(239): C, 50.2; H, 3.76; N, 5.85; CH_3CO-, 36.0. Found: C, 50.1; H, 3.72; N, 5.81; CH_3CO-, 36.9. Propionylation of the nitroinositols gave in a similar manner, **the dipropionyl-5-nitroresorcinol**, m. p. 115°, from 70% ethanol. *Anal.* Calcd. for $C_{12}H_{13}O_6N$ (267): C, 53.9; H, 4.86; N, 5.24. Found: C, 53.7; H, 4.90; N, 5.20. On hydrolysis of the two above substances with 50% alcoholic 0.5 *N* potassium hydroxide, the known 5-nitro resorcinol, m. p. 157–159°, was isolated in the usual manner and gave, on methylation, the known 3,5-methoxynitrobenzene, m. p. 89.5°.

On dissolving 0.5 g. of pentaacetyl-nitrodesoxyinositol III, as described under (11), in 5 cc. of hot pyridine, it was transformed almost quantitatively into diacetyl-5-nitroresorcinol.

Acknowledgment.—The authors wish to express their gratitude to the Nutrition Foundation, Inc., for the support of this work.

Summary

The cyclization of 6-nitro-6-desoxy-D-glucose and 6-nitro-6-desoxy-L-idose to a mixture of nitrodesoxyinositols is described. Starting from either of the nitrodesoxy hexoses, the same mixture of nitrodesoxyinositols was obtained. A reaction mechanism for the cyclization is proposed.

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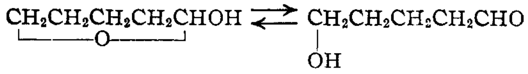
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Hydroxylation of 2,3-Dihydropyran and the Application of Desoxyaldopentoses in the Browning Reaction[1]

BY CHARLES D. HURD AND CHARLES D. KELSO

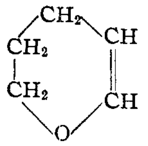
The reaction of reducing sugars with amino acids, leading to the evolution of carbon dioxide and the development of an intense brown color was studied by Maillard.[2] This general subject of the "browning reaction" has been one of considerable interest in recent years, since it seems to be intimately associated with the color changes observed in many foodstuffs during processing or storage.

To extend our knowledge of the fundamentals of this reaction, two model aldoses were synthesized for test purposes. One was tetrahydropyran-2-ol, made by hydration of dihydropyran (I), following the directions[3] of Schniepp and Geller. This is stated to exist in equilibrium (95:5) with 5-hydroxypentanal

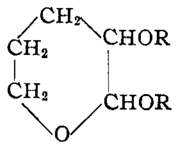


$$\underbrace{CH_2CH_2CH_2CH_2CHOH}_{O} \rightleftarrows CH_2\underset{OH}{CH_2}CH_2CH_2CHO$$

This material may be regarded as a 2,3,4-tridesoxyaldopentose. The substance is similar to

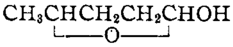


I



II (R = H)
III (R = Ac)

4-hydroxypentanal, $CH_2CHOHCH_2CH_2CHO$, which was synthesized by Helferich[4] and shown to exist primarily in the cyclic modification



$$\underbrace{CH_3CHCH_2CH_2CHOH}_{O}$$

The second model sugar was tetrahydropyran-2,3-diol (II). This substance is new. It may be regarded as a 3,4-didesoxyaldopentose, thereby providing an aldose molecule with inert beta and gamma positions. In solution the cyclic alpha and beta forms of II should be in equilibrium with the open-chain structure, $HOCH_2CH_2CH_2CHOH$-CHO, just as the alpha and beta forms of a glycose are in equilibrium with the glyconaldehyde.

Synthesis of II was readily accomplished from I by use of hydrogen peroxide in *t*-butyl alcohol using osmium tetroxide as catalyst. This follows the type of synthesis devised by Milas and coworkers[5] for such syntheses as these: isobutylene glycol from isobutylene, ethylene glycol from ethylene, racemic acid from fumaric acid, glycerol from allyl alcohol, glycolaldehyde from vinyl acetate or vinyl ether, etc. Glycals, according to Hockett and co-workers,[6] behave analogously.

Although hydroxylation of double bonds by hydrogen peroxide ordinarily produces *cis* glycols,[5] it seems reasonable to think that both *cis* and *trans* hydroxyls are present in II because of the equilibration reaction mentioned above. Besides II, the reaction product also contained a considerable C_{10}-fraction revealing both non-reducing and reducing isomers. The non-reducing compound was shown to be 3,4-didesoxyaldopentosyl 3,4-didesoxyaldopentoside (IV). Products II and IV accounted for half of the I used. An additional 10–15% was accounted for by reducing disaccharide and 6% by a fraction, some of which is reducing, which may contain trisaccharide.

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[1] The subject matter of this paper has been undertaken in coöperation with the Committee on Food Research of the Quartermaster Food and Container Institute for the Armed Forces under a contract with Northwestern University. The opinions and conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or endorsement of the War Department.

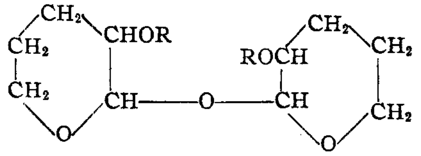
[2] Maillard, *Compt. rend.*, **154**, 66 (1912); *Ann. chim.*, [9] **5**, 258 (1916).

[3] Schniepp and Geller, THIS JOURNAL, **68**, 1646 (1946).

[4] Helferich, *Ber.*, **52**, 1128, 1802 (1919).

[5] Milas and Sussman, THIS JOURNAL, **58**, 1302 (1936); **59**, 2345 (1937); Milas, Sussman and Mason, *ibid.*, **61**, 1844 (1939); Milas and Maloney, *ibid.*, **62**, 1842 (1940).

[6] Hockett, Sapp and Millman, *ibid.*, **63**, 2051 (1941); Hockett and Millman, *ibid.*, **63**, 2587 (1941).



IV (R = H)
V (R = Ac)

Structures II and IV are apparent from the following evidence: (1) correct carbon and hydrogen analyses; (2) II reduces Benedict solution, while IV is non-reducing; (3) IV is quantitatively converted to II by dilute hydrochloric acid at 70°. This is proven by the identity of the 2,4-dinitrophenylosazones formed from II and from the hydrolysis product of IV and by the fact that the hydrolysis product reduces Benedict solution; (4) II and IV yield bis-3,5-dinitrobenzoic esters on treatment with 3,5-dinitrobenzoyl chloride in pyridine. Similarly, on acetylation, II gives rise to 2,3-diacetoxytetrahydropyran (III) and IV yields 2-acetyl-3,4-didesoxyaldopentosyl 2-acetyl-3,4-didesoxyaldopentoside (V). II has been obtained only as a thick oil, whereas IV is crystalline (m. p. 142.5–143°).

The crystalline nature of IV suggests that it may be a D,L pair or one *meso* form. Out of four possible D,L pairs and two *meso* forms for IV, only one D,L pair and one *meso* form would be expected if IV was related only to the *cis* forms of II.

In the browning studies it was demonstrated that 2,3,4-tridesoxyaldopentose or tetrahydropyran-2-ol underwent only a slight discoloration when heated with glycine solution, whereas 3,4-didesoxyaldopentose browned more readily even than D-glucose itself. Evidently, therefore, a δ-hydroxy aldehyde does not undergo the browning reaction, whereas an α,δ-dihydroxy aldehyde does do so. It seems that the α-hydroxy group is required for this reaction. Results are shown in Table I. In these experiments the solutions in question were heated at 90–95° under reflux condensers for four hours. Carbon dioxide was evolved from solutions 1 and 3. Initial and final absorptions at 4900 Å. were observed, using a Beckman spectrophotometer. The *p*H was that of the natural, unadjusted solutions. The four-hour samples of solutions 1, 2, and 3 were also taken for absorption spectra measurements between 3300–2550 Å. Solutions 1 and 3 revealed a definite maximum at 2950 Å., whereas solution 2 showed no such maximum.

TABLE I

PER CENT. ABSORPTION AT 4900 Å.

Hours	0		4	
Solution	*p*H	% abs.	*p*H	% abs.
1	5.2	11	4.1	98
2	4.5	8	4.0	11
3	5.6	1	5.2	57.5
4	5.95	3.2	5.5	7.5
5	6.6	0	5.5	0

Solution 1. Equal volumes of 1.0 *M* 3,4-didesoxyaldopentose and 1.0 *M* glycine
2. 1.0 *M* 3,4-didesoxyaldopentose alone
3. Equal volumes of 1.0 *M* D-glucose and 1.0 *M* glycine
4. Equal volumes of 1.0 *M* 2,3,4-tridesoxyaldopentose and 1.0 *M* glycine
5. 1.0 *M* 2,3,4-tridesoxyaldopentose alone

Experimental

Hydroxylation of 2,3-Dihydropyran.—2,3-Dihydropyran (196 g., 2.3 moles), obtained from the du Pont Company, and 5 ml. of osmium tetroxide catalyst (0.5 g. OsO_4 in 100 ml. of *t*-butyl alcohol) were placed in a 2-liter, 3-neck flask and 1320 ml. of hydrogen peroxide solution (6% H_2O_2 in *t*-butyl alcohol[5]) was added dropwise with stirring at −10 to +5° over a period of four hours. Additional catalyst solution (3 ml.) was added after two hours and after all of the peroxide solution had been added. The reaction is highly exothermic and care must be exercised not to add the peroxide at too fast a rate. The solution was allowed to stand overnight. The solvent was removed under reduced pressure at a bath temperature of 60° or below. The residue (255 g.) was acetylated by dissolving it in 500 ml. of pyridine and adding 750 ml. of acetic anhydride at 10°. The solution was allowed to warm to room temperature and stand overnight. After destruction of the unused acetic anhydride by addition of excess 75% ethyl alcohol, the solvent was removed at reduced pressure. The residue (335 g.) was allowed to stand overnight, whereupon some crystallization was noted, leading to 53 g. of V, which was collected on a filter. The solid was recrystallized from methyl alcohol: m. p. 132–133°. It sublimes at a pressure of 1 mm. of mercury.

Anal. Calcd. for $C_{14}H_{22}O_7$: C, 55.61; H, 7.34. Found: C, 55.78; H, 7.38.

The filtrate, after separation of V, was distilled at 1 mm., yielding 135 g. of crude 2,3-diacetoxytetrahydropyran (III) (b. p. 96–115°). Redistillation of this material gave 115 g. of product collected at 108–120° and 2–5 mm.

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.43; H, 7.74.

The residue (120 g.) after removal of V and III was dissolved in 100 ml. of methanol and cooled to 0°. Another 12 g. of crude V separated and was collected on a filter. Methanol was distilled from the filtrate and the residue was distilled at low pressure[7] into two fractions, VI and VII. At a bath temperature of 150–170° and a pressure of 10^{-6} to 10^{-3} mm., there was collected 48.4 g. of VI, a mixture of V and its isomers (the diacetate of the "disaccharide" portion). At a bath temperature of 170–200° and the same pressure was collected the acetate of the higher-boiling portion (VII); yield, 19.7 g.

The over-all yield data for utilization of 2,3-dihydropyran are as follows: 135 g. or 28.6% of III, 65 g. or 18.5% of V, 48.4 g. or 13.5% of a mixture of V and a diacetate of a reducing disaccharide, 19.7 g. or 6.3% of an acetate of a higher-boiling fraction.

Hydroxylation, Second Method.—The products of another comparable run were processed without the acetylation procedure. In this experiment 70 ml. of dihydropyran was taken and other reagents were used proportionately. After the solvent had been removed under reduced pressure, the resulting sirupy product was subjected to continuous extraction with cyclohexane (100 ml.). Sixteen grams of the product was insoluble in the hot hydrocarbon, whereas 41 g. was extracted. Of this 41-g. portion, 33.6 g. (A) was a sirup soluble in ether, and 7.4 g. (B) was a white solid insoluble in ether. Fraction A was essentially II (37% yield), and fraction B was proved by analysis (Found: C, 55.50; H, 8.76) and m. p. 141° to be IV (8% yield).

Deacetylation of 2,3-Diacetoxytetrahydropyran (III).—Twelve grams of III was dissolved in 100 ml. of absolute

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[7] Hurd, Liggett and Gordon, THIS JOURNAL, **63**, 2656 (1941).

methanol and 8 ml. of 0.4 *N* barium methoxide solution was added. After forty-eight hours at 0°, the solution was carbonated by addition of Dry Ice, and the methyl alcohol was evaporated off at room temperature. Treatment of the residue with dry ether resulted in formation of a white amorphous precipitate (barium salts). After filtration and distillation of the solvent, finally at 52° (10 mm.), there remained 6.0 g. (85% yield) of water white, thick liquid. In other runs, yields of II have been 95–97%.

Anal. Calcd. for $C_5H_{10}O_3$: C, 50.88; H, 8.54. Found: C, 51.63; H, 8.54.

This material is soluble in water, ether and most other organic solvents except hexane. It reduces Benedict solution at once at 90° and reacts with phenylhydrazine to give a red oil.

3,4-Didesoxypentose 2,4-Dinitrophenylosazone.—Tetrahydropyran-2,3-diol (0.5 g.) was dissolved in 200 ml. of absolute ethanol and 2.5 g. of 2,4-dinitrophenylhydrazine was added. The reaction mixture was refluxed several minutes. Then 5 ml. of concd. hydrochloric acid was added and the refluxing was resumed, whereupon the color changed to dark brown. After fifteen minutes of refluxing, the reaction mixture was cooled and filtered (yield, 1.1 g.). Three recrystallizations from acetone led to a red-orange, crystalline solid of m. p. 242°.

Anal. Calcd. for $C_{17}H_{16}N_8O_9$: N, 23.52. Found: N, 23.35.

Tetrahydropyran-2,3-diol Bis-3,5-dinitrobenzoate.—One gram of II was dissolved in 10 ml. of pyridine. Three grams of 3,5-dinitrobenzoyl chloride was added. The reaction mixture was allowed to stand overnight at room temperature and was then treated with water and 5% aqueous sodium carbonate. The gummy product weighed 3 g. Three recrystallizations from a 3:1 mixture of ethanol and ethyl acetate led to a crystalline product melting at 174.5–175.5°.

Anal. Calcd. for $C_{19}H_{14}N_4O_{13}$: N, 11.06. Found: N, 10.95.

Deacetylation of 2-Acetyl-3,4-didesoxyaldopentosyl 2-Acetyl-3,4-didesoxyaldopentoside (V) into (IV).—The V (8.5 g., m. p. 132–133°), which had been recrystallized twice from methanol, was dissolved in 200 ml. of absolute methanol and deacetylated as above (dilute sulfuric acid instead of carbon dioxide was used to destroy the barium methoxide). It was necessary to allow the reaction to proceed for six days because of the limited solubility of IV in cold methanol. The product was worked up as above except that the residue was extracted with ethyl acetate instead of ether. The yield was 5.7 g. or 92%. The product was crystallized twice from ethyl acetate and sublimed before analysis (m. p. 141.5–142°).

Anal. Calcd. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.42; H, 8.35.

This material (IV) is water soluble, is non-reducing to Benedict solution, and does not react with phenylhydrazine. A dinitrobenzoyl derivative of this material may be prepared as above (m. p. 245–246° after three recrystallizations from a 3:1 mixture of ethyl acetate and acetic anhydride).

Anal. Calcd. for $C_{24}H_{22}N_4O_{15}$: N, 9.24. Found: N, 9.35.

Hydrolysis of IV into II.—Acid hydrolysis of IV was carried out by dissolving 1 g. of the solid in 25 ml. of water, adding 1.5 ml. of concd. hydrochloric acid, and heating to 70–80° for thirty minutes. The solution was cooled, neutralized to phenolphthalein with 10% sodium hydroxide solution, and one drop of concd. hydrochloric acid added. This solution reduced Benedict solution, whereas the solution before treatment with acid was non-reducing. The solution was evaporated to dryness at room temperature with the aid of an air jet. The residue was treated with ether and the ether solution decanted from sodium chloride and evaporated, leading to 1 g. of clear sirup. This was placed in reaction with 2,4-dinitrophenylhydrazine as above The product melted at 242–243° after two recrystallizations from acetone and showed no m. p. depression when mixed with the 2,4-dinitrophenylosazone of II described above.

Deacetylation of Fractions VI and VII from High Vacuum Distillation.—These water insoluble acetates were deacetylated as above Fraction VI was first dissolved in methyl alcohol and crystallization was allowed to take place to remove the bulk of V present. The filtrate after removal of the solid was evaporated leaving an oily residue which showed no tendency to crystallize. This residue (8.5 g.) was deacetylated in 90.5% yield (5.8 g.). The product is water soluble and reduces Benedict solution strongly. Attempts to prepare pure derivatives of this material have failed.

Fraction VII showed no tendency to crystallize and was deacetylated in 80% yield to a water soluble, reducing material.

Acknowledgments.—Combustion analyses (C, H, N) were performed by P. Craig, M. M. Ledyard, and N. Mold.

Summary

Mono- and disaccharide-like compounds have been obtained by hydroxylation of 2,3-dihydropyran, using hydrogen peroxide in *t*-butyl alcohol and osmium tetroxide. The implications of the fact that tetrahydropyran-2,3-diol may be regarded as 3,4-didesoxyaldopentose are expounded. This compound gives rise to a strong brown coloration in its reaction with glycine, whereas 2,3,4-tridesoxyaldopentose (tetrahydropyran-2-ol) does not, thereby demonstrating the importance of the α-hydroxy aldehyde function in this reaction.

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