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PREPARATION OF 1,6-ANHYDRO-3,4-DIDEOXY-β-D-*glycero*-HEX-3-ENOPYRANOS-2-ULOSE (LEVOGLUCOSENONE) AND SOME DERIVATIVES THEREOF

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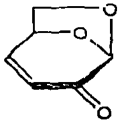
ABSTRACT

1,6-Anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose (levoglucosenone) was prepared on a laboratory scale by pyrolysis of H_3PO_4-treated, Kraft waste-paper. The aldehyde components of the pyrolyzate were removed by reaction with 5,5-dimethyl-1,3-cyclohexanedione (dimedone), and levoglucosenone was obtained in 3.3% yield by distillation of the remaining material. A variety of deoxy, keto, and branched-chain sugars was obtained by reduction of levoglucosenone, and by its reaction with Grignard reagents under different conditions.

INTRODUCTION

Pyrolysis of cellulose results in transglycosylation, dehydration, and subsequent decomposition and charring reactions[1-4] which provide a variety of compounds. In recent studies, 1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose (levoglucosenone) (**1**) has been detected in several laboratories from the pyrolysis of cellulose in the presence of acid catalysts. Various structures have been assigned to this compound, namely, 1,5-anhydro-2,3-dideoxy-β-D-pent-2-enofuranose[5] (**2**) and *cis*-4,5-epoxy-2-pentenal[6] (**3**), as well as the levoglucosenone structure[7]. The correct structure of this compound as being the last-mentioned was confirmed in our laboratory through isolation and analysis of its crystalline (2,4-dinitrophenyl)-hydrazone (DNPH) derivative[8].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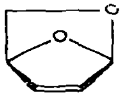
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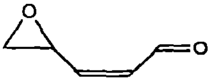
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In previous studies, **1** was isolated by preparative, gas-liquid chromatography of the pyrolyzate[6-8]. As dehydration of the D-glucosyl residues in cellulose plays an important role in the course of cellulosic fires, and as levoglucosenone could serve as an important intermediate for pyrolytic conversion of the enormous amounts of cellulosic wastes into useful chemicals, we have investigated the laboratory-scale production of this compound, and its conversion into several new deoxy, keto, branched-chain, and unsaturated compounds.

RESULTS AND DISCUSSION

Compound **1** was previously produced[5–8] from the pyrolysis of acidified cellulose in the temperature range of 300 to 350°. In preliminary experiments, 5-mg samples of cellulose, starch, newsprint, and Kraft paper (brown paper-bags) containing 5% of phosphoric acid (H_3PO_4) were pyrolyzed at 350° in a pyrolysis apparatus connected directly to a gas chromatograph. The results presented in Table I reveal that **1** can be produced in comparable yields from the acid-catalyzed pyrolysis of various materials, including starch, and waste paper that contains residual hemicelluloses and lignin. This is in sharp contrast to the pyrolytic production of 1,6-anhydro-β-D-glucopyranose (levoglucosan), in which the presence of impurities affects the transglycosylation and dehydration reactions so as to lower the yield[9], and a high vacuum is required for rapid removal of the product from the heated reaction-zone in order to prevent further degradation[2]. Kraft waste-paper was selected as a readily available and cheap raw-material for the subsequent preparation of **1** on an increased scale.

TABLE I

YIELDS OF LEVOGLUCOSENONE (**1**) FROM PYROLYSIS[a] OF VARIOUS MATERIALS AT 350°

Material	*Yield*	
	From neat (%)	*From 5% H_3PO_4-treated (%)*
Cellulose	1.2	11.1
Starch	0.3	9.0
Newsprint (with ink)	T[b]	9.1
Kraft shopping-bags	T	10.2

[a] Determined by pyrolyzing 5-mg samples and directly analyzing the volatile compounds by g.l.c.
[b] T = trace.

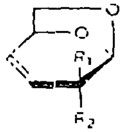
In the laboratory-scale preparation, 8-g batches of Kraft paper impregnated with ~5% of H_3PO_4 were pyrolyzed under nitrogen in a glass-tube furnace. To minimize the excessive decomposition of the products in the hot furnace-tube, a lower temperature (275°) was used. Analysis of a chloroform solution of the crude pyrolyzate by g.l.c. showed the presence of **1** and 2-furaldehyde as the major components in the ratio of ~4:1. Analysis of the pyrolyzate obtained from the pyrolysis of acidified cellulose, however, showed a ratio of **1** to 2-furaldehyde of ~8:1. The 2-furaldehyde component is partly derived from dehydration of the D-glucosyl residues in cellulose[10], and partly from the dehydration of the pentosyl residues in the hemicellulose present[11]. The aldehyde compounds in the crude pyrolyzate were removed by reaction with 5,5-dimethyl 1,3-cyclohexanedione (dimedone) in aqueous ethanol solution at 100°. Analysis of the residue by g.l.c. showed complete removal of 2-furaldehyde along with other aldehyde impurities.

Levoglucosenone was isolated by vacuum distillation of the aldehyde-free pyrolyzate. The fraction distilling at 55–60°/1.5 torr was shown by g.l.c. to contain 96% of levoglucosenone; this fraction was obtained in an overall yield of 3.3% (based on the weight of starting Kraft paper), and was sufficiently pure for synthetic purposes. The product was a strongly levorotatory liquid that furnished crystalline DNPH and semicarbazone derivatives.

Reduction of **1** with lithium aluminum hydride in ether was stereoselective, producing a mixture containing 84% of 1,6-anhydro-3,4-dideoxy-β-D-*erythro*-hex-3-enopyranose (**4**) and 8% of its C-2 epimer (1,6-anhydro-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose, **5**) Compound **4**, formed in an overall yield of 74%, was characterized by its 3,5-dinitrobenzoyl derivative. The configuration of **4** was assigned by n.m.r spectroscopy, which showed no spin–spin coupling between the C-1 and C-2 protons. This lack of coupling would indicate a dihedral angle of ~90° between H-1 and H-2, which would be consistent with a *trans* disposition for these atoms on this six-membered, heterocyclic ring

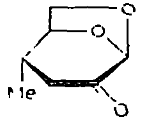
In the presence of 5% Pd–$BaSO_4$, compound **1** was readily hydrogenated to give 1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hexopyranos-2-ulose (**6**) in 85% yield. This compound was characterized by its DNPH derivative.

The reduction of both the ketone and the carbon–carbon double bond of **1** gave 1,6-anhydro-3,4-dideoxy-β-D-*erythro*-hexopyranose (**7**) as an oil; this compound was prepared both by lithium aluminum hydride reduction of **6** (in 70% yield), and by hydrogenation of **4** (in 84% yield). The reduction of **6** with lithium aluminum hydride was also stereoselective, the product mixture containing 91% of **7**, indicating that the saturation of the double bond did not change the stereoselective nature of the lithium aluminum hydride reduction.



4 $R_1 = H, R_2 = OH$
5 $R_1 = OH, R_2 = H$
8 $R_1 = CH_3, R_2 = OH$
9 $R_1 = OH, R_2 = Me$

6



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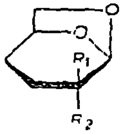
In addition to the new deoxy and keto sugars, different branched-chain sugars were prepared by reaction of **1** with a Grignard reagent under controlled conditions. Compound **1** reacted with methylmagnesium iodide at room temperature to give the

1,2-addition product, namely, 1,6-anhydro-3,4-dideoxy-2-*C*-methyl-β-D-*erythro*-hex-3-enopyranose (**8**) in 56% yield, along with 6% of its C-2 epimer (1,6-anhydro-3,4-dideoxy-2-*C*-methyl-β-D-*threo*-hex-3-enopyranose, **9**) and 6% of the 1,4-addition product (1,6-anhydro-3,4-dideoxy-4-*C*-methyl-β-D-*erythro*-hexopyranos-2-ulose, **10**). The main product, **8**, was isolated as an oil by column chromatography, and was characterized by the 3,5-dinitrobenzoyl derivative of its hydrogenated product.

The reaction of **1** with methylmagnesium iodide at −78° in the presence of[12,13] tetrakis[iodo(tributylphosphine)copper(I)], $(Bu_3PCuI)_4$, produced mainly the 1,4-addition product, **10**, in 64% yield, along with 18% of the 1,2-addition products, **8** and **9**. The addition of the methyl group to the β-carbon atom of the α,β-unsaturated ketone was stereospecific, and **10** was the only 1,4-addition product detected. The 1,4-addition product was isolated by column chromatography as an oil, and was characterized by its DNPH derivative. The configuration of this product was assigned from its n.m.r. spectrum, which showed no spin-spin coupling between H-4 and H-5, indicating a *trans* disposition between these protons.



7 $R_1 = H, R_2 = OH$
11 $R_1 = Me, R_2 = OH$
12 $R_1 = OH$ $R_2 = Me$

The Grignard reaction of **6** and methylmagnesium iodide at room temperature was not stereoselective. The product mixture contained almost equal amounts of 1,6-anhydro-3,4-dideoxy-2-*C*-methyl-β-D-*erythro*-hexopyranose (**11**) and 1,6-anhydro-3,4-dideoxy-2-*C*-methyl-β-D-*threo*-hexopyranose (**12**) as oils that were not clearly resolved by column chromatography. However, these two compounds could be characterized by their 3,5-dinitrobenzoyl derivatives, respectively prepared from the early and late chromatographic fractions. The configurations of compounds **11**, **12**, and **8** were determined by n.m.r. spectroscopy with the aid of a lanthanide shift-reagent.

EXPERIMENTAL

Analytical and separation methods. — Melting points were determined in a Fisher-Johns melting-point apparatus and are uncorrected. Optical rotations were determined with a Bendix Model 1169 automatic polarimeter. N.m.r. spectra were recorded with a Varian EM 360 60-MHz spectrometer, using tetramethylsilane as the internal reference-standard. I.r. spectra were recorded with a Beckman IR-33 spectrophotometer. G.l.c. of the reaction products was performed in a Varian Model 1800 gas chromatograph having a flame-ionization detector, employing nitrogen as the carrier gas. A column (3.66 m × 3.17 mm o.d.) of 5% of Carbowax 20M on Gas Chrom Q (100–120 mesh) was used for separation. The chromatographic peaks were quantified with an Autolab Model 6300 digital integrator. Column-chromatographic separation of the reaction products was performed in a column (1.5 cm o.d. × 40 cm) of silica gel, with toluene as the eluant. Thin-layer chromatography (t.l.c.) was conducted on silica IB-F (Bakerflex) chromatographic sheets, using 2:1 ether–pentane. Elemental analyses were performed by Galbraith Laboratories, Inc.

Screening of different substrates. — The yields of **1** from the pyrolysis of microcrystalline cellulose, corn starch, inked newsprint, and Kraft paper (brown paper-bags) were determined. The newsprint and Kraft paper were first pulverized in a Wiley mill to a powder (<20 mesh). All of the powdered materials were then soaked in an aqueous or tetrahydrofuran solution containing 5% of H_3PO_4 (based on the weight of the material). The solvents were removed, first in a rotary evaporator under diminished pressure, and then in a vacuum desiccator below 50°. The dry materials were stored under anhydrous conditions.

Accurately weighed, ~5-mg samples of the acidified substrates were pyrolyzed at 350° in a modified, Perkin-Elmer pyrolysis unit connected directly to the carrier-gas stream of a gas chromatograph (for the quantitative determination of the pyrolysis products).

Laboratory-scale preparation of levoglucosenone (**1**). — Batches (8 g each) of acid-treated, Kraft paper were pyrolyzed in a tube furnace preheated to 275°, under a nitrogen flow-rate of 1 liter.min^{-1}. After ~10 min (when the evolution of volatile compounds was almost complete), the system was cooled to room temperature, and the condensed products were washed out with chloroform, dried ($MgSO_4$), and evaporated. The combined, crude pyrolyzate (18 g) obtained from 208 g of substrate was dissolved in 50% aqueous ethanol (70 ml). The solution was treated with 4 drops of piperidine and dimedone (4 g), and heated on a steam bath for 10 min. The bismethone derivatives of the aldehydes precipitated on cooling, and were removed by filtration. The filtrate was concentrated, and the aqueous concentrate was extracted with chloroform; the extract was dried ($MgSO_4$), filtered, and evaporated to dryness, and the residue was distilled at 1.5 torr. The fraction collected between 55 and 60° yielded 6.8 g of a light-yellow liquid (3.3% by weight) containing 96% of **1** (as shown by g.l.c. analysis); $[\alpha]_D^{26}$ −458° (*c* 3.97, chloroform), lit.[7] $[\alpha]_D^{25}$ −460°. The DNPH derivative of the product had m.p. 214–215°, lit[8] m.p. 214–215°.

The semicarbazone prepared by reaction of the product (0.5 g) with semicarbazide hydrochloride (1.0 g) and sodium acetate (1.5 g) in water (10 ml) had, after crystallization from methanol, m.p. 223–226° (dec.), $[\alpha]_D^{26}$ −241° (*c* 3.99, 1:1 pyridine–acetic acid).

Anal. Calc. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.76; H, 4.83; N, 23.02.

*1,6-Anhydro-3,4-dideoxy-β-*D-erythro*-hex-3-enopyranose* (**4**). — A solution of **1** (0.797 g, 6.33 mmol) in dry ether (16 ml) was added dropwise to $LiAlH_4$ (0.240 g) in dry ether (20 ml), and stirred for 1 h. The excess of $LiAlH_4$ was then decomposed by careful addition of water. The mixture was diluted with methanol, filtered through Norit, and the filtrate evaporated, yielding an oil (0.711 g). The g.l.c. analysis of the oil before and after trimethylsilylation showed it to contain 84% of **4** (74% yield), 8% of its C-2 epimer **5**, and 8% of a product that did not form a trimethylsilyl derivative (indicating the lack of a hydroxyl group). The i.r. spectrum of the oil showed a broad, hydroxyl band at 3400 cm^{-1}, but no carbonyl absorption band. Compound **4**, isolated by g.l.c., had a n.m.r. spectrum that showed that there was no spin–spin coupling between H-1 and H-2, thereby confirming the assigned configuration.

Compound **4** was characterized by the 3,5-dinitrobenzoyl derivative obtained from the crude product: m.p. 158–160°, $[\alpha]_D^{26}$ +12.3° (*c* 4.88, chloroform).

Anal. Calc. for $C_{13}H_{10}N_2O_8$: C, 48.46; H, 3.13; N, 8.69. Found: C, 48.34; H, 3.08; N, 8.42.

*1,6-Anhydro-3,4-dideoxy-β-*D-glycero-*hexopyranos-2-ulose* (**6**). — A solution of **1** (0.787 g, 6.25 mmol) in ethyl acetate (25 ml) was hydrogenated for 4 h at 1 atm. in the presence of 1.6 g of 5% Pd–BaSO$_4$. After removal of the catalyst and the solvent, this yielded 0.677 g (85%) of **6** as an oil. The i.r. spectrum showed strong absorption at 1745 cm^{-1}, but absorption in the O–H stretching region was absent.

This compound was characterized as its DNPH derivative: m.p. 205–206°, $[\alpha]_D^{26}$ −58.4° (*c* 5.14, chloroform).

Anal. Calc. for $C_{12}H_{12}N_4O_6$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.91; H, 3.95; N, 18.01.

*1,6-Anhydro-3,4-dideoxy-β-*D-erythro-*hexopyranose* (**7**). — *A. By hydrogenation of* **4**. Hydrogenation of **4** (0.287 g, 2.24 mmol) for 4 h at 1 atm in the presence of 0.6 g of 5% Pd–BaSO$_4$ yielded 0.243 g (84%) of **7** as an oil, which was characterized by its 3,5-dinitrobenzoyl derivative: m.p. 165–167°, $[\alpha]_D^{26}$ −90.2° (*c* 5.32, chloroform).

Anal. Calc. for $C_{13}H_{12}N_2O_8$: C, 48.16; H, 3.73; N, 8.64. Found: C, 48.56; H, 3.78; N, 8.54.

B. By reduction of **6**. Compound **6** (0.677 g, 5.29 mmol) was reduced with LiAlH$_4$ by the method described for the preparation of **4**, yielding 0.528 g of an oil which contained 91% of **7** (70% yield), and gave a 3,5-dinitrobenzoyl derivative having m.p. 165–167°; mixed m.p. with the product described in *A*, 165–167°. The configuration of **7** was found to be the same as that of **4**.

*1,6-Anhydro-3,4-dideoxy-2-C-methyl-β-*D-erythro-*hex-3-enopyranose* (**8**). — A solution of **1** (0.5 g, 4 mmol) in ether (10 ml) was added dropwise at room temperature, in a nitrogen atmosphere, to a solution of MeMgI [prepared by the dropwise addition of MeI (3 g) to Mg (0.5 g) in ether]. The excess of the Grignard reagent was decomposed by careful addition of water. The mixture was then thoroughly extracted with ether, the extract was dried (MgSO$_4$), decolorized (Norit), and filtered, and the filtrate evaporated under vacuum, yielding 0.450 g of an oil that contained 71% of **8** (56% yield), 7% of its C-2 epimer **9**, and 8% of **10**. Separation by column chromatography gave 0.289 g (51%) of pure **8**, characterized by its hydrogenation product **11** as described later.

*1,6-Anhydro-3,4-dideoxy-4-C-methyl-β-*D-erythro-*hexopyranos-2-ulose* (**10**). — A solution of **1** (1 g, 8 mmol) and $(Bu_3PCuI)_4$ (0.0392 g, 0.1 mmol; prepared by the method of Kauffman and Teter[14]) in ether (15 ml) was added dropwise at −78°, under a nitrogen atmosphere, to a solution of MeMgI [prepared by the addition of MeI (5.68 g) to Mg (0.96 g) in ether (25 ml)]. The solution was then stirred for 30 min, and the excess of reagent was decomposed by careful addition of a saturated solution of NH_4Cl. The mixture was then extracted with ether, and the extract was dried ($MgSO_4$), decolorized (Norit), and filtered, and the filtrate evaporated, yielding 0.93 g of an oil that contained 78% of **10** (64% yield), 15% of **8**, and 7% of **9**. Column-chromatographic separation of the mixture gave 0.501 g (44%) of pure **10**. The n.m.r. spectrum of **10** showed no spin–spin coupling between H-4 and H-5, establishing the *trans* disposition at C-4 and C-5.

Compound **10** was characterized by its DNPH derivative: m.p. 215–216°, $[\alpha]_D^{26}$ −150° (*c* 3.53, chloroform).

Anal. Calc. for $C_{13}H_{14}N_4O_6$: C, 48.45; H, 4.38; N, 17.38. Found: C, 48.27; H, 4.33; N, 17.59.

*1,6-Anhydro-3,4-dideoxy-2-C-methyl-β-*D-erythro-*hexopyranose* (**11**) *and 1,6-anhydro-3,4-dideoxy-2-C-methyl-β-*D-threo-*hexopyranose* (**12**). — The method described for the preparation of **8** was employed, using **6** (0.8 g, 6.3 mmol), MeI (5 g), and Mg (0.9 g). The oily product (0.560 g) contained almost equal amounts of **11** and **12**, as shown by g.l.c. analysis.

These compounds could not be separated by column chromatography; however, the 3,5-dinitrobenzoyl derivative prepared from the early chromatographic fraction differed from the one prepared from the late fractions. After recrystallization, the former had m.p. 134–135°, $[\alpha]_D^{20}$ −41.5° (*c* 2.65, chloroform).

Anal. Calc. for $C_{14}H_{14}N_2O_8$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.56; H, 4.21; N, 8.30.

The latter compound had m.p. 168–169°, $[\alpha]_D^{26}$ −80.0° (*c* 3.00, chloroform).

Anal. Calc. for $C_{14}H_{14}N_2O_8$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.62; H, 4.15; N, 8.27.

The configurations of these compounds were determined by n.m.r. spectroscopy with the aid of the europium(III) reagent $Eu(fod)_3$. The n.m.r. spectrum of the product mixture containing equal amounts of **11** and **12**, shown in spectrum A in Fig. 1, contained two hydroxyl signals of equal size at δ 2.5 and 2.8, with only one sharp signal at δ 5.0 for the anomeric protons. In order to increase the concentration of one of the two isomers, compound **8** was hydrogenated and the product added to the solution. This increased the size of the hydroxyl signal at δ 2.5, as shown in spectrum B in Fig. 1. Upon gradual addition of $Eu(fod)_3$, as shown in spectra C and D, the larger hydroxyl signal at δ 2.5 shifted significantly, to lower field, while the other remained relatively unchanged. In addition, the common signal for the anomeric protons at δ 5.0 was gradually separated into two peaks. The peak that shifted to

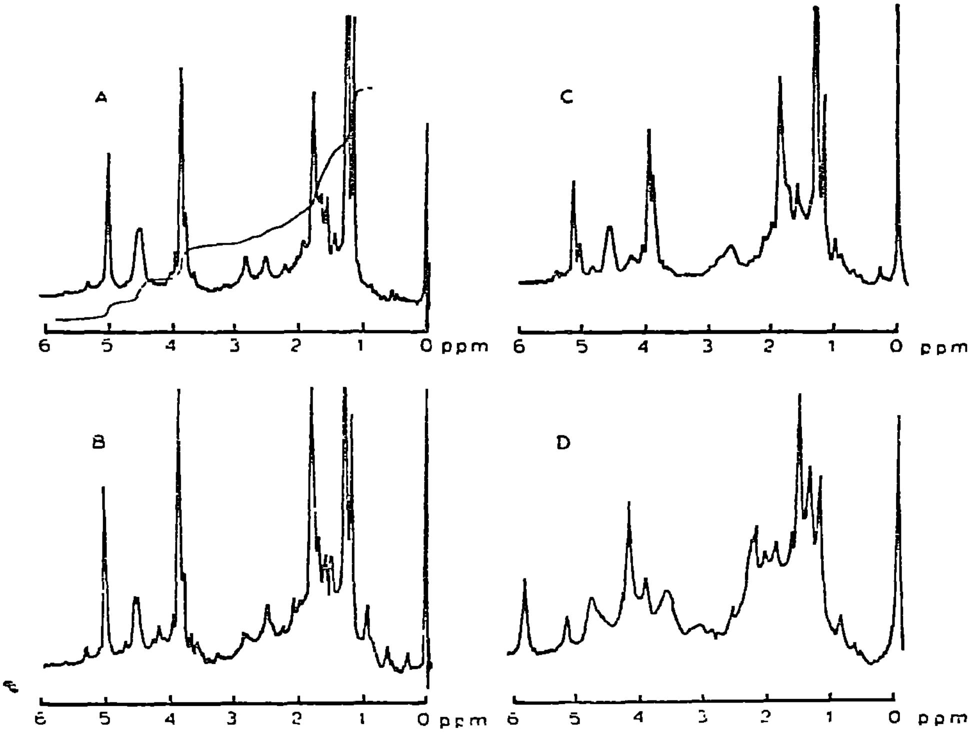


Fig. 1. Gradual change in n.m.r. spectra: (A) Grignard reaction products of **6**, containing equal amounts of **11** and **12**; (B) after adding the hydrogenation product of **8**; (C) after adding Eu(fod)$_3$; and (D) at the end of the addition of Eu(fod)$_3$.

lower field was larger than that remaining relatively unchanged. Therefore, the compound prepared by hydrogenation of **8** is isomer **11**, which has the more accessible hydroxyl group. The 3,5-dinitrobenzoyl derivatives of **11** and **12** were identified by comparing their melting points with the melting points of the corresponding derivative obtained from the hydrogenated product from **8**.

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