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THE REACTION OF UNSATURATED CARBOHYDRATES WITH CARBON MONOXIDE AND HYDROGEN

IV. STRUCTURE AND STEREOCHEMISTRY OF ANHYDRODEOXYHEPTITOLS FROM 3,4,6-TRI-*O*-ACETYL-D-GALACTAL

ALEX ROSENTHAL AND DEREK ABSON
Department of Chemistry, University of British Columbia, Vancouver, British Columbia

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ABSTRACT

3,4,6-Tri-*O*-acetyl-D-galactal reacted with carbon monoxide and hydrogen in the presence of dicobalt octacarbonyl to yield 2,6-anhydro-3-deoxy-D-*galacto*-heptitol (I) and 2,6-anhydro-3-deoxy-D-*talo*-heptitol (II). The stereochemistry of (I) and (II) has been established by correlation with 2,6-anhydro-3-deoxy-D-*gluco*-heptitol (VI) of known configuration. Evidence that both (I) and (II) are formed by the addition of a hydroxmethyl group to C-1 of the glycal is also furnished by the proton n.m.r. spectra of the normal and deuterated anhydrodeoxyheptitols.

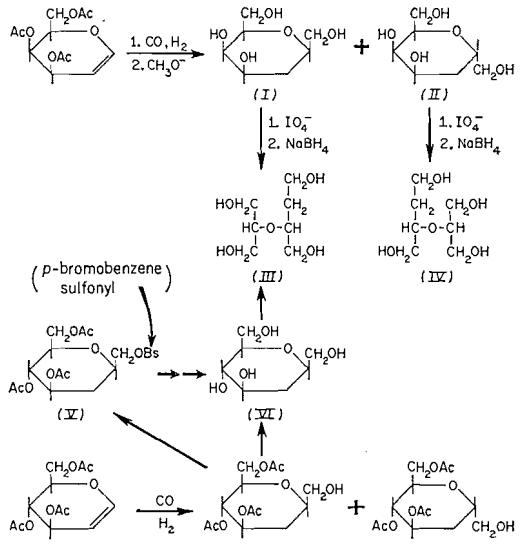
Part I of this series (1) described the action of carbon monoxide and hydrogen on 3,4,6-tri-*O*-acetyl-D-galactal, and presented evidence for the formation of an anhydrodeoxyheptitol of unknown stereochemistry. It has since been found that 3,4,6-tri-*O*-acetyl-D-galactal reacts under oxo conditions in a manner entirely analogous to other glycals investigated (2, 3) to yield as the major products a pair of isomeric anhydrodeoxyheptitols (I) and (II), formed by the addition of a hydroxymethyl group to C-1 of the unsaturated carbohydrate. The stereochemistry of (I) and (II) has been elucidated by an analysis of their proton n.m.r. spectra and by correlation with 2,6-anhydro-3-deoxy-D-*gluco*-heptitol (VI), whose structure has been proved by crystallographic X-ray analysis (4).

3,4,6-Tri-*O*-acetyl-D-galactal (5) was reacted in a high-pressure apparatus with carbon monoxide and hydrogen in the presence of dicobalt octacarbonyl, under conditions similar to those described previously (1). The reaction product was separated from the catalyst by chromatography on a Florisil column, and deacetylated with methanolic sodium methoxide. The two major reaction products (I) and (II), after separation by preparative paper chromatography, were obtained in approximately equal amounts.

DISCUSSION

Both (I) and (II) consumed 1 molar equivalent of periodate (0.95 and 0.98 respectively) as measured by the spectrophotometric method of Dixon and Lipkin (6). Fraction (II) reacted with acetone in the presence of sulfuric acid to form a monoisopropylidene derivative (VII), which on treatment with *p*-toluenesulfonyl chloride in pyridine gave a compound (VIII) containing two tosyloxy groups. The latter compound on heating with sodium iodide in acetone solution liberated 2 equivalents of sodium *p*-toluenesulfonate. Thus it is highly likely that (II) contains two primary hydroxyl groups and two adjacent *cis* secondary hydroxyl groups. Compound (I) was characterized as the tetra-*O*-(*p*-nitrobenzoyl) derivative.

Evidence that both (I) and (II) have unbranched carbon skeletons was furnished by their proton nuclear magnetic resonance (n.m.r.) spectra, measured in D_2O solution (Fig. 1*a* and *c*). These both show a group of signals at lower field (3.3–4.3 p.p.m.) with total area corresponding to 8 hydrogens, and a further group at higher field (1.3–2.3 p.p.m.), area = 2 hydrogens. The higher field signals can clearly be assigned to hydrogens attached



to C-3 of the anhydrodeoxyheptitols, this being the only carbon atom which is not directly linked to oxygen, and the fact that two such hydrogens are present in both (I) and (II) must mean that the two compounds differ only in the configuration of the hydroxymethyl group about C-2. This tentative assignment was then rigorously established by classical chemical methods in the following way. Oxidative cleavage of (I) and (II) with periodic acid followed by sodium borohydride reduction of the resulting dialdehydes gave a pair of enantiomeric tetrol ethers (III) and (IV). Each had only one asymmetric center, and the enantiomers had similar infrared spectra, and equal and opposite specific rotations. Treatment of (III) and (IV) with *p*-nitrobenzoyl chloride in pyridine afforded the enantiomeric tetra-*O*-(*p*-nitrobenzoyl) derivatives, which had identical infrared spectra and melting points and differed only in the sign of rotation.

The configuration of C-2 of both epimeric 2,6-anhydro-3-deoxyheptitols was readily established by application of proton n.m.r. spectroscopy, as previously described (2), to the 3-deoxy-3-deuterioanhydroheptitols (IX) and (X) which were produced when 3,4,6-tri-*O*-acetyl-D-galactal was reacted with carbon monoxide and deuterium. Thus, as shown in Fig. 1*b*, the narrow quartet structure (width about 17 c.p.s.) of the signal of intensity 1 at around $\delta = 1.7$ requires the C-3 proton to be in an equatorial orientation and coupled with the C-2 and C-4 axial hydrogens. On the other hand, as depicted in Fig. 1*d*, the corresponding wider multiplet of signals (width about 35 c.p.s.) of intensity 1 at the field ($\delta = 1.9$) suggests the C-3 proton of compound (X) to be in an axial orientation and coupled with the C-4 axial and C-2 equatorial hydrogens. Therefore, compounds (IX) and (X) are 2,6-anhydro-3-deoxy-D-*galacto*-heptitol-1,1,3-$^2H_3$ and 2,6-anhydro-3-deoxy-D-*talo*-heptitol-1,1,3-$^2H_3$, respectively.

Unequivocal confirmation of the C-2 configuration of the anhydrodeoxyheptitols (I) and (II) was provided by correlating (I) and (II) with 2,6-anhydro-3-deoxy-D-*gluco*-heptitol (VI). The latter compound had been produced by application of the oxo reaction to 3,4,6-tri-*O*-acetyl-D-glucal (4). The absolute configuration of the 1-*O*-(*p*-bromobenzenesulfonyl) derivative (V) had been previously proved by X-ray analysis (4), and (V) has been converted by standard procedures into (VI). The latter compound on periodate oxidation followed by sodium borohydride reduction of the dialdehyde gave a tetrol ether

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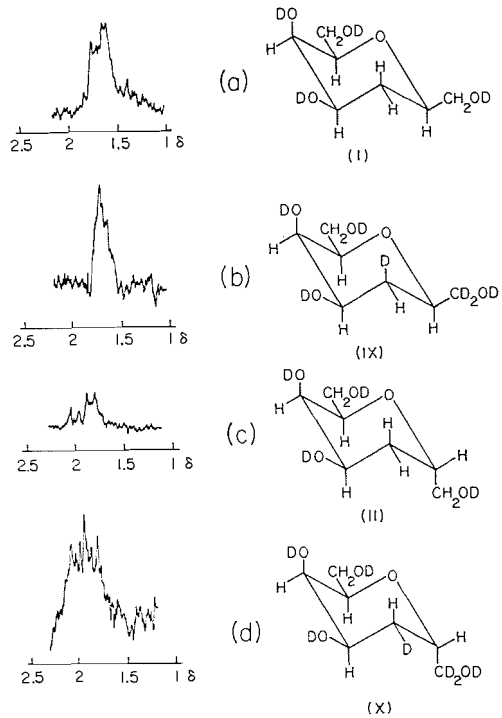

FIG. 1. Proton n.m.r. spectra in D_2O solution at 60 mc with chemical shifts given in p.p.m. from tetramethylsilane as zero; (*a*) 2,6-anhydro-3-deoxy-D-*galacto*-heptitol (I); (*b*) 2,6-anhydro-3-deoxy-D-*galacto*-heptitol-1,1,3-$^2H_3$ (*cis*) (IX); (*c*) 2,6-anhydro-3-deoxy-D-*talo*-heptitol (II); (*d*) 2,6-anhydro-3-deoxy-D-*talo*-heptitol-1,1,3-$^2H_3$ (*cis*) (X). (Only signals of protons attached to C-3 are shown.)

having an infrared spectrum and specific rotation similar to the dextrorotatory tetrol ether (III) derived from the anhydrodeoxyhexitol (1), and formed a tetra-*O*-(*p*-nitrobenzoyl) derivative identical with that obtained from (III) on the basis of melting point, mixed melting point, infrared spectrum, and specific rotation. Therefore (I), having the same configuration at C-2 as 2,6-anhydro-3-deoxy-D-*gluco*-heptitol, is 2,6-anhydro-3-deoxy-D-*galacto*-heptitol, and (II), the C-2 isomer of (I), is 2,6-anhydro-3-deoxy-D-*talo*-heptitol.

EXPERIMENTAL

General Considerations

Conditions for chromatographic separations and measurement of n.m.r. and infrared spectra have been described previously (2).

Preparation of *p*-nitrobenzoyl derivatives was carried out by a procedure similar to that of Gorin (7).

Microanalyses were by Mrs. Aldridge of this department and by Dr. A. Bernhardt, Mülheim (Ruhr), West Germany.

*Reaction of 3,4,6-Tri-O-acetyl-*D*-galactal with Carbon Monoxide and Hydrogen to Yield 2,6-Anhydro-3-deoxy-*D*-galacto-heptitol (I) and 2,6-Anhydro-3-deoxy-*D*-talo-heptitol (II)*

A solution of 3,4,6-tri-*O*-acetyl-D-galactal (15 g) and dicobalt octacarbonyl (3.5 g) in dry purified benzene (50 ml) was shaken with carbon monoxide (1 300 p.s.i.) and hydrogen (1 900 p.s.i.) in a high-pressure autoclave at a temperature of 130–135° for approximately 2 h. The resulting solution was transferred to a column (14 × 8 cm diameter) of Florisil and the catalyst was eluted with 30–60° petroleum ether. Elution with benzene–ethanol (9:1, v/v) and evaporation of solvent then gave 13.5 g of syrupy product. Deacetylation with 0.1 *N* sodium methoxide in methanol at room temperature for 18 h and removal of solvent gave a water-soluble product which, after deionization with Amberlite IR 120 (H^+) resin and freeze drying, afforded a partially crystalline mixture of (I) and (II) in approximately equal amounts, together with traces of sugars. Fractionation of the mixture of anhydrodeoxyheptitols was carried out by preparative paper chromatography. From an amount of 0.43 g of crude mixture, 0.16 g (37%) of fraction I and 0.14 g (33%) of fraction II were isolated.

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Characterization of Fractions (I) and (II)

*Fraction (I) (2,6-anhydro-3-deoxy-*D*-galacto-heptitol)* was crystallized from methanol – isopropyl ether; m.p. 158–159°; $[\alpha]_D^{27}$ +24° (*c*, 0.8 in water);* R_F = 0.24.

Anal. Calcd. for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.50; H, 8.07.

*2,6-Anhydro-3-deoxy-1,4,5,7-tetra-O-(p-nitrobenzoyl)-*D*-galacto-heptitol*

Fraction (I) (35 mg) was treated with *p*-nitrobenzoyl chloride in pyridine to yield a tetra-*O*-(*p*-nitrobenzoyl) derivative (95 mg, 72%), which was recrystallized from ethyl acetate – petroleum ether (30–60°); m.p. 210–211°; $[\alpha]_D^{23}$ −12° (*c*, 2.0 in chloroform).

Anal. Calcd. for $C_{35}H_{26}O_{17}N_4$: C, 54.28; H, 3.38; N, 7.23. Found: C, 54.61; H, 3.50; N, 7.47.

*Fraction (II) (2,6-anhydro-3-deoxy-*D*-talo-heptitol)* was crystallized from methanol – isopropyl ether; m.p. 168°; $[\alpha]_D^{27}$ +68° (*c*, 1.1 in water); R_F = 0.21.

Anal. Calcd. for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 46.94; H, 8.22.

*2,6-Anhydro-3-deoxy-4,5-O-isopropylidene-*D*-talo-heptitol (VII)*

Fraction (II) (55 mg) in dry, purified acetone (2 ml) containing 4% H_2SO_4 was stirred at room temperature for 20 h. Neutralization with sodium hydroxide solution, filtration, and evaporation of solvent gave an oil, which was extracted with boiling carbon tetrachloride to yield the mono-*O*-isopropylidene derivative (23 mg). Further treatment of the carbon tetrachloride insoluble residue with acidified acetone gave an additional amount (21 mg) of product (66% overall yield). The combined extracts were recrystallized from carbon tetrachloride; m.p. 104–105°; $[\alpha]_D^{21}$ +12° (*c*, 1.6 in chloroform).

Anal. Calcd. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.82; H, 7.97.

*2,6-Anhydro-3-deoxy-4,5-O-isopropylidene-1,7-di-O-tosyl-*D*-talo-heptitol (VIII)*

To a solution of (VII) (33 mg) in dry pyridine (1.0 ml) was added *p*-toluenesulfonyl chloride (66 mg). After standing for 18 h at room temperature the solution was stirred with water (0.1 ml). More water was added until the solution became turbid, and on standing, crystals (50 mg, 63%) of the di-*O*-tosyl derivative formed. The product was recrystallized from methanol; m.p. 135°; $[\alpha]_D^{23}$ −42° (*c*, 1.7 in chloroform).

Anal. Calcd. for $C_{24}H_{30}O_9S_2$: C, 54.78; H, 5.74. Found: C, 55.08; H, 6.01.

When a solution of the di-*O*-tosyl derivative (VIII) (8.4 mg) and sodium iodide (25 mg) in acetone (0.4 ml) was heated in a sealed tube at 118° for 26 h sodium *p*-toluenesulfonate (6.4 mg) was precipitated in an amount equivalent to the replacement of two tosyloxy groups by iodine. When the reaction was carried out at 100° for 30 min the amount of sodium *p*-toluenesulfonate isolated was approximately equivalent to the replacement of only one tosyloxy group.

Structure and Stereochemistry of Fractions (I) and (II)

*2-Deoxy-3-O-(1,3-dihydroxy-2-propyl)-*L*-glycero-tetritol (III) from 2,6-Anhydro-3-deoxy-*D*-gluco-heptitol (VI)*

Oxidation of (VI) with 0.1 *M* periodic acid followed by reduction of the resulting dialdehyde with sodium borohydride in water, according to the procedure described previously (2), gave the tetrol ether (III), $[\alpha]_D^{22}$ +26° (*c*, 2.9 in water), which formed a tetra-*O*-(*p*-nitrobenzoyl) derivative; m.p. 151–152°; $[\alpha]_D^{21}$ +22° (*c*, 1.2 in chloroform).

Periodate oxidation and sodium borohydride reduction of (I) under similar conditions gave the tetrol ether (III); $[\alpha]_D^{25}$ +21° (*c*, 3.7 in water). This formed a tetra-*O*-(*p*-nitrobenzoyl) derivative which was recrystallized from ethyl acetate; m.p. 150–151°, undepressed on admixture with the corresponding derivative of the tetrol ether derived from (VI); $[\alpha]_D^{24}$ +23° (*c*, 0.9 in chloroform).

Anal. Calcd. for $C_{35}H_{28}O_{17}N_4$: C, 54.13; H, 3.63; N, 7.21. Found: C, 54.46; H, 3.55; N, 7.29.

In a similar manner (II) gave the tetrol ether (IV) (2-deoxy-3-*O*-(1,3-dihydroxy-2-propyl)-D-*glycero*-tetritol), $[\alpha]_D^{25}$ −23° (*c*, 3.2 in water), which formed a tetra-*O*-(*p*-nitrobenzoyl) derivative; m.p. 150–151°; $[\alpha]_D^{24}$ −23° (*c*, 1.1 in chloroform).

Anal. Calcd. for $C_{35}H_{28}O_{17}N_4$: C, 54.13; H, 3.63. Found: C, 54.55; H, 3.71.

The infrared spectra of the tetra-*O*-(*p*-nitrobenzoyl) derivatives of the tetrol ethers (III) and (IV) were identical.

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3,4,6-Tri-*O*-acetyl-D-galactal was reacted with carbon monoxide and deuterium at 130°, under similar conditions to those used in the preparation of the normal anhydrodeoxyheptitols, to yield the above-mentioned deuterated heptitols (IX) and (X). The configuration of C-2 of both heptitols was determined by proton n.m.r. analysis (see Discussion).

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**It is now thought that the compound previously reported as having $[\alpha]_D$ +38° (1) was not pure.*

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The sample of the tetra-*O*-(*p*-nitrobenzoyl) derivative of the tetrol ether derived from (VI) was prepared by Mr. H. J. Koch.

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