed to evaporate slowly to 3 ml. Phenylhydrazine acetate (300 mg.) in 3 ml. of aqueous solution was added, and the mixture was heated on a boiling water bath. The crystalline phenylosazone which formed in 15 min. was filtered and washed successively with water, dilute acetic acid, and ethanol–petroleum ether; yield, 64 mg., 185–187° dec. Pure 6-deoxy-5-methyl-D-*threo*-hexose phenylosazone was obtained on crystallization from ethanol–water; 188–190° dec.

Anal. Calcd. for $C_{19}H_{24}N_4O_3$: C, 64.02; H, 6.79; N, 15.72. Found: C, 64.27; H, 6.82; N, 15.61.

5-*S*-Ethyl-5-thio-L-arabinose Diethyl Dithioacetal

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Treatment of tetra-*O*-acetyl-α-L-arabinopyranose (I) with ethanethiol in the presence of boron trifluoride resulted, after saponification, in crystalline 5-*S*-ethyl-5-thio-L-arabinose diethyl dithioacetal (IV), whose structure was established by hydrogenolysis with Raney nickel followed by oxidative degradation of the sirupy pentanetriol obtained.

It has been reported by Wolfrom and Thompson[2] that the treatment of hexa-*O*-acetyl-D-*gluco*-heptulose with ethanethiol in the presence of zinc chloride and Drierite[3] results in the replacement of two acetoxy groups with thioethyl groups. It was demonstrated that only one thioethyl function occupied a glycosidic position. No attempt was made to locate the second thioethyl moiety. It was later demonstrated by Lemieux[4] that penta-*O*-acetyl-β-D-glucopyranose reacted with ethanethiol under these conditions to yield, after deacetylation, 2-*S*-ethyl-2-thio-D-glucose(mannose) diethyl dithioacetal. This latter observation led to the conjecture that these reaction conditions might have value in the synthesis of 2-deoxy sugar precursors.

Since tetra-*O*-acetyl-α-L-arabinopyranose (I) has the same stereochemistry on carbon atoms C-1–C-3 as penta-*O*-acetyl-β-D-glucopyranose, reactions

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[2] M. L. Wolfrom and A. Thompson, *J. Am. Chem. Soc.*, **56**, 1804 (1934).

[3] Anhydrous calcium sulfate, a product of the W. A. Hammond Drierite Co., Xenia, Ohio.

[4] R. U. Lemieux, *Can. J. Chem.*, **29**, 1079 (1951).