THE SYNTHESIS OF 3-HEXULOSES

PART II. DERIVATIVES OF 1-DEOXY-L-*arabo*-3-HEXULOSE (SYN. 6-DEOXY-L-*lyxo*-4-HEXULOSE)

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ABSTRACT

Oxidation of 1,3:2,5-di-*O*-methylene-L-rhamnitol yielded 2,5:4,6-di-*O*-methylene-1-deoxy-L-*arabo*-3-hexulose, which was characterized as its 2,5-dichlorophenylhydrazone and by reduction to derivatives of L-rhamnitol and of 6-deoxy-L-talitol. Oxidation of 2,5-*O*-methylene-L-rhamnitol 1-benzoate yielded a syrupy 3,4-diketose which was characterized as the crystalline quinoxaline derivative. Attempts to convert 1,2:4,5-di-*O*-isopropylidene-D-mannitol 6-benzoate to a ketose were unsuccessful.

INTRODUCTION

The chemistry of the 3-ketose sugars has attracted attention during recent years because of their possible formation as intermediates in the breakdown of sugars (1); because a 3-pentulose derivative is postulated as an intermediate in the fixation of carbon dioxide during photosynthesis (2); and because of their potential value as intermediates in the synthesis of branched-chain sugars (3) and amino sugars (4). The first 3-hexulose was prepared by oxidation of L-fucitol with *Acetobacter suboxydans* to yield 1-deoxy-D-*xylo*-3-hexulose (Richtmyer *et al.* (5)). The first chemical synthesis of a 3-hexulose, from L-ascorbic acid, was described in Part I of this series (6). Oxidation of sugar alcohols to 3-hexuloses has been achieved by Sugihara and Yuen (7), who oxidized an isopropylidenated D-mannitol to a D-*lyxo*-3-hexulose derivative, and by Yuen and Sugihara (8), who oxidized a substituted D,L-galactitol and isolated from the product a crystalline *xylo*-3-hexulose. Stoodley (9) oxidized ribitol with mercuric acetate and obtained *erythro*-3-pentulose. A crystalline 3-heptulose was prepared by Schaeffer (10), who oxidized a branched-chain octose with periodate. The present work describes the preparation of 1-deoxy-L-*arabo*-3-hexulose derivatives from L-rhamnitol. This ketose is valuable as a possible intermediate in the preparation of L-streptose and other branched-chain sugars (11).

L-Rhamnitol condenses with formaldehyde in the presence of an acid catalyst to yield 1,3:2,5-di-*O*-methylene-L-rhamnitol (I) (12). This compound possesses a hydroxyl grouping on C_4 which is readily oxidized by chromium trioxide in glacial acetic acid – benzene (13) mixture to yield the crystalline ketose derivative 2,5:4,6-di-*O*-methylene-1-deoxy-L-*arabo*-3-hexulose (II), which gave a crystalline 2,5-dichlorophenylhydrazone. The ketose was readily reduced by sodium borohydride to yield the original di-*O*-methylene derivative and 1,3:2,5-di-*O*-methylene-6-deoxy-L-talitol. The latter material was produced in 55% yield when the reduction was carried out in absolute methanol solution (14) by addition of a methanolic sodium borohydride solution stabilized by sodium methoxide. The identification of the 6-deoxy-L-talitol was confirmed by its rate of movement on paper chromatographs and by comparing the retention time of the derived acetate with that of an authentic specimen on gas–liquid chromatograms (15).

Acetolysis of 1,3:2,5-di-*O*-methylene-L-rhamnitol followed by saponification of the product yielded 2,5-*O*-methylene-L-rhamnitol (12), which formed a 1-benzoate derivative. This compound, which possesses hydroxyl groups on C_3 and C_4, is readily oxidized

to a syrupy α-diketo compound (III) which with *O*-phenylenediamine yielded a quinoxaline compound (IV). Attempts to convert the α-diketo derivative to a streptosonic acid (11) analogue by a benzilic acid type rearrangement did not lead to the isolation of any identifiable products but tests indicated an α-hydroxycarboxylic acid was present.

It is likely that the hydroxyl group on C_4 of di-*O*-methylene-L-rhamnitol is oxidized easily because it is present in a relatively strain-free seven-membered ring in which the hydroxyl group is readily accessible. The oxidation of the axial 3-hydroxyl group in 2,4-*O*-methylene-xylitol 1,5-dibenzoates has been successfully achieved by Sera (16)but the oxidation of the equatorial 3-hydroxyl group on the corresponding ribitol derivative is difficult (unpublished results). It was considered likely that an isolated exocylic hydroxyl group would be more easily oxidized. To test this hypothesis 1,2:4,5-di-*O*-isopropylidene-D-mannitol 6-benzoate (17, 18) was prepared and submitted to oxidation. Unfortunately, no 3-hexulose derivative could be isolated from this reaction, perhaps because of the benzoate group on C_6 with which the hydroxyl group on C_3 may form a hydrogen bond. The 1,2:4,5-di-*O*-isopropylidene-D-mannitol gave a crystalline dibenzoate which on hydrolysis yielded the 1,4-di-*O*-benzoyl D-mannitol. This material was oxidized by periodate to a 2,5-di-*O*-benzoyl D-arabinose which is a potentially useful intermediate in the synthesis of disaccharides.

EXPERIMENTAL

All evaporations were carried out under reduced pressure and below 50°. Optical rotations were measured at 22±2°. Qualitative chromatography was carried out using the descending method (19) on Whatman No. 1 filter paper in the following solvents system (v/v): (A) butan-1-ol/ethanol/water, 3:1:1; (B) butan-1-ol/pyridine/water, 10:3:3; (C) ethyl acetate/acetic acid/formic acid/water, 18:3:1:4.

Ketoses were detected on paper chromatograms by the orcinol – trichloroacetic acid spray reagent (20) or with the *p*-anisidine hydrochloride spray reagent (21). Non-reducing compounds were detected by either the alkaline silver nitrate spray reagent (22) or by the ceric spray reagent (23). Rates of movement are quoted relative to L-rhamnose (R_{Rh}). Infrared spectra were measured using a Perkin–Elmer model 21 spectrophotometer or a Beckman IR-5B machine, as a 6% (w/v) chloroform solution or as a dispersion (0.8%) in a potassium bromide pellet. Ultraviolet spectra were measured using a Beckman DK-1 recording spectrometer.

2,5:4,6-Di-O-methylene-1-deoxy-L-arabo-3-hexulose (Cf. Ref. 13)

To a solution of 1,3:2,5-di-*O*-methylene-L-rhamnitol (12) (8.42 g) in benzene (160 ml) was added a hot solution of chromium trioxide (5.0 g, 1.1 mole equiv) in glacial acetic acid (440 ml) and water (4.44 ml). The mixture was heated at 85° for 40 minutes under reflux. The resultant solution was evaporated to a dark green syrup, which was dissolved in chloroform (200 ml). The solution was extracted with portions of cold *N* potassium carbonate solution until no further color was removed (1800 ml). Each extract was counterextracted with chloroform and the chloroform extracts were combined, washed with water, and dried (Na_2SO_4). Evaporation of the chloroform solution yielded the ketose (II) (5.64 g, 67%), which after recrystallization from ethanol had m.p. 151–152° and $[\alpha]_D$ +3.3° (*c*, 1.0, $CHCl_3$). The infrared spectrum showed a strong C=O stretching band at 1720 (approx.) cm^{-1}. The ketose gave a weak reaction with *p*-anisidine hydrochloride spray but a strong response to the alkaline silver nitrate spray. It gave a positive test for a ketose, a positive Molisch test, and reduced cold Fehling's solution. It had R_{Rh} 2.0 in solvent A and showed an absorption in the ultraviolet in aqueous solution at 297 mμ. Analysis: Calc. for $C_8H_{12}O_6$: C, 51.1%; H, 6.4%. Found: C, 50.9%; H, 6.45%.

When the ketose (0.225 g) was heated with 2,5-dichlorophenylhydrazine (0.23 g) in methanol (10 ml) a pale yellow crystalline hydrazone was produced. This, after three recrystallizations from ethyl acetate – chloroform, had m.p. 221° and $[\alpha]_D$ −154° (*c*, 1.0 in $CHCl_3$). Analysis: Calc. for $C_{14}H_{16}O_4Cl_2N_2$: C, 48.4%; H, 4.65%; Cl, 20.4%; N, 8.1%. Found: C, 48.2%; H, 4.7%; Cl, 20.7%; N, 8.1%.

Reduction of the Ketose

Reduction of the ketose with sodium borohydride yielded a mixture of the 1,3:2,5-di-*O*-methylene derivatives of L-rhamnitol and of L-talitol, the relative proportions of which were determined by the reaction conditions. Experimental details of a typical reduction are given below.

The ketose (II) (0.05 g) in 50% methanol (10 ml) was reduced by the dropwise addition at 0° of a sodium borohydride solution in 50% methanol (0.19 g, 10 ml). After 13 hours acetone was added to destroy excess borohydride, and sodium ions were removed from solution (IR-120 H resin). The acidic reaction mixture

was evaporated to dryness and boric acid was removed by distillation of methanol from the residues. The solid was then hydrolyzed by hot *N* hydrochloric acid (10 ml) and the cooled solution was deionized (Duolite A-4 OH) and concentrated to a syrup, which was acetylated (pyridine, acetic anhydride, 1 ml of each). The acetylated product was analyzed by gas–liquid chromatography. It contained L-rhamnitol and 6-deoxy-L-talitol acetates in the approximate ratio of 2 to 1. When the reaction was repeated, but substituting 50% ethanol for 50% methanol, the ratio of L-rhamnitol to 6-deoxy-L-talitol was 85:15.

When the reduction was carried out in absolute methanol plus sodium methoxide a much greater proportion of the 6-deoxy-L-talitol derivative was produced which could be isolated in a crystalline form. A typical experiment is given below.

1,3:2,5-Di-O-methylene-6-deoxy-L-talitol

2,5:4,6-Di-*O*-methylene-1-deoxy-L-*arabo*-3-hexulose (II) (0.87 g) in absolute methanol (15 ml) was reduced at 0° by the addition of sodium borohydride (0.9 g) in sodium methoxide solution (6 ml, 0.33 *N*); after 19 hours the product was isolated as described above. The crystals were recrystallized from acetone–petrol (b.p. 35–60°) and were obtained in 53% yield (0.46 g). The product had m.p. 122°, depressed to 96–97° on admixture with the L-rhamnitol derivative, and $[\alpha]_D$ +78° (*c*, 0.86 in $CHCl_3$). The infrared spectra of the L-rhamnitol and 6-deoxy-L-talitol derivative were different. Analysis: Calc. for $C_8H_{14}O_5$: C, 50.5%; H, 7.4%. Found: C, 50.5%; H, 7.4%. On hydrolysis (*N* HCl) the 2,5:4,6-di-*O*-methylene-6-deoxy-L-talitol yielded the syrupy sugar which was not separable from authentic material on paper chromatograms and the acetate was indistinguishable from an authentic specimen in the gas–liquid chromatographic apparatus.

1-Deoxy-L-arabo-*3-hexulose*

Attempts to prepare the sugar from the dimethylene compound either by acidic hydrolysis or by acetolysis were unsuccessful. In a typical experiment the di-*O*-methylene ketose (0.1 g) was hydrolyzed with *N* hydrochloric acid (20 ml) for 1 hour at 100°. Chromatographic analysis of the product showed the presence of seven components of R_{Rh} 0.33, 0.78, 1.02, 1.2, 1.95, 2.15, and 2.58. All except the component at R_{Rh} 1.02 gave a yellow color with the *p*-anisidine hydrochloride reagent. No crystalline derivative could be isolated.

Acetolysis Experiments

To the ketose derivative (II) (2 g) in 5 ml of a mixture of acetic acid (7.5 ml) and acetic anhydride (17.5 ml) was added 5.5 ml of an ice-cold acetolyzing mixture composed of sulphuric acid (1 ml), acetic anhydride (35 ml) and acetic acid (15 ml). The ketose derivative (II) dissolved at once and the solution gradually developed a violet color. After 1 hour it was poured onto ice and the mixture became green in color. The product was isolated by chloroform extraction in the usual way. Concentration of the chloroform extract yielded a syrup which did not crystallize. Two components were detected chromatographically (solvent A) with R_{Rh} 1.6 (positive test with alkaline silver nitrate) and R_{Rh} 1.78 (positive test with *p*-anisidine hydrochloride spray). Catalytic saponification (Zemplen) yielded a syrupy mixture which contained a major component at R_{Rh} 2.32 (solvent A).

2,5-O-Methylene-L-rhamnitol 1-Benzoate

To 2,5-*O*-methylene-L-rhamnitol (12) (4.4 g) in dry pyridine (20 ml) at 0° was added benzoyl chloride (3.15 ml, 1.1 mole equiv) dropwise during 5 minutes. After 20 hours at 21° the solution was poured onto ice (35 g). The product was extracted with chloroform in the usual way. Evaporation of the solvent left a crystalline residue which was recrystallized from acetone–petrol (b.p. 36–60°). Yield 4.4 g of m.p. 102° and $[\alpha]_D$ +69° (*c*, 1.0 in $CHCl_3$). Analysis: Calc. for $C_{14}H_{18}O_6$: C, 59.6%; H, 6.4%. Found: C, 59.3%; H, 6.3%.

Oxidation of 2,5-O-Methylene-L-rhamnitol 1-Benzoate to 2,5-O-Methylene-6-deoxy-L-threo-3,4-hexulodiose 1-Benzoate

The benzoate (0.86 g) in a mixture of benzene (15 ml), acetic acid (61 ml), and water (0.61 ml) was oxidized with chromium trioxide (0.67 g, 2.2 mole equiv). The mixture was heated at 80° for 35 minutes and the product (III, 0.39 g) was isolated as a yellow syrup by the procedure described above. Infrared examination of the syrup showed the absence of OH groups and a slight shift in the wavelength of the C=O stretching hand.

Characterization of the Oxidation Product

The syrupy diketose (0.1 g) was dissolved in ethanol (3 ml) and the solution was added to a solution of *O*-phenylenediamine (0.1 g) in ethanol (3 ml). The mixture was heated at 75° for 20 minutes and cooled. The resulting buff-colored crystals were collected and recrystallized from ethanol. The small needle-like crystals (50 mg) had m.p. 149°. Analysis: Calc. for $C_{20}H_{18}O_4N_2$: C, 68.6%; H, 5.2%; N, 8.0%. Found: C, 68.4%; H, 5.1%; N, 8.3%. The syrupy diketo compound (III, 0.804 g) was mixed with water (10 ml) and sodium hydroxide (4 ml, *N*); to aid solution methanol (7 ml) was added. After 2¼ hours the solution had become deep orange in color. After a further 5 minutes at 80° the cooled solution was extracted with chloroform to remove methyl benzoate. The residual aqueous layer was deionized (Amberlite IR-120 H) and the lemon yellow effluent was evaporated to yield a crystalline solid, identified as benzoic acid, m.p. 120°. The residual syrup gave tests for an α-hydroxy acid ($FeCl_3$) and showed absorption in the infrared

characteristic of a hydroxy carboxylic acid. Attempts to prepare a crystalline methyl ester by refluxing the syrup with methanolic hydrogen chloride were unsuccessful.

Derivatives of 1,2:4,5-Di-O-isopropylidene-D-mannitol

2,3:5,6-Di-*O*-isopropylidene-D-mannose was synthesized by the method of Van Grunenberg *et al.* (24). The product (5 g) was reduced by adding its solution in aqueous methanol to an ice-cold, stirred solution of sodium borohydride (5 g) in water (150 ml). (Note: If the order of addition is reversed very poor yields are obtained.) After 24 hours the solution gave a negative Molisch test for hexoses and excess of borohydride was destroyed by the addition of acetone (150 ml). The solution was evaporated and the residue was extracted with ether. The product was recrystallized with difficulty from ether–petrol. It had m.p. 50° (literature 52° (17)) and was obtained in a yield of 3.5 g. When the reduction was made with lithium aluminum hydride a similar yield was obtained.

1-O-Benzoyl 2,3:5,6-Di-O-isopropylidene-D-mannitol

A solution of 1,2:4,5-di-*O*-isopropylidene-D-mannitol (2.3 g) in dry pyridine (15 ml) was cooled at 0° and to it benzoyl chloride (1.1 ml) was added dropwise and with stirring and cooling during 15 minutes. After 24 hours at 20° the mixture was poured onto ice and the solution was extracted with ether. The extracts were washed successively with *N* hydrochloric acid, sodium bicarbonate solution, and water and then dried (Na_2SO_4). Evaporation of the ether left a syrup which rapidly crystallized. The product (2.03 g) was crystallized from ethanol and had m.p. 109°, $[\alpha]_D$ +6° (*c*, 2.5 $CHCl_3$). Analysis: Calc. for $C_{19}H_{26}O_7$: C, 62.3%; H, 7.15%. Found: C, 62.2%; H, 6.8%.

1-O-Benzoyl D-Mannitol

The 1-*O*-benzoyl 2,3:5,6-di-*O*-isopropylidene-D-mannitol (6.5 g) was dissolved in 30% acetic acid (10 ml) and the solution was heated at 86° for 15 minutes. Evaporation of the solution yielded crystalline 1-*O*-benzoyl D-mannitol (0.221 g) of m.p. 178°. Analysis: Calc. for $C_{13}H_{18}O_7$: C, 54.5%; H, 6.3%. Found: C, 54.15%; H, 6.3%. On prolonged oxidation this product consumed 5.15 mole of periodate and produced 1.05 mole of formaldehyde and 3.4 mole of formic acid per mole. Theory requires the formation of 1 mole of formaldehyde and 3 moles of formic acid per mole. The high results are due to overoxidation.

1,4-Di-O-benzoyl 2,3:5,6-Di-O-isopropylidene-D-mannitol

To dry 1,2:4,5-di-*O*-isopropylidene-D-mannitol (2 g) dissolved in dry pyridine (20 ml) was added benzoyl chloride (6 ml) with stirring at 0° during 40 minutes. The product was isolated in the usual way by extraction with ether. Evaporation of the ether yielded the 1,4-di-*O*-benzoyl derivative (3.01 g) of m.p. 136° and $[\alpha]_D$ −34° (*c*, 2.5 $CHCl_3$) after recrystallization from ethanol. Analysis: Calc. for $C_{26}H_{30}O_8$: C, 66.4%; H, 6.4%. Found: C, 66.1%; H, 6.4%.

1,4-Di-O-benzoyl D-Mannitol

Acetic acid (40%, 10 ml) was added to 1,4-di-*O*-benzoyl 2,3:5,6-di-*O*-isopropylidene-D-mannitol (1.0 g) and the mixture was heated at 85° for 30 minutes. Because the compound had not all dissolved 50% acetic acid (10 ml) was added and the solution was heated for a further 30 minutes. The solution was cooled, unchanged material (0.179 g) was collected by filtration, and the filtrate was evaporated to an oil which solidified. It had m.p. 111° and $[\alpha]_D$ −12° (*c*, 1.0 acetone) and was difficult to recrystallize. Analysis: Calc. for $C_{20}H_{22}O_8$: C, 61.5%; H, 5.7%. Found: C, 61.2%; H, 5.8%.

Periodate Oxidation

The product gave the following yields of formaldehyde (A) uptake of periodate (B) in moles per mole at the times indicated. (A): 0.94 (0.17 hr); 0.98 (0.67 hr); 0.98 (2.67 hr); and 0.98 (20.17 hr). (B): 0.91 (0.27 hr); 1.33 (1.15 hr); 1.39 (2.8 hr); 1.47 (8.5 hr); and 1.75 (22.5 hr). Attempts to oxidize 2,3:5,6-di-*O*-isopropylidene-D-mannitol 1-benzoate with chromium trioxide in pyridine or in glacial acetic acid led to recovery of starting material.

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