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# HYDROGENOLYSIS OF CARBOHYDRATES

## IV. 1,2-*O*-*ISO*PROPYLIDENE-D-GLUCOFURANOSE[1]

P. A. J. GORIN AND A. S. PERLIN

ABSTRACT

1,2-*O*-*Iso*propylidene-D-glucofuranose was treated with hydrogen at 180° C. and 2900 p.s.i. using copper chromium oxide catalyst and dioxane as solvent. The major isolated products were a hexanediol (2.4%), a mixture of hexanetriols (6.5%), a hexanetetrol (4.3%), and an *iso*propylidene-aldohexose (4.2%) which differed from the starting material. The latter product yielded L-idose on hydrolysis, showing clearly that isomerization of carbon 5 of monoacetone-D-glucose occurs under the reaction conditions used.

The diol and the major components of the triol mixture were found to possess a 1,2-glycol group which was derived mainly from the 5,6-glycol group of the original monoacetone-D-glucose. Thus, hydrogenolysis of 1,2-*O*-*iso*propylidene-D-glucofuranose-1-$C^{14}$ afforded the 1,2-hexanediol and mixed triols containing only about 30% of the total specific activity in carbon 1. The tetrol was shown to be 1,2,5,6-hexanetetrol. The results suggest that the carbon–oxygen bonds at carbons 5 and 6 of *iso*propylidene-D-glucose are least prone to hydrogenolysis and that those at carbons 3 and 4 are most readily cleaved.

When methyl glycosides are subjected to hydrogenolysis in the presence of copper chromium oxide catalyst one of the major reactions involves reductive cleavage of the carbon–oxygen bond at the anomeric center with formation of an anhydro derivative (1, 2, 3). Thus methyl-$\beta$-L-arabopyranoside is attacked primarily at carbon–oxygen bonds 1, and 2 or 4, giving a mixture of 1,5-anhydro-2- and -4-deoxypentitols (*cis*- and *trans*-pyran-2,3-diols) (1). Likewise, methyl-$\alpha$-D-glucopyranoside yields mainly a mixture of 1,5-anhydrodeoxyhexitols (2, 3). Sugar derivatives other than glycosides are now being examined to evaluate the stability of various substituent groups to hydrogenolysis, one objective being the possible discovery of resistant-blocking groups or of substituents easily cleaved, which may facilitate the preparation of deoxy sugars. The present paper concerns the hydrogenolysis of one of these derivatives, 1,2-*O*-*iso*propylidene-D-glucofuranose.

Under reaction conditions slightly milder than used earlier for the methyl glycosides, i.e., at about 180° C., at hydrogen pressures of 2000–3000 p.s.i., and with dioxane as solvent, the *iso*propylidene group was found to be more stable than a glycosidic methoxyl group, over half of the starting material remaining unchanged; no reaction occurred at 150° C., and at 250° C. extensive hydrogenolysis was evident. Among the reaction products obtained at 180° C. a sugar other than D-glucose was detected after hydrolytic removal of the *iso*propylidene groups. This sugar was isolated in 4.2% yield by cellulose-column chromatography (4) as a levorotatory sirup ($[\alpha]_D$ $-10°$) which formed a crystalline 1-benzyl-1-phenylhydrazone. The rate of movement of the sugar on a paper chromatogram ($R_F$ = xylose) suggested that the compound might be deoxy-hexose. However, treatment of the sugar with 1.5 moles of lead tetraacetate in acetic acid and hydrolysis of the resulting formate esters gave two products which were indistinguishable from xylose and threose on a paper chromatogram. Since under the same conditions D-glucose gives D-arabinose and D-erythrose (5), it was evident that the configuration of the

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hydroxyl group at carbon 5 of the D-glucose had been altered during the hydrogenation reaction. The sugar was shown, in fact, to be L-idose, for on treatment with phenylhydrazine acetate it yielded L-idose phenylosazone (L-sorbosazone) and on reduction followed by acetylation it gave L-iditol hexaacetate (6).

The conversion of D-glucose into L-idose affords a clear demonstration of a sugar isomerization promoted by catalytic hydrogenation conditions. Taken together with the recent finding (3) that dihydro-D-altral is formed from methyl-$\alpha$-D-glucopyranoside and the observation (7) that under similar conditions D-xylose, D-ribose, and D- and L-lyxose are obtainable from methyl-$\beta$-L-arabopyranoside, the present results suggest that extensive isomerization may occur during hydrogenolysis reactions. Cyclic alcohols are known to isomerize in the presence of Raney nickel or platinum catalysts and hydrogen (8). It has been postulated that an intermediate ketone is formed in this reaction so that the over-all reaction represents a dehydrogenation followed by hydrogenation. A similar mechanism may be operative also in the current isomerizations of carbohydrates but, as yet, no evidence is forthcoming to support such a possibility. An apparent isomerization has recently been encountered in the catalytic hydrogenation of hexahydroxybenzene for preparation of inositols (9).

In addition to *iso*propylidene-L-idose, the hydrogenolysis of 1,2-*O*-*iso*propylidene-D-glucofuranose gave a mixture of hexanepolyols, comprising a diol, at least two triols, and a tetrol, in yields of 2.4%, 6.5%, and 4.3%, respectively, based on the weight of starting material. The tetrol, which was readily isolated from an aqueous solution after extraction of the other reaction products into chloroform, was crystalline and yielded a crystalline tetraacetate. When treated with periodate it consumed 2 moles of oxidant and liberated 2 moles of formaldehyde, but gave neither formic acid nor acetaldehyde. These properties served to characterize the tetrol as 1,2,5,6-hexanetetrol (3,4-dideoxyhexitol).

The diol and triol fractions, obtained from the chloroform extract, were separated by cellulose column chromatography. The diol, which yielded a crystalline bis-*p*-nitrobenzoate, was shown to be 1,2-hexanediol for it consumed 1 mole of periodate with production of 1 mole of formaldehyde. The sirupy triol fraction consumed almost 1 mole of oxidant and yielded close to 1 mole of formaldehyde, establishing the presence of a 1,2-diol group as a main structural feature of the triols present. Periodic acid oxidation of the triols followed by reduction with sodium borohydride (10) yielded a mixture of alcohols which could not be completely resolved into pure components via the derived *p*-nitrobenzoates. One apparently pure tris-*p*-nitrobenzoate was obtained in low yield on recrystallization from ethyl acetate. The resistance of its parent triol to periodate oxidation indicates either a 1,3,5- or a 1,3,6-hexanetriol structure, making this minor component the only hydrogenolysis product isolated which is not reconcilable with Adkins' $\beta$-hydrogenation rule (11). Because of the possibility that isomerization had occurred during formation of the various polyols, the configuration of the secondary hydroxyls cannot be assigned with certainty by reference to the parent compound, D-glucose.

The 1,2-glycol group of the diol and triols was derived principally from the 5,6-glycol group of the original D-glucose derivative. This was shown by hydrogenolysis of 1,2-*O*-*iso*propylidene-D-glucofuranose-1-$C^{14}$. The labelled diol and triols obtained from the latter compound were oxidized with periodate yielding formaldehyde (isolated as the dimedon derivative), which accounted for only 24% and 35%, respectively, of the

specific activity of the acetone-glucose-1-$C^{14}$. Further, when the diol was oxidized with the permanganate–periodate reagent (12), it yielded *n*-valeric acid possessing an activity which corresponded to 73% of that of the starting material; likewise, the mixture of pentanediols derived from the hexanetriol-$C^{14}$ fraction by sodium periodate oxidation followed by sodium borohydride reduction accounted for 70% of the total activity. About three-quarters of the 1,2-glycol groups of the diol and triol originate from carbons 5 and 6 of the D-glucose and the remainder from carbons 1 and 2, implying that at least two different mechanisms operate in the hydrogenolysis of the *iso*propylidene group, one involving cleavage of ketal carbon–oxygen bonds, the other, of alcohol or the hemiacetal carbon–oxygen bonds.

It appears unlikely that the polyols are formed as a result of hydrolysis of the *iso*-propylidene group (although the solvent was not rigorously dried, and water is a product of the reaction). This is suggested by hydrogenolysis control runs using hexitols (13), presumably the first products formed if the acetone group is hydrolyzed off, in which the variety of products was much greater than found in the present instance. The formation of these polyols is taken, rather, as an indication of the relative stability to hydrogenolysis of the various carbon–oxygen bonds in 1,2-*O*-*iso*propylidene-D-glucose. Accordingly, the bonds at carbons 3 and 4 are by far the least stable, while those at carbons 5 and 6 are most resistant to reductive cleavage. These relative stabilities may be altered substantially, however, by modification of the *iso*propylidene-D-glucose molecule. For example, the corresponding 3-*O*-methyl- and 6-deoxy-derivatives are unaffected by treatment under the same reaction conditions (13). Still other substituents at different positions may induce greater susceptibility to hydrogenolysis. The utilization of variations of this kind, it is anticipated, should extend the usefulness of catalytic hydrogenation in the synthesis of carbohydrate derivatives.

## EXPERIMENTAL

Paper chromatography was carried out on Whatman No. 1 filter paper using *n*-butanol–ethanol–water (40:11:19 v/v) as solvent. Spray reagents used were *p*-anisidine hydrochloride in butanol (14), aniline oxalate (15), and ammoniacal silver nitrate (16). Melting points are uncorrected. Evaporations were carried out under reduced pressure. Optical rotations were measured at 27° C.

Radioactive samples were combusted and the specific activity of the carbon dioxide liberated was measured by the procedure of Buchanan and Nakao (17).

### *Hydrogenolysis of 1,2-O-Isopropylidene-D-glucofuranose-1-$C^{14}$*

The *iso*propylidene-D-glucose-1-$C^{14}$ (22.5 g.; 6.84 mμc./mM.) in dioxane (400 ml.) was hydrogenated at 2000–2900 p.s.i. for 6 hours at 180° C. using copper chromium oxide (6.0 g.) as catalyst. Removal of the catalyst and solvent left a colorless sirup, an aqueous solution of which was continuously extracted with chloroform.

### *1,2,5,6-Hexanetetrol*

The aqueous solution which had been extracted with chloroform was evaporated, giving a sirup (2.0 g.) which crystallized from methanol–acetone. Two recrystallizations from the same solvent mixture gave a hexanetetrol (0.66 g.), m.p. 95°–97° C. and $[\alpha]_D$ 0° (*c*, 1.5, saturated borax) (1 dm. tube). Calculated for $C_6H_{14}O_4$: C, 47.98%; H, 9.40%. Found: C, 47.75%; H, 9.42%. The periodate equivalent, measured by the arsenite method (18), was 80 (calculated value, 75) and the formaldehyde equivalent, measured by the

chromotropic acid method (19), was 63 (calculated value, 75). No formic acid (20) or acetaldehyde (21) was formed.

Acetylated by the hot sodium acetate method the tetrol gave a tetraacetate which, after two recrystallizations from acetone – light petroleum (b.p. 60°–80° C.), had m.p. 76°–77° C. and $[\alpha]_D$ 0° (*c*, 5.5, $CHCl_3$) (1 dm. tube). Calculated for $C_{14}H_{22}O_8$: C, 52.82%; H, 6.97%. Found: C, 52.85%; H, 7.30%.

*1,2-Hexanediol*

The chloroform extract (above) was evaporated to a sirup, which was dissolved in hot ethyl acetate (100 ml.). On cooling, unchanged 1,2-*O-iso*propylidene-D-glucofuranose was deposited and the filtered mother liquor was evaporated to a sirup (6.2 g.). The latter was dissolved in 0.1 *N* sulphuric acid (50 cc.) and hydrolyzed at 100° C. for 1 hour. The acid was neutralized ($BaCO_3$), and the solution filtered and evaporated to give a sirup. Paper chromatographic examination indicated a mixture with $R_F$'s corresponding to glucose and a deoxy-hexose (*p*-anisidine hydrochloride spray) and also a triol together with smaller amounts of diol (ammoniacal silver nitrate spray).

The mixture was fractionated on a cellulose column. Benzene–ethanol–water (500:50:1 v/v) eluted the diol, which was obtained as a mobile sirup, $[\alpha]_D$ −12° (*c*, 2.0, saturated borax), distilling at 160°–170° C. (air bath) at 1 mm., and having a specific activity of 9.28 mμc./mM. (calc. 10.2 mμc./mM.). Yield 290 mg. Calculated for $C_6H_{14}O_2$: C, 60.98%; H, 11.94%. Found: C, 60.40%; H, 12.14%. It had a periodate equivalent of 124 and a formaldehyde equivalent of 104. Calculated periodate and formaldehyde equivalents, 118. The product had an infrared spectrum identical with that of an authentic specimen (22).

The diol (67 mg.) was converted to the bis-*p*-nitrobenzoate, which after two recrystallizations from ethanol had m.p. 91°–93° C. Yield 67 mg. Racemic 1,2-hexanediol bis-*p*-nitrobenzoate has m.p. 101.5°–102.5° C. (22); the lower melting point of the current material may be due to the presence of mixed D- and L-forms or of one isomer, the diol being optically active. Calculated for $C_{20}H_{20}O_8N_2$: C, 57.69%; H, 4.84%. Found: C, 57.40%; H, 4.79%.

The diol (59 mg.) was oxidized with periodic acid (0.21 g.) in water (10 ml.), and the solution was then distilled into a solution of dimedon (0.50 g.) in 50 ml. of 0.15 *M* phosphate buffer of pH 7.0. The formaldehyde dimedon which formed was filtered off and twice recrystallized from ethanol; yield 21 mg., m.p. 190°–191° C., specific activity 0.78 mμc./mM., corresponding to an activity of 13.3 mμc./mM. for C-1. Calculated for $C_{17}H_{24}O_4$: C, 69.83%; H, 8.27%. Found: C, 70.05%; H, 8.31%.

The diol (75 mg.) was oxidized for 4 hours with a solution (150 ml.) containing potassium permanganate (14 mg.), sodium periodate (580 mg.), and potassium carbonate (183 mg.) (12), excess reagent being destroyed with sodium bisulphite and 0.1 *N* sulphuric acid. The clear solution was extracted continuously with ether and the resulting extract was neutralized with dilute sodium hydroxide and then evaporated to dryness. The residue was dissolved in water (1 ml.), ethanol (10 ml.) added, followed by *p*-bromophenacyl bromide (180 mg.). After being refluxed for 1 hour, the solution was evaporated to dryness and the product was recrystallized three times from aqueous ethanol. The product had m.p. 71° C., undepressed on admixture with *n*-valeric acid *p*-bromophenacyl ester, and a specific activity of 3.13 mμc./mM. corresponding to an activity of 40.5 mμc./mM. for C-1. Calculated for $C_{13}H_{15}O_3Br$: Br, 26.7%. Found: Br, 26.2%.

*Hexanetriol Fraction*

The triol fraction (0.89 g.) was eluted from the cellulose column by *n*-butanol; it had $[\alpha]_D$ $-3°$ (*c*, 1.6, saturated borax) and a specific activity of 9.50 mμc./mM. (Calc. 10.2 mμc./mM.). Oxidation of the material with periodic acid indicated a periodate equivalent of 143 and a formaldehyde equivalent of 140.

The triol (224 mg.) was oxidized in water (10 ml.) containing periodic acid (500 mg.). After 15 minutes a slurry of barium carbonate was added to remove excess iodate and periodate and the solution was filtered. The filtrate was treated with sodium borohydride (200 mg.) and after 15 minutes the solution was acidified with dilute sulphuric acid, then continuously extracted with ether, and the extract was evaporated repeatedly with methanol to remove boric acid. A sirupy product (143 mg.) was obtained and a 55 mg. portion was converted to its *p*-nitrobenzoate by the same method as described previously. Two fractions were obtained after several fractional crystallizations from ethyl acetate and ethyl acetate – light petroleum (b.p. 50°–60° C.). The major portion (33 mg.) had m.p. 153°–156° C. (an authentic specimen of 1,5-pentanediol bis-*p*-nitrobenzoate prepared in the same way had m.p. 101°–103° C.) and an infrared spectrum similar to that of 1,5-pentanediol bis-*p*-nitrobenzoate. Calculated for $C_{19}H_{18}O_8N_2$: C, 56.71%; H, 4.51%. Found: C, 57.17%; H, 4.72%. The specific activity of the bis-*p*-nitrobenzoate was 2.11 mμc./mM. On the basis of the infrared spectrum and periodate oxidation data, the product possibly comprises a mixture of 1,5-pentanediol bis-*p*-nitrobenzoate and an impurity, thus indicating a 1,2,6-structure for the parent hexanetriol. The minor *p*-nitrobenzoate component (5 mg.) had m.p. 171°–173° C. and a tris-*p*-nitrobenzoate structure was indicated by the carbon and hydrogen microanalyses. Calculated for $C_{27}H_{23}O_{12}N_3$: C, 55.77%; H, 3.99%. Found: C, 55.49%; H, 3.93%.

L-*Idose*

Elution of the cellulose column with *n*-butanol one-quarter saturated with water gave a reducing sugar as a sirup (0.94 g.) with $[\alpha]_D$ $-10°$ (*c*, 0.8, water). The sugar was oxidized with lead tetraacetate in acetic acid (5). After 2, 5, 10, and 30 minutes 2.02, 2.08, 2.12, and 2.14 moles/mole of reagent were consumed respectively. Oxidation of the sugar with 1.5 moles/mole of reagent gave a mixture, which, after removal of inorganic material from the solution and hydrolysis of the resulting formate esters, was indistinguishable from xylose and threose on a paper chromatogram.

The sugar (0.35 g.) was heated for 4 hours at 100° C. in an aqueous solution (20 ml.) containing phenylhydrazine (0.89 ml.) and acetic acid (1 ml.). On cooling, yellow crystals were deposited and were filtered off and recrystallized twice from methanol–benzene. The product (0.16 g.) had m.p. 170°–172° C. and $[\alpha]_D$ $-13.8°$ (*c*, 1.0, pyridine–ethanol (1:1 v/v)) and was indistinguishable from L-sorbose phenylosazone (23) by its X-ray diffraction pattern and mixed melting point. Calculated for $C_{18}H_{22}O_4N_4$: C, 60.32%; H, 6.19%. Found: C, 60.51%; H, 6.09%.

The aldose (98 mg.) was refluxed for 15 minutes in a water (10 ml.) – ethanol (5 ml.) mixture containing 1-benzyl-1-phenylhydrazine hydrochloride (110 mg.). The solution was evaporated to a sirup which crystallized. Three recrystallizations from benzene – ethyl acetate afforded L-idose 1-benzyl-1-phenylhydrazone (104 mg.) having m.p. 113°–115° C. and $[\alpha]_D$ $-19°$ (*c*, 1.2, ethanol). Calculated for $C_{19}H_{24}O_5N_2$: C, 63.32%; H, 6.71%. Found: C, 62.94%; H, 6.79%.

The aldose (140 mg.) was dissolved in a solution of sodium borohydride (100 mg.) in water (10 ml.). After 3 hours excess reagent was destroyed with acetic acid and the

solution then treated with Amberlite IR-120. The solution was evaporated to dryness and excess boric acid was removed by repeated evaporations of the product in methanol; yield, 126 mg., of which 104 mg. was acetylated at 100° C. in a mixture of acetic anhydride (2 ml.) and sodium acetate (0.2 g.) for 1 hour. The acetate crystallized from ethanol, and recrystallization from the same solvent gave a product (95 mg.) having m.p. 123°–124° C. and $[\alpha]_D$ −23° (*c*, 1.1, chloroform). An X-ray diffraction pattern and mixed melting point showed that the compound was L-iditol hexaacetate (6). Calculated for $C_{18}H_{26}O_{12}$: C, 49.77%; H, 6.03%. Found: C, 50.01%; H, 5.99%.

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