

SYNTHESIS OF A DERIVATIVE OF 1-DEOXY-D-*erythro*-2,3-HEXODIULOSE AND ITS CONVERSION INTO NONENZYMIC BROWNING PRODUCTS

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ABSTRACT

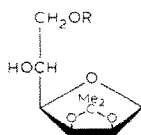
A new synthesis of 1-deoxy-4,5-*O*-isopropylidene-D-*erythro*-2,3-hexodiulose (**5**), a stable derivative of the elusive 1-deoxy-D-*erythro*-2,3-hexodiulose (**6**), starting from 3,6-anhydro-4,5-*O*-isopropylidene-D-mannitol (**1**) is described. Acid hydrolysis of **5** produced **6**, which without isolation was treated with piperidine acetate to yield piperidino-hexose-reductone (**7**) and 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one (**8**). A third component in the reaction mixture has been tentatively assigned from mass-spectroscopic data the structure 4-hydroxy-2-hydroxymethyl-5-methyl-3(2*H*)-furanone (**9**).

INTRODUCTION

In sugar-amine reactions, such nonenzymic browning-products as acetylformoin¹, secondary amino-hexose-reductones¹, maltol², isomaltol² (2-acetyl-3-hydroxyfuran), 2,3-dihydro-3,5-dihydroxy-6-methyl-4*H*-pyran-4-one³, and *C*-methyl fission products have been postulated to arise through a common intermediate, namely 1-deoxy-D-*erythro*-2,3-hexodiulose (**6**). Formation of the diulose **6** has been represented as, first, conversion of an amine and aldose into the Amadori product (1-amino-1-deoxy-2-ketose) and, second, a 2,3-enolization of the Amadori product followed by elimination of amine. Simon's¹ study on the mode of formation of piperidino-hexose-reductone (**7**) from ¹⁴C-labeled D-glucose provided evidence for the mode of formation of **6** from the Amadori product. Mills and Hodge⁴ isolated 2,3-dihydro-3,5-dihydroxy-6-methyl-4*H*-pyran-4-one (**8**) from the volatile portion of a vacuum pyrolyzate of 1-deoxy-1-(L-proline)-D-fructose, the Amadori product from L-proline and D-glucose. van den Ouweland and Peer³ isolated **7** and **8** from the acid-catalyzed transformation of 1-deoxy-1-piperidino-D-fructose.

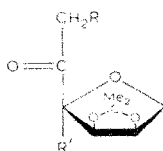
*Deceased: 21 October 1981.

[†]The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.



1 R = H

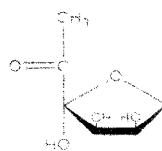
2 R = Ts



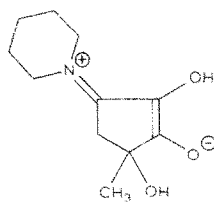
3 R = OTs, R' = H

4 R = H, R' = OCH₂Ph

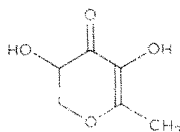
5 R = H, R' = OH



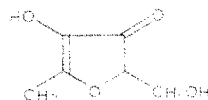
6



7



8



9

Ishizu *et al.*⁵ reported that acid hydrolysis of 1,5-anhydro-6-deoxy-D-lyxohex-5-enitol gives 1-deoxy-D-fructose, which was converted by phenylhydrazine into 1-deoxy-D-fructose phenylsazone. Treatment of this phenylsazone with nitrous acid produced the diulose **6**, which was stable only in acid solution and decomposed upon freeze drying.

A synthesis of **6** or a stable derivative was undertaken so that its further dehydration reactions could be investigated under the conditions first used with D-glucose².

RESULTS AND DISCUSSION

Treatment of 3,6-anhydro-4,5-*O*-isopropylidene-D-mannitol (**1**) with one molar equivalent of *p*-toluenesulfonyl chloride preferentially converted **1** into 3,6-anhydro-4,5-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-D-mannitol (**2**) in 67% yield. Conversion of the 2-hydroxyl group in **2** into a keto group was readily performed with catalytic amounts of ruthenium tetroxide, generated from ruthenium dioxide in the presence of potassium periodate and potassium carbonate⁶, to give 3,6-anhydro-4,5-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-D-fructose (**3**).

When the fructose derivative **3** was heated in benzyl alcohol containing triethylamine and *p*-toluenesulfonic acid, the benzyl glycoside of 1-deoxy-4,5-*O*-isopropylidene-D-*erythro*-2,3-hexodiulose (**4**) was formed. This interesting acid-catalyzed transformation of an α -keto *p*-toluenesulfonate into a glycoside of a methyl ketone was reported by Dmytraczenko *et al.*⁷ in a similar compound. These authors used ¹H-n.m.r. spectroscopy to assign the configuration of their product. The ¹H-n.m.r. spectrum of **4** did not allow any definitive configurational assignment; the assignment shown in formula **4** was made by analogy with the product of

Dmytraczenko *et al.* Catalytic hydrogenolysis of **4** over palladium removed the benzyl group to give 1-deoxy-4,5-*O*-isopropylidene-D-erythro-2,3-hexodiulose (**5**) as a stable, crystalline compound.

The known bis(phenylhydrazone) of 1-deoxy-D-erythro-2,3-hexodiulose was prepared after hydrolytic removal of the isopropylidene blocking group from **5**. T.l.c. indicated that decomposition of **6** occurred during this hydrolysis. Observation here on the instability of the diulose **6** agrees with an earlier report⁵, thus making isolation of pure **6** unlikely.

Treatment of aqueous solutions of **6** with ethanolic solutions of piperidine acetate gave piperidino-hexose reductone (**7**), 2,3-dihydro-3,5-dihydroxy-6-methyl-4*H*-pyran-4-one (**8**), a compound tentatively identified as 4-hydroxy-2-hydroxymethyl-5-methyl-3(2*H*)-furanone (**9**), and three unidentified compounds as the major products. Compound **7** (20%) crystallized from an ether extract of the mixture and was identified by its m.p. and its i.r. spectrum.

After isolation of **7**, the ether extract was evaporated to a syrup, and the remaining compounds were isolated by preparative g.l.c. The percentage yields of major products listed in Table I are based on total material obtained from the ether extract, and were determined from peak areas of the gas chromatogram. Partial decomposition of **6** on hydrolytic removal of the isopropylidene group from **5** precludes basing the yields on starting material.

Compound **8** was identified by comparison of its g.l.c. retention-time with the retention time of an authentic sample, and by mass-spectral analysis.

Compound **9** was tentatively identified as 4-hydroxy-2-hydroxymethyl-5-methyl-3(2*H*)-furanone on the basis of its mass spectrum. The mass spectrum of **9** shows a minimal peak for the molecular ion M^+ (m/z 144). The low intensity is attributed to rapid loss of water from **9** to form the compound of m/z 126, which contains an exocyclic methylene group at C-2. The fragment m/z 111 would result from loss of a methyl group fragment m/z 126. Loss of both methyl and hydroxymethyl groups from **9** produces fragment m/z 98. The intense peak at m/z 84 is attributed to cleavage of the C-2-C-3 and C-5-O bonds of the m/z 126 fragment with formation of $[O=C-C(OH)=CCH_3]^+$ and ketene.

Three prominent peaks in the mass spectrum of 4-hydroxy-2,5-dimethyl-3(2*H*)-furanone, a compound closely related to **9**, are indicated: an m/z 85 fragment $[HO-C=C(CH_3)-COH]^+$ formed by C-2-C-3 and C-5-O bond cleavage; an m/z 57 fragment $[HO-C=C=O]^+$ formed by C-2-C-3 and C-4-C-5 bond cleavage; and an m/z 43 $[CH_3C=O]^+$ formed by C-2-O bond cleavage.

Structures for the unidentified compounds could not be deduced from their mass-spectral data. The possibility exists that these compounds constitute degradation products of **6** formed during removal of the isopropylidene group. Maltol and isomaltol, compounds previously isolated from sugar-amine browning reactions, were not identified in the mixtures. Under conditions similar to those utilized in this study, maltol and isomaltol have been isolated only from the disaccharides maltose and lactose².

EXPERIMENTAL

General methods. — Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. I.r. spectra were obtained for solutions in chloroform or with KBr discs with a Perkin-Elmer 621 spectrophotometer. N.m.r. spectra were recorded by a Varian HA-100 spectrometer with tetramethylsilane as the internal reference standard ($\delta = 0.00$). Mass spectra were produced with a Nuclide 12-90-G spectrometer equipped with a probe inlet. Silica Gel G served as the adsorbent for t.l.c. The developing solvents were *A*, 2:1 ethyl acetate-hexane (v/v) and *B*, 200:47:15:1 benzene-ethanol-water-conc. ammonia^s (v/v). The spray reagents used for detection were 18:1:1 ethanol-anisaldehyde-conc. sulfuric acid (v/v)⁹ and 5% ammoniacal silver nitrate. G.l.c. analyses and preparations were performed with an F&M Model 810 instrument equipped with a thermal-conductivity detector and a poly(oxyethylene) column (Carbowax 20M, 15% on 80-100 mesh Gas-Chrom Q 2.74 m \times 6.35 mm stainless-steel column); 60 mL of helium per min; injection port at 205°; on-column injection: the initial temperature was 80° for 6 min and was then temperature-programmed at 60° per min to 130°, and finally temperature-programmed at 2° per min to 205°. G.l.c. samples were collected in capillary tubes cooled in Dry Ice.

3,6-Anhydro-4,5-O-isopropylidene-1-O-tosyl-D-mannitol (2). — 3,6-Anhydro-4,5-O-isopropylidene-D-mannitol¹⁰ (**1**, 16 g) was dissolved in 130 mL of dry pyridine. The solution was cooled to 0° and *p*-toluenesulfonyl chloride (15 g in 75 mL dichloromethane) was added during 1 h. The mixture was kept for an additional h at 0° and for 18 h at room temperature. The mixture was then taken up in chloroform, and washed with dilute, ice-cold hydrochloric acid, sodium hydrogen-carbonate solution, and distilled water. The chloroform extract was dried over Drierite and the solution evaporated to a colorless solid. The crude material was recrystallized from methanol to yield **2** (19 g, 67%), m.p. 137-138.5, $[\alpha]_D^{20} = -28^\circ$ (*c* 0.23, chloroform).

Anal. Calc. for C₁₆H₂₂O₇S: C, 53.6; H, 6.19. Found: C, 53.7; H, 6.20.

3,6-Anhydro-4,5-O-isopropylidene-1-O-tosyl-D-fructose (3). — To a solution of **2** (17 g) in alcohol-free chloroform (150 mL) was added ruthenium dioxide (0.3 g) and a mixture of potassium periodate (18 g) and potassium carbonate (3 g) in water (100 mL). The mixture was stirred vigorously for 19 h. 2-Propanol (50 mL) was added, and stirring was continued an additional 0.5 h. The mixture was filtered and separated. The aqueous phase was extracted with chloroform (2 \times 100 mL), and the combined chloroform extract was concentrated under diminished pressure to a syrup. The syrup was taken up in anhydrous ether and the solution kept at -12° to yield **3** (11.1 g, 65%), m.p. 75-77°, $[\alpha]_D^{20} = -66.5^\circ$ (*c* 0.97, methanol).

Anal. Calc. for C₁₆H₂₀O₇S: C, 53.9; H, 5.63. Found: C, 54.1; H, 5.80.

Benzyl 1-deoxy-4,5-O-isopropylidene-D-erythro-2,3-hexodiulo-3,6-furanoside (4). — Triethylamine (4 g) and *p*-toluenesulfonic acid (3.8 g) were added to a solution of **3** (7.12 g, 0.02 mol) in benzyl alcohol (200 mL). The solution was heated

for 30 h at 70°. The cooled mixture was taken up in chloroform, washed successively with dilute hydrochloric acid, dilute sodium hydrogencarbonate solution, and distilled water. The chloroform extract was dried over Drierite and concentrated under diminished pressure for removal of chloroform. Benzyl alcohol was removed by evaporation at low pressure with the aid of a vacuum pump. The product was separated from the syrupy residue by elution from a column of silica gel with 1:1 ethyl acetate–hexane. The yield of **4**, a colorless syrup, was 4.6 g (79%), $[\alpha]_D^{20} -124^\circ$ (c 0.75, methanol); $\nu_{\max}^{\text{CCl}_4}$ 1715 (C=O), 1600, and 1493 cm^{-1} (phenyl); n.m.r. data (CCl_4): δ 1.22s, 1.40s (6 H, CMe_2), 2.20s (3 H, Ac), 3.76q (1 H, H-6), 4.05d (1 H, H-6), 4.25q (2 H, benzyl CH_2), 4.73q (1 H, H-5), 4.54d (1 H, H-4), and 7.22s (5 H, Ph).

Anal. Calc. for $\text{C}_{16}\text{H}_{20}\text{O}_4$: C, 65.7; H, 6.90. Found: C, 65.8; H, 7.19.

1-Deoxy-4,5-O-isopropylidene-D-erythro-2,3-hexodiulose (5). — Compound **4** (4 g) was hydrogenolyzed in acetone–ethanol (100 mL, 1:1) in the presence of 10% palladium-on-charcoal (1 g) for 10 h at 1 atm, 25°. The mixture was filtered and the filtrate evaporated to a colorless syrup that was crystallized by dissolving it in the minimum quantity of ethyl acetate, adding hexane to incipient turbidity, and cooling to -12° . The yield of colorless **5** was 1.8 g (65%), m.p. 98–99.5°, $[\alpha]_D^{20} -65^\circ$ (c 0.79, methanol); $\nu_{\max}^{\text{CHCl}_3}$ 3490 (OH) and 1720 cm^{-1} (C=O); n.m.r. (CDCl_3): δ 1.30s, 150s (6 H, CMe_2), 2.36s (3 H, Ac), 4.11d (2 H, H-6,6'), 4.29 broad s (1 H, OH), 4.54d (1 H, H-4), 4.87 octet (1 H, H-5).

Anal. Calc. for $\text{C}_9\text{H}_{14}\text{O}_5$: C, 53.5; H, 6.98. Found: C, 53.4; H, 7.10.

Phenylosazone of 1-deoxy-D-erythro-2,3-hexodiulose. — A solution of **5** (0.2 g) in water (2 mL) was heated for 2 h at 60° with an excess of cation-exchange resin (Amberlite IR-120, H^+ form). The mixture was filtered and the resin washed with water (5 mL). Sodium acetate (1.5 g) and phenylhydrazine hydrochloride (1.0 g) dissolved in water (5 mL) were added to the filtrate, and the mixture was kept at room temperature overnight. The precipitate formed was collected, washed with water, and air-dried. Recrystallization from ethyl acetate–hexane gave an orange-colored osazone, m.p. 137–141°, $[\alpha]_D^{20} -30.6^\circ$ (c 0.75, pyridine); lit.⁵ m.p. 137–140°, $[\alpha]_{5780}^{21} -28^\circ$ (c 1.3, pyridine).

Reaction of 1-deoxy-D-erythro-2,3-hexodiulose with piperidine acetate. — 1-Deoxy-4,5-O-isopropylidene-D-erythro-2,3-hexodiulose (**5**, 0.2 g) was dissolved in water (1 mL). Amberlite IR-120 resin (H^+ form) was added, and the mixture was heated, with magnetic stirring, for 2 h at 55–60°. T.l.c. then indicated that no starting material remained and that some decomposition had occurred as evidenced by streaking on the chromatogram. The aqueous solution was clarified by filtration, and the resin was washed with abs. ethanol (5 mL). An ethanolic solution (5 mL) containing piperidine (87 mg) and acetic acid (64 mg) was added to the aqueous alcoholic solution containing **6**, and the mixture was heated for 20 h at 75°. The amber-colored mixture was evaporated under diminished pressure to a syrup, which was taken up in water and extracted continuously with ether for 8 h. After drying the ether extract over Drierite, concentrating the filtered extract to ~5 mL,

TABLE I

GAS LIQUID CHROMATOGRAPHY AND MASS-SPECTRAL DATA FOR REACTION PRODUCTS OF 1-DEOXY-D-erythro-2,3-HEXODIULOSE AND PIPERIDINE ACETATE

Compound	Gas retention time (min)	Yield (%)	Mass spectra (m/z and relative %)
2,3-Dihydro-3,5-dihydroxy-6-methyl-4 <i>H</i> -pyran-4-one (8)	62	8.8	144(18), 101(19), 73(18), 72(23), 55(37), 45(21), 44(55), 43(100)
4-Hydroxy-2-hydroxymethyl-5-methyl-3(2 <i>H</i>)-furanone (9)	16	21	126(12), 111(20), 98(35), 85(33), 84(73), 57(52), 56(44), 55(22), 43(100), 42(34)
Unidentified			
A	25	5.4	126(3), 111(5), 99(6), 98(100), 32(10), 31(21), 29(13)
B	37	10.2	159(100), 108(19), 107(17), 97(63), 91(32), 79(20), 59(27), 55(28), 43(22)
C	42	14.9	104(46), 91(100), 66(39), 61(92), 58(18), 43(91), 31(21)

and cooling to -12° , crystalline piperidino-hexose reductone was obtained. The yield was 12.5 mg (20%), m.p. 228–230° (dec.); lit.¹¹ m.p. 230°. The m.p. of a mixture of the isolated compound and authentic piperidino-hexose reductone was not lowered. The i.r. spectrum of the isolated material was identical to the i.r. spectrum of the known compound.

The ether filtrate from the compound isolated was examined by t.l.c. with solvent system *B*. 2,3-Dihydro-3,5-dihydroxy-6-methylpyran-4-one (R_f 0.34) and residual piperidino-hexose reductone (R_f 0.30) were identified by spotting authentic compounds as guides. Two additional compounds were detected at R_f 0.66 and 0.61.

The ether filtrate was concentrated to a syrup (55 mg), dissolved in methanol, and the major products isolated by g.l.c. (Table I).

ACKNOWLEDGMENTS

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