THE REACTION OF UNSATURATED CARBOHYDRATES WITH CARBON MONOXIDE AND HYDROGEN

II. STRUCTURE AND STEREOCHEMISTRY OF THE ANHYDRODEOXYHEXITOLS FROM 3,4-DI-O-ACETYL-D-XYLAL

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ABSTRACT

3,4-Di-O-acetyl-D-xylal reacted with carbon monoxide and hydrogen in the presence of dicobalt octacarbonyl to yield 1,5-anhydro-4-deoxy-D-arabino-hexitol (I) and 1,5-anhydro-4-deoxy-D-arabino-hexitol (I) and 1,5-anhydro-4-deoxy-L-xylo-hexitol (II). The stereochemistry at C-5 of the hexitols was elucidated by correlation with the triol ether (VI) obtained by sodium borohydride reduction of the periodate oxidation product of 1,4-anhydro-5-deoxy-D-arabino-hexitol (VII). Reaction of 3,4-di-O-acetyl-D-xylal with carbon monoxide and deuterium afforded 1,5-anhydro-4-deoxy-D-arabino-hexitol-4,6,6-H₃² (VIII) and 1,5-anhydro-4-deoxy-L-xylo-hexitol-4,6,6-H₃² (IX). Examination of the nuclear magnetic resonance (n.m.r.) spectra of the normal and deuterated anhydro-deoxyhexitols confirmed the structural assignments and showed that *cis*-addition to the double bond takes place to give (IX).



It has been reported previously (1, 2) that 3,4,6-tri-O-acetyl-D-galactal reacted with carbon monoxide and hydrogen under oxo conditions (3) to yield an anhydrodeoxy-heptitol of unknown stereochemistry. It has now been found that pentals react similarly to yield anhydrodeoxyhexitols in which a hydroxymethyl group has been added to C-1 of the pental. The present paper in the series deals with the oxo reaction of 3,4-di-O-acetyl-D-xylal and offers conclusive proof by chemical means of the stereochemistry of the hexitols obtained. In addition, the mechanism of the addition of carbon monoxide and hydrogen to the glycal has been determined by the use of tracer studies.

The 3,4-di-O-acetyl-D-xylal, prepared by a modification of the procedure of Helferich and co-workers (4), was reacted with a mixture of carbon monoxide and hydrogen at a

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pressure of about 4000 p.s.i. and at a temperature of about 130° in the presence of preformed dicobalt octacarbonyl as catalyst to yield a mixture of products. This was freed from catalyst by filtration through Florisil. After the solvent was removed, the mixture was deacetylated with sodium methoxide in methanol to yield the anhydrodeoxyhexitols (I) and (II). These were subsequently separated by paper chromatography.

The stereochemistry of C-5 of each of the hexitols (I) and (II) was resolved in the following way. Periodate oxidation of these hexitols yielded the dialdehydes (III) and (IV). Sodium borohydride reduction of these dialdehydes afforded the enantiomorphic triol ethers (V) and (VI), having similar infrared spectra and equal but opposite optical rotations. In addition, (V) and (VI) were converted into crystalline p-nitrobenzoates having similar infrared spectra and melting points. In connection with the problem of determining the structures of the p-nitrobenzoates of the triol ethers, it was noted that Gorin had previously reported (5) the preparation of a p-nitrobenzoate of a triol ether (V) or (VI). Direct comparison (m.p., mixed m.p., and infrared spectra) revealed that the tris-p-nitrobenzoate of Gorin's compound (III) was identical with the tris-p-nitrobenzoate of compound (V).

The configuration of C-3 of the triol ether (VI) was then correlated with that of C-4 of 1,4-anhydro-5-deoxy-D-arabino-hexitol (VII). The latter new compound was prepared by sodium borohydride reduction of the known 3,6-anhydro-2-deoxy-D-lyxo-hexose (6). Periodate oxidation of (VII) followed by sodium borohydride reduction of the dialdehyde yielded a triol ether having an optical rotation and infrared spectrum respectively similar to those of the triol ether (VI). Further confirmation of the identity of the two triol ethers was obtained by comparing the crystalline *p*-nitrobenzoates of each (same m.p., mixed m.p., and infrared spectra). Thus, the configuration of C-5 of the hexitol (II) is identical with that of C-4 of 1,4-anhydro-5-deoxy-D-arabino-hexitol, and compounds (I) and (II) are 1,5-anhydro-4-deoxy-D-arabino-hexitol and 1,5-anhydro-4-deoxy-L-xylo-hexitol, respectively.

In conjunction with the study of the structure of each of the hexitols (I) and (II) by classical chemical methods, a parallel investigation of their structures by use of proton n.m.r. has also been carried out. The interpretation of the n.m.r. spectra of (I) and (II) (shown in Fig. 1(A) and (B)) was greatly aided by the excellent n.m.r. analyses of the structures of chalcose (4.6-dideoxy-3-O-methyl-D-xylo-hexose) and of its methyl glycoside (7), and by comparison of the spectra of (I) and (II) with those of their deuterated analogues prepared by reacting 3,4-di-O-acetyl-p-xylal with carbon monoxide and deuterium. The n.m.r. spectra of the deuterated analogues (VIII) and (IX) are shown in Fig. 1(C) and 1(D). Based on the fact that the equatorial C-4 hydrogen of the methylene group of chalcose absorbed at around $\delta = 2.05$ and the axial C-4 hydrogen at around $\delta = 1.0$ to 1.58 (7), the signal at $\delta = 2.0$ in Fig. 1(D) might be attributed to the single equatorial hydrogen on C-4 of the deuterated compound (IX). In Fig. 1(B) both the equatorial and the axial C-4 hydrogen signals at $\delta = 2.0$ and 1.5, respectively, are clearly distinguishable. To account for the wide signal of the axial C-4 hydrogen (about 34 c.p.s.), it is suggested that the hydrogens on C-5 and on C-3 are axial. The three coupling constants of the axial C-4 hydrogen would therefore be $J_{4a,3a} J_{4a,5a}$, and $J_{4a,4e}$ since it would be coupled with the two neighboring hydrogens on C-3 and C-5 and to the equatorial hydrogen on C-4. The fact that the axial C-4 hydrogen of chalcose (7), which gave a series of peaks having a width of 34.5 c.p.s., is also coupled to axial hydrogens on C-5 and on C-3 supports the above postulation. The splitting of the equatorial hydrogen signal around $\delta = 2.0$ clearly

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FIG. 1. Proton n.m.r. spectra in D₂O solution at 60 mc with chemical shifts given in p.p.m. from tetramethylsilane as zero: (A) 1,5-anhydro-4-deoxy-D-arabino-hexitol; (B) 1,5-anhydro-4-deoxy-L-xylo-hexitol; (C) 1,5-anhydro-4-deoxy-D-arabino-hexitol-4,6,6-H₃²; (D) 1,5-anhydro-4-deoxy-L-xylo-hexitol-4,6,6-H₃²; (D) 1,5-anhydro-4-deoxy-L-xylo-hexitol-4,6,6-H₃; (D) 1,5-anhydro-4-deoxy-L-xylo-hexitol-4,6,6-H₃; (D)



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shows the large spin coupling to the geminal hydrogen ($J_{4a,4e}$ approximately 12.5 c.p.s.), and further small splittings by coupling to the adjacent axial hydrogens on C-3 and C-5. Therefore, the hydroxymethyl group in (II) must be in an equatorial position. It is apparent that analysis of the n.m.r. spectra 1B and 1D reveals the stereochemistry of

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Can. J. Chem. Downloaded from www.nrcresearchpress.com by 193.61.135.80 on 11/14/14 For personal use only. the hexitol (II) and of the deuterated analogue (IX). An important part of the evidence for axial deuterium in (IX) is the narrowness (~ 9 c.p.s.) of the signal at 2.0 p.p.m. (had the proton in (IX) been axial, the signal would have been wider (~ 20 c.p.s.) as well as being at higher field). It is also noteworthy that the deuterated analogue (IX) must have been formed by a *cis*-addition of the hydroxymethyl group and of the deuterium to the 1,2-unsaturated bond of 3,4-di-O-acetyl-p-xylal.

The n.m.r. spectra of the normal and deuterated hexitols (I) and (VIII) (Fig. 1(A) and 1(C)) do not reveal the stereochemistry of C-5 because of overlapping of the C-4 axial and equatorial hydrogen signals.

EXPERIMENTAL

General Considerations The solvent used for paper chromatographic separations was water-saturated 1-butanol containing 5% ethanol and 1% concentrated ammonium hydroxide. The hexitols were detected with ammoniacal silver nitrate (8) or with sodium metaperiodate - Schiff's reagent (9).

The oxo product, first freed from catalyst, was also separated into slightly impure fractions by chromatography on neutral alumina using benzene-methanol (98:2/v:v) as developer. Analysis of the productmixture was readily carried out using thin layer chromatography on alumina with benzene:methanol (96:4) as developer.

The Florisil was obtained from the Floridin Company, Tallahassee, Florida, United States.

The oxo product was dried by azeotroping with anhydrous benzene followed by methanol, and then deacetylated (10) with 0.1 N sodium methoxide in methanol (or in a 1:1 mixture of anhydrous chloroform – methanol) at about 5° for 1 day. Sodium ions were removed by stirring (or elution through a column) with Amberlite IR-120 (H^+) resin. Solutions were evaporated under reduced pressure.

The n.m.r. spectra were obtained in a Varian A-60 instrument using tetramethylsilane as the external standard (set at $\delta = 0$). The infrared analyses were done on a Perkin-Elmer spectrophotometer, Model 21, using a sodium chloride crystal. Microanalyses were done by Mrs. Aldridge of this department and by Dr. A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut für Kohlenforschung, Mülheim (Ruhr), West Germany.

Preparation of 3,4-Di-O-acetyl-D-xylal

The 3,4-di-O-acetyl-D-xylal was prepared according to a modification of the procedure of Helferich and co-workers (4). During the addition of the tri-O-acetyl- α -D-xylosyl bromide to the zinc – acetic acid mixture, the reactants were kept at -5 to -10° for 3 h. Prior to filtration, Celite was added to coagulate the zinc and hasten filtration. Pieces of solid carbon dioxide were added during the filtration process to keep the reaction mixture at -10° . It was imperative that the crude 3,4-di-O-acetyl-D-xylal be distilled immediately under reduced pressure to prevent undue decomposition of the product; yield about 60%. All operations in the preparation of 3,4-di-O-acetyl-D-xylal were carried out in the same day.

Reaction of 3,4-Di-O-acetyl-D-xylal with Carbon Monoxide and Hydrogen to Yield 1,5-Anhydro-4-deoxy-Darabino-hexitol (I) and 1,5-Anhydro-4-deoxy-L-xylo-hexitol (II)

To a mixture of 3,4-di-O-acetyl-D-xylal (5.6 g) in dry, purified benzene (25 ml) contained in a 300-ml shaker bomb was added preformed dicobalt octacarbonyl (1-2 g). After flushing the bomb with carbon monoxide, carbon monoxide (500 p.s.i.) and hydrogen (2500 p.s.i.) were added and the reactants heated with rocking at 125-130° for about 2 h. The reactants were then added to a column of Florisil (8×8 cm diam.) and after the solvent had passed through the dicobalt octacarbonyl was eluted with 30-60° petroleum ether. The product was then eluted with benzene-ethanol (10:1/v:v). Evaporation of the eluent under reduced pressure yielded 6.0 g of sirup. The product contained the anhydrohexitols and traces of sugars. When the same substrate was reacted under similar conditions except at a temperature of about 115° for 0.5 h, the product consisted of 50% unreacted 3,4-di-O-acetyl-D-xylal, about 20% of sugars, and about 30% of the same anhydrohexitols as obtained in the 130° experiment.

The oxo product was then deacetylated with sodium methoxide in methanol (10). Fractionation of the deacetylated product was carried out by preparative paper chromatography or by cellulose column chromatography; ratio of fraction (I) and (II) was about 1:1. When the deacetylated product contained appreciable quantities of sugars, better separation of the hexitols was obtained if the mixture was first treated with sodium borohydride in water to reduce the sugars.

Characterization of Fraction (I)

Fraction (I) (1,5-anhydro-4-deoxy-D-*arabino*-hexitol) was crystallized from methanol – isopropyl ether; m.p. 102°; $[\alpha]_D^{20} - 13^\circ$ (c, 6.3 in water); $R_F = 0.47$. Calc. for C₆H₁₂O₄: C, 48.64; H, 8.16. Found: C, 48.35; H, 8.10.

Preparation of 1,5-Anhydro-4-deoxy-2,3,6-tri-O-p-nitrobenzoyl-D-arabino-hexitol

1,5-Anhydro-4-deoxy-D-arabino-hexitol was converted into a tris-*p*-nitrobenzoate according to the procedure used by Gorin (5); m.p. 215°; $[\alpha]_{D^{20}} -50^{\circ}$ (c, 1.0 in chloroform). Calc. for C₂₇H₂₁O₁₃N₃: C, 54.60; H, 3.60. Found: C, 54.56; H, 3.86.

Characterization of Fraction (II)

Fraction (II) (1,5-anhydro-4-deoxy-L-xylo-hexitol) could not be crystallized; $[\alpha]_D^{20} - 44^\circ$ (c, 6.4 in water); $R_F = 0.41$. Calc. for C₆H₁₂O₄: C, 48.64; H, 8.16. Found: C, 48.36; H, 8.39.

Preparation of 2,3,6-Tri-O-acetyl-1,5-anhydro-4-deoxy-L-xylo-hexitol

The 1,5-anhydro-4-deoxy-L-xylo-hexitol (70 mg) was acetylated with acetic anhydride – pyridine to yield 109 mg of 2,3,6-tri-O-acetyl-1,5-anhydro-4-deoxy-L-xylo-hexitol. Recrystallization of the crude acetate from ether – petroleum ether (30–60°) afforded the pure acetate; m.p. 80–81°; $[\alpha]_{D^{22}} - 41°$ (c, 0.8 in chloroform). Calc. for C₁₂H₁₈O₇: C, 52.55; H, 6.62. Found: C, 52.82; H, 6.58.

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

Compound (I) was oxidized with 0.1 *M* periodic acid to yield the dialdehyde (III), which was reduced with sodium borohydride in water, according to the procedure of Gorin (5), to the triol ether (V); $[\alpha]_{D}^{23} - 19^{\circ}$ (c, 2.0 in water). The triol ether was *p*-nitrobenzoylated to afford a tris-*p*-nitrobenzoate, m.p. 102–103°; $[\alpha]_{D}^{22} - 28^{\circ}$ (c, 1.1 in chloroform). Calc. for $C_{27}H_{23}O_{13}N_{3}$: C, 54.30; H, 3.99. Found: C, 54.57; H, 3.95. The infrared spectra of the tris-*p*-nitrobenzoate of the triol ether (V) and of the tris-*p*-nitrobenzoate of the triol ether vanishing and the tris-*p*-nitrobenzoate of the triol ether (V) and of the tris-*p*-nitrobenzoate of the triol ether in the following part of the experimental) were identical.

In a similar way to that described above, compound (II) was oxidized with periodic acid and the dialdehyde (IV) then reduced with sodium borohydride to yield the triol ether (VI) as a sirup; $[\alpha]_{D}^{25} + 17^{\circ}$ (c, 1.7 in water). The triol ether (VI) was then *p*-nitrobenzoylated; m.p. 102–103°; $[\alpha]_{D}^{24} + 26^{\circ}$ (c, 1.4 in chloroform). Calc. for C₂₇H₂₅O₁₅N₃: C, 54.30; H, 3.99. Found: C, 54.63; H, 4.09. The mixed m.p. of this *p*-nitrobenzoate and the *p*-nitrobenzoate obtained from 1,4-anhydro-5-deoxy-D-arabino-hexitol was 100–102°. The infrared spectra of the two nitrobenzoates were similar.

Synthesis of 1,4-Anhydro-5-deoxy-D-arabino-hexitol (VII)

An amount of 95 mg of "3,6-anhydro-2-deoxy-D-galactose" (6) was reduced with sodium borohydride (50 mg) in water (1 ml) for 1 h. The product, 1,4-anhydro-5-deoxy-D-arabino-hexitol (86 mg) was a colorless oil; $[\alpha]_D^{25} + 21^\circ$ (c, 1.7 in ethanol).

Preparation of 1,4-Anhydro-5-deoxy-2,3,6-tri-O-p-nitrobenzoyl-D-arabino-hexitol

1,4-Anhydro-5-deoxy-D-arabino-hexitol was reacted with p-nitrobenzoyl chloride in the usual way to yield 1,4-anhydro-5-deoxy-2,3,6-tri-O-p-nitrobenzoyl-D-arabino-hexitol, m.p. $159-160^{\circ}$; $[\alpha]_{D}^{22} - 96^{\circ}$ (c, 0.7 in chloroform). Calc. for C₂₇H₂₁O₁₃N₃: C, 54.46; H, 3.56. Found: C, 54.61; H, 3.86.

Conversion of 1,4-Anhydro-5-deoxy-D-arabino-hexitol into 2-Deoxy-3-O-(2-hydroxyethyl)-L-glycero-tetritol (VI)

1,4-Anhydro-4-deoxy-D-arabino-hexitol (55 mg) was oxidized with 0.1 M periodic acid and the product then reduced with sodium borohydride; yield: 51 mg; $[\alpha]_D^{24} + 17^\circ$ (c, 2.0 in water). The infrared spectrum of this product was similar to those of the triol ethers (V) and (VI).

A 30-mg portion of the triol ether obtained from 1,4-anhydro-5-deoxy-D-arabino-hexitol was p-nitrobenzoylated in the usual way; m.p. 101–102°; $[\alpha]_{D}^{24}$ +27° (c, 1.1 in chloroform). Calc. for C₂₇H₂₅O₁₃N₃: C, 54.30; H, 3.99. Found: C, 54.61; H, 4.00.

Reaction of 3,4-Di-O-acetyl-D-xylal with Carbon Monoxide and Deuterium to Yield 1,5-Anhydro-4-deoxy-Darabino-hexitol-4,6,6-H₃²(cis) (VIII) and 1,5-Anhydro-4-deoxy-L-xylo-hexitol-4,6,6-H₃² (cis) (IX)

The 3,4-di-O-acetyl-D-xylal was reacted with carbon monoxide and deuterium at 130° under similar conditions to those described in the first experiment to yield the above-mentioned deuterated hexitols (VIII) and (IX). The stereochemistry of the deuterium atoms was determined by proton n.m.r. analysis (see Discussion).

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