[CONTRIBUTION FROM THE PRAIRIE REGIONAL LABORATORY, NATIONAL RESEARCH COUNCIL OF CANADA]

Hydrogenolysis of Methyl β-L-Arabopyranoside to 3,4-Dihydroxytetrahydro-2-pyrans[1]

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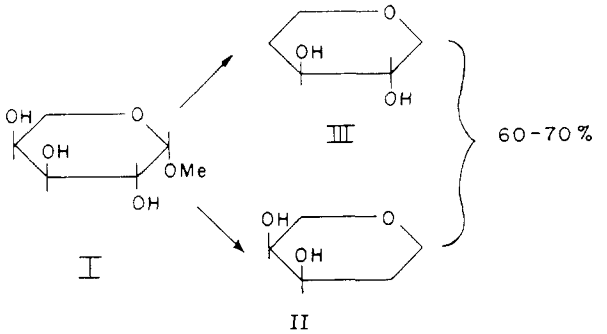
Methyl β-L-arabopyranoside was subjected to hydrogenolysis using a copper chromite catalyst and dioxane as solvent. Reductive cleavage of the Cl to CH_3O linkage was found to occur as well as reduction of one hydroxyl group, and a mixture of *cis*- and *trans*-3,4-dihydroxytetrahydro-2-pyran in a ratio of 2:3 was isolated in high yield. 5-Methoxy-1,2-, 2,3- and 3,4-pentanediol were formed as by-products.

The action of hydrogen upon reducing sugars, glycosides and polyols at high pressures and temperatures and in the presence of an activating catalyst has been the scope of a large number of investigations. Chief interest has been centered, however, on the hydrogenation of reducing sugars to sugar alcohols, which, for instance, has resulted in the conversion of sorbitol from a laboratory curiosity into a cheap industrial chemical. Aside from patents covering processes for the reductive cleavage of reducing sugars to glycerol, propylene and ethylene glycol, little attention has been given to the hydrogenolysis of carbohydrates and their derivatives. Zartman and Adkins' work[3] published 23 years ago, still supplies most of the information. This work and the results of other investigators[4] suggested that a carbohydrate in the first stage of the hydrogenolysis is transformed to linear and cyclic polyhydric alcohols with retention of the carbon skeleton and that the lower molecular weight glycols such as ethylene and propylene glycol are formed in the second stage of the reaction. It was hoped that milder conditions as well as shorter reaction times would give the polyhydric alcohols without further degradation of the carbon chain.

Methyl β-L-arabopyranoside was chosen as starting material because it is readily available[5] and from the work of Natta, *et al.*,[6] it was clear that the carbon skeleton of a pentose would be relatively stable to the hydrogenolysis conditions necessary to cleave carbon–oxygen bonds. The number of possible isomers resulting from such a carbon–oxygen bond cleavage was also expected to be smaller for a pentose than for a hexose. The glycoside was chosen to avoid immediate reduction of the hemiacetal group. For reasons of stability and to facilitate the determination of water and methanol after hydrogenolysis, dry dioxane was used as solvent. Temperature, pressure and reaction time were varied over a wide range, but it was found that below 200° and 100 atm. the reaction was very sluggish, and unchanged starting material was always present. At 240° and 250 atm. the hydrogen uptake was complete after 6 hr. and the isolated products, when subjected to the same hydrogenolysis conditions a second time, did not take up more hydrogen. Different types of copper chromite catalysts worked equally well and yielded the same products. However, the catalyst suffered decomposition if the glycoside sample had an appreciable reducing value with Somogyi reagent.[7] Recrystallization from methanol was generally necessary to yield a suitable starting material.

Isolation of the reaction products as described in the Experimental part showed that the path taken by the reaction under the above conditions was markedly different from that found by earlier investigators. No starting material was present; 62% of the glycosidic methoxyl group was recovered as methanol and the remaining 38% as methoxyl groups in the less volatile products; no methanol had been formed by hydrogenolysis of carbon–carbon bonds. The quantity of water formed in the reaction, 1.15 moles, corresponded to a loss of about one hydroxyl group for each glycoside molecule. Fractional distillation yielded only negligible amounts of material having a boiling range in the neighborhood of those of ethylene or propylene glycol, but the compounds did not consume any periodate. Almost all of the material distilled between 69–78° at 30 μ and no higher boiling residue could be observed, suggesting that in this main fraction the original carbon chain had been retained. The low methoxyl content of this fraction indicated that it was a mixture of methoxyl-containing and methoxyl-free compounds. Acid treatment followed by fractional distillation yielded 60–70% of a methoxyl-free diol whose boiling point, molecular formula and refractive index suggested a dihydroxytetrahydropyran. Preparation of derivatives and comparison with authentic samples[8] confirmed that the hydrogenolysis of methyl β-L-arabopyranoside (I) had yielded, with retention of the pyran ring



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[1] H. F. Bauer and D. E. Stuetz, Abstracts of Papers, 128th Meeting, American Chemical Society, Minneapolis, Minn., Sept. 11 to 16, 1955; issued as N.R.C. No. 4025.

[2] National Research Council of Canada Post Doctorate Fellow.

[3] W. H. Zartman and Homer Adkins, THIS JOURNAL, **55**, 4559 (1933).

[4] C. W. Lenth and R. N. Du Puis, *Ind. Eng. Chem.*, **37**, 152 (1945)

[5] B. Helferich and W. Schaefer, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 364.

[6] G. Natta, R. Rigamonti and E. Beati, *Ber.*, **76**, 641 (1943).

[7] M. Somogyi, *J. Biol. Chem.*, **160**, 61 (1945); N. Nelson, *ibid.*, **153**, 375 (1944).

[8] O. Heuberger and L. N. Owen, *J. Chem. Soc.*, 910 (1952).

and reductive cleavage of the Cl to OCH_3 group, a mixture of *cis*- and *trans*-3,4-dihydroxytetrahydro-2-pyran (II, III) in 60–70% yield.

The isomeric 3,4-dihydroxytetrahydro-2-pyrans used for comparison were prepared by hydroxylating 5,6-dihydro-2-pyran. The *trans* isomer III was obtained in good yield by hydroxylation with performic acid,[8] but *cis*-hydroxylation with permanganate was tedious and gave small yields. However, *cis*-hydroxylation with osmium tetroxide resulted in an almost quantitative yield of the pure diol II. The formation of both isomers would be expected to result from a competitive reductive removal of the hydroxyl group on either C2 or C4 of the arabinoside. This observation is in accordance with the rule established by Adkins,[9] which states that 1,3-glycols are most easily hydrogenolyzed and the resulting alcohols, once formed, as well as 1,2-glycols are stable under the same conditions. The ratio of the isomeric 3,4-dihydroxytetrahydro-2-pyrans was determined by two methods. The melting diagram was determined for the pure isomeric ditosyl derivatives and the melting behavior of the unknown mixture used to determine the *cis* to *trans* ratio. Secondly, the strong difference in the rate of oxidation by lead tetraacetate (Fig. 1) was used to support the figures obtained by the first method and the data were found to agree well. The difference in rates of lead tetraacetate oxidation also permitted the isolation of the pure *trans*-3,4-dihydroxytetrahydro-2-pyran from the isomer mixture.

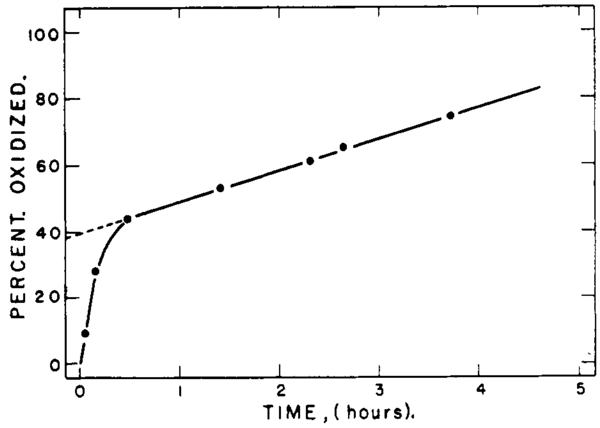

Fig. 1.—Rate of lead tetraacetate consumption by the mixture of the isomeric 3,4-dihydroxytetrahydro-2-pyrans at 25°.

In addition to the isomeric dihydroxytetrahydropyrans, methoxyl-containing material had formed during the hydrogenolysis. This methoxyl-rich fraction accounted for the remaining 35% of the hydrogenolysis products. Its high boiling point, methoxyl content and its consumption of periodate suggested that the compounds present had retained the five-carbon chain and the methoxyl group on the original C1 and possessed an average of one 1,2-glycol group per molecule. Since 1,3-glycols could be excluded on the basis of Adkins' rule, the hydroxyl groups were most likely present at the 1,2-, 2,3- or 3,4-positions of the 5-methoxypentanediols; it was also possible that 5-methoxy-1,4-pentanediol was present in trace amounts. The probable hydrogenolysis of the Cl-to-ring oxygen bond in competition with the Cl-to-methoxyl oxygen bond serves to explain the formation of the methoxy pentanediols. For further evidence and in order to determine the proportions of the single methoxy pentanediols, the mixture was oxidized with sodium periodate and the formaldehyde and acetaldehyde produced were determined. The aldehydes were then oxidized to the corresponding carboxylic acids, the acids were separated by chromatography and acetic and propionic acid were determined quantitatively. The data suggested that, besides the dihydroxytetrahydropyrans, about 8% of 5-methoxy-1,2-pentanediol, 20% of 5-methoxy-2,3-pentanediol and 13% of 5-methoxy-3,4-pentanediol had been formed during the hydrogenolysis of methyl β-L-arabopyranoside. It is noteworthy that, once ring fission has occurred,the primary hydroxyl group seems to be the one most easily removed.

Several problems that arose during this work remain unsolved. For instance, the dihydroxytetrahydropyrans isolated from the reaction mixtures were optically inactive, possibly through isomerization during the hydrogenolysis. Further, it cannot be concluded from the data whether cleavage of the ether linkage and hydrogenolysis of the hydroxyl groups are simultaneous or consecutive reactions.

Experimental

All melting points are corrected and were measured with a Leitz heating stage microscope. All infrared spectra were recorded with a Perkin–Elmer model 21 spectrometer equipped with a sodium chloride prism. Samples were mounted by the potassium bromide disk technique.[10]

Hydrogenolysis Procedure.—Equipment as described by Adkins,[9] dioxane purified and dried by distillation over sodium and copper chromite catalyst[9] were used in all experiments. Methyl β-L-arabopyranoside (m.p. 171.5°), 10.0 g., dissolved in 150 ml. of dioxane, was placed in the bomb, 2.0 g. of catalyst was added and the vessel was flushed with hydrogen. After raising the hydrogen pressure to 170 atm. the hydrogen supply was closed and the vessel was heated to 240° which resulted in an initial pressure increase to 240–260 atm. After 6 hr. reaction time the vessel was allowed to cool to room temperature and the catalyst was separated from the reaction mixture by pressure filtration through a filter covered with a layer of Celite. Most of the solvent was distilled using an efficient condenser and ice-cooled receiver. The remainder of the solvent was removed *in vacuo* and the sirup was dried for 2 hr. on an oil-pump. The resulting product, 7.55 g., was clear and colorless and showed the following constants: $n^{25}\text{D}$ 1.4659, $[\alpha]^{20}\text{D}$ +4.9° (*c* 4.45 in dioxane), OMe 7.1%. Paper chromatography showed that no starting material was present in the product.

If the hydrogen uptake had been slow and the catalyst had decomposed in part or completely during the reaction to the red inactive form, the reaction mixture was usually found to contain appreciable amounts of starting material. Small amounts of reducing compounds in the starting material, determinable with Somogyi reagent,[7] were found to be responsible for decomposition of the catalyst. The hydrogenolysis proceeded satisfactorily when the amount of reducing material had been lowered to 0.05% or less (expressed as free arabinose) by crystallization from methanol.

Determination of Water and Methanol.—Water and methanol were determined in the dioxane distilled from the hydrogenolysis mixture. The water, determined by titration with Karl Fischer reagent, amounted to 1.15 moles of water

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[9] Homer Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wisc., Fourth Printing.

[10] O. Schiedt and H. Reinwein, *Z. Naturforsch.*, **7б**, 270 (1952).

per mole of glycoside hydrogenolyzed. Methanol was determined by the procedure of Boss,[11] and 0.62 mole of methanol per mole of glycoside was detected.

cis- **and** ***trans*-3,4-Dihydroxytetrahydro-2-pyran (II, III).**—By fractional distillation with a small column the sirup, 7.55 g., obtained by hydrogenolysis of methyl β-L-arabopyranoside was divided into three fractions, the first one boiling between 38–39° and 30 μ pressure, 0.21 g., n^{20}D 1.4401, with a methoxyl content of 11.97%; the second one, between 65–67.5°, 0.17 g., n^{20}D 1.4602, with a methoxyl content of 15.75% and a third and main fraction, boiling at 69–78°, 6.18 g., n^{20}D 1.4802, with a methoxyl content of 6.06%. The third fraction, 2.0 g., was refluxed with 7% hydrochloric acid for 3 hr., the solution was deionized by passing it through a weakly basic resin (Amberlite IR4B) and concentrated *in vacuo* to yield, after distillation at 10 μ and a bath temperature of 90–100°, 1.75 g. of a colorless sirup (II, III) which contained no methoxyl groups and was optically inactive.

Anal. Calcd. for $C_5H_{10}O_3$: C, 50.83; H, 8.53. Found: C, 50.53; H, 8.62.

cis- **and** ***trans*-Di-*O*-*p*-toluenesulfonyl-3,4-dihydroxytetrahydro-2-pyran.**—The mixture of *cis-* and *trans*-3,4-dihydroxytetrahydro-2-pyran, 0.30 g., was dissolved in 5 ml. of dry pyridine and added to an ice-cooled solution of *p*-toluenesulfonyl chloride, 1.5 g., in 5 ml. of dry pyridine. The mixture was allowed to stand at room temperature for 18 hr. after which time the precipitate which formed on careful addition of ice to the pyridine solution was collected by centrifugation. One recrystallization from ethanol yielded 1.0 g. of a material, m.p. 124.5–149°.

Anal. Calcd. for $C_{19}H_{22}O_7S_2$: C, 53.50; H, 5.20. Found: C, 53.62; H, 5.16.

Ten fractional crystallizations from ethanol yielded as the more soluble compound *cis*-di-*O*-*p*-toluenesulfonyl-3,4-dihydroxytetrahydro-2-pyran, m.p. 127–129°, which did not depress the melting point of an authentic sample[8]; the infrared absorption spectrum was identical with that of the known specimen. The less soluble compound was identified as *trans*-di-*O*-*p*-toluenesulfonyl-3,4-dihydroxytetrahydro-2-pyran, by its melting point 158–162°, undepressed by admixture with an authentic sample,[8] and by comparison of its infrared absorption spectrum with that of the known compound.

***cis*-3,4-Dihydroxytetrahydro-2-pyran from 5,6-Dihydro-2-pyran.**—A solution of 5,6-dihydro-2-pyran,[12] 168 mg., and dry pyridine, 320 mg., in 3 ml. of dry ether was added to a solution of 508 mg. of osmium tetroxide in 8 ml. of dry ether. The brown crystalline precipitate, 822 mg., was filtered off after 1 hr. at room temperature and was dissolved in 5 ml. of chloroform. A solution of 224 mg. of potassium hydroxide and 728 mg. of mannitol in 15 ml. of water was added to the chloroform solution and the mixture shaken till the chloroform layer was colorless. Continuous extraction of the aqueous layer with chloroform for 36 hr. and distillation of the sirup after removal of the chloroform yielded 176 mg. of *cis*-3,4-dihydroxytetrahydro-2-pyran. Tosylation of the diol as described above yielded, after one crystallization from ethanol, pure *cis*-di-*O*-*p*-toluenesulfonyl-3,4-dihydroxytetrahydro-2-pyran, m.p. 133–134°; Heuberger and Owen[8] reported m.p. 131–132°.

Anal. Calcd. for $C_{19}H_{22}O_7S_2$: C, 53.50; H, 5.20. Found: C, 53.39; H, 5.20.

Lead Tetraacetate Oxidation of the Mixture of *cis-* and *trans*-3,4-Dihydroxytetrahydro-2-pyrans.—The diol mixture, 25.40 mg., was dissolved in 5 ml. of glacial acetic acid. Two milliliters of this solution was added at time zero to 10 ml. of a solution of 90 mg. of lead tetraacetate in 45 ml. of glacial acetic acid. A reaction blank was started at the same time. One-milliliter aliquots were withdrawn at chosen intervals and the lead tetraacetate consumed was measured.[13] The results are recorded in Fig. 1.

For the isolation of pure *trans*-3,4-dihydroxytetrahydro-2-pyran, the mixture of isomers, 0.472 g., was oxidized with 1.777 g. of lead tetraacetate in 77 ml. of glacial acetic acid for 50 minutes. After that period the reaction was stopped by addition of 7.2 ml. of a 10% oxalic acid dihydrate solution in acetic acid and the lead oxalate was removed by filtration. The acetic acid was evaporated, the remaining sirup was dissolved in water, the aqueous solution was extracted three times with ether and the water removed *in vacuo*. Distillation of the sirup at 10 μ and a bath temperature of 90–100° yielded 0.22 g. of *trans*-3,4-dihydroxytetrahydro-2-pyran whose ditosylate, prepared as described above, after one crystallization from ethanol, melted at 161.5–163.0°.

Periodate Oxidation of the Crude Hydrogenolysis Mixture. Determination of the Aldehydes.—Periodate uptake of the crude sirup obtained on hydrogenolysis of methyl β-L-arabopyranoside was measured[14] and the reaction was found to be completed after 50 minutes at room temperature. The sirup, 2.47 g., consumed 19.5 mmoles of periodate with formation of 1.62 mmoles of formaldehyde[15] and 3.97 mmoles of acetaldehyde.[16] Methoxyacetaldehyde and propionaldehyde did not interfere in the acetaldehyde determination. The methoxyacetaldehyde was generated by periodate oxidation of 1-methoxyglycerol.

Periodate Oxidation of the Crude Hydrogenolysis Mixture. Oxidation of the Aldehydes and Determination of the Acids.—A solution of the crude sirup, 2.47 g., in 10 ml. of water was added to a solution of 6.42 g. of sodium metaperiodate in 100 ml. of water. After 50 minutes at room temperature the hydrogen-ion concentration of the solution was adjusted to *p*H 7 by addition of sodium carbonate. A solution of potassium permanganate, 3.16 g., and potassium bicarbonate, 3.36 g., in 100 ml. of water was then added dropwise during 60 minutes to the stirred periodate oxidation mixture and the temperature was kept below 30°. The permanganate deficiency is compensated by an excess of periodate.[17] After removal of the manganese dioxide by pressure filtration through a bed of Celite and washing of the filter cake with hot water, the combined filtrates were evaporated *in vacuo*. A cooled, saturated solution of sodium bisulfite, 10 ml., and 150 ml. of ether were added to the residue, and the aqueous layer was acidified to about *p*H 3 by careful addition of 10% sulfuric acid. The iodine formed was thus instantaneously reduced. After 6 hr. of continuous extraction with ether, the extract was dried with sodium sulfate, filtered and the acids were precipitated as their ammonium salts by bubbling dry ammonia through the ether solution. The salts were collected by filtration, the acids liberated with 2 *N* sulfuric acid and continuously extracted for 12 hr. with di-*n*-butyl ether from their aqueous solution. After drying about 75% of the dibutyl ether was distilled and the distillate containing the volatile acids was made up to 50 ml. with dibutyl ether in a volumetric flask. Titration of an aliquot of this solution with *N* sodium hydroxide indicated the presence of 5.79 meq. of acid in the 50 ml. of dibutyl ether. The dibutyl ether solution, 0.6 ml., was added to the top of a column made from 3.0 g. of silicic acid and the chromatogram was developed with di-*n*-butyl ether which had been equilibrated with water and methyl Cellosolve.[18] The position of the bands was identical with the position of the acetic and propionic acid bands of a test run on the same column. The 50 ml. of dibutyl ether original solution was found to contain 3.58 mmoles of acetic acid and 2.43 mmoles of propionic acid. The acids were further identified as their benzylthiuronium salts[19] by mixed melting points with authentic specimen.

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(11) R. N. Boss, *Anal. Chem.*, **20**, 964 (1948).

(12) Sigurd Olsen, *Acta Chem. Scand.*, **5**, 1168 (1951).

(13) R. Criegee, *Ber.*, **64**, 260 (1931).

(14) E. L. Jackson, *Organic Reactions*, **2**, 357 (1944).

(15) M. Lambert and A. C. Neish, *Can. J. Research*, **28B**, 83 (1950).

(16) P. Desnuelle and M. Naudet, *Bull. soc. chim.*, **12**, 871 (1945).

(17) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

(18) V. Zbinovsky, *Anal. Chem.*, **27**, 764 (1955).

(19) J. J. Donleavy, THIS JOURNAL, **58**, 1004 (1936).