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On the formation of reductic acid from pentoses or hexuronic acids

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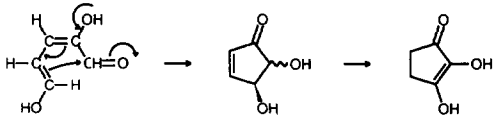
ABSTRACT

Careful hydrolysis of (±)-*cis*- or (±)-*trans*-tetrahydro-2,5-dimethoxy-2-furaldehyde dimethyl acetal proceeded via 5,5-dimethoxy-4-oxopentanal to give (±)-*trans*-4-hydroxy-5-methoxy-2-cyclopentenone and (±)-*trans*-4,5-dihydroxy-2-cyclopentenone. The latter product did not isomerize to 2,3-dihydroxy-2-cyclopentenone (reductic acid) on prolonged reaction.

INTRODUCTION

Although 2,5-dihydroxy-2,4-pentadienal has never been isolated, some of its geometrical isomers have been proposed as key intermediates in the degradation of pentoses or hexuronic acids. Thus, one isomer (**1**) is believed[1] to cyclize by aldol condensation to the cyclopentenone **2** †, which then tautomerizes to the so-called reductic acid (**3**), see Scheme 1. The stereochemistry of **2** is not known.

Isomer **1** has also been proposed as a precursor of certain phenolic degradation products[2–4]. In order to confirm this, we needed a compound related to **1** but stable enough to permit isolation. For this purpose, tetrahydro-2,5-dimethoxy-2-furaldehyde dimethyl acetal (**6** in Scheme 2) was chosen, because its ethyl analogue had been converted previously into a phenolic compound (3,8-dihydroxy-2-methylchromone)[3]. The present paper deals with the preparation and hydrolysis of **6**. The hydrolysis invariably produced the *trans* isomer (**2t**) of **2**, but no reductic acid (**3**).



1 **2** **3**

Scheme 1. Proposed formation mechanism of reductic acid.

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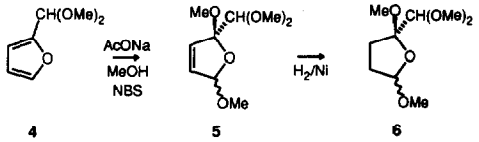
† All chiral compounds were obtained as racemic mixtures, but only one enantiomer is shown.



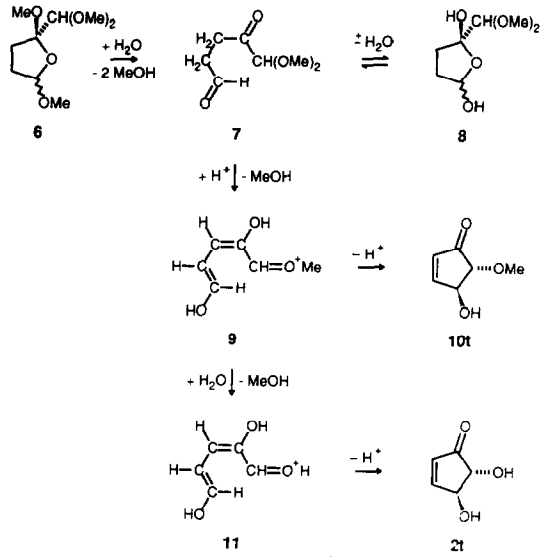
4 5 6

Scheme 2. Preparation of compound **6** (diastereomeric mixture).

RESULTS AND DISCUSSION

Compound **6** has been prepared from 2-furaldehyde dimethyl acetal (**4**) via the 2,5-dihydro derivative[5] (**5**), see Scheme 2. After some improvements, we preferred a procedure described for the ethyl analogue[2]. Compound **5** was fractionated by chromatography into the known[6] *cis* and *trans* isomers (5h6c and **5t**), which were hydrogenated to the corresponding isomers (**6c** and **6t**) of **6**. Since the isomers **6c** and **6t** behaved in the same way as their mixture (**6**) on hydrolysis, only the hydrolysis of **6** will be described.

Careful hydrolysis converted **6** into the new 5,5-dimethoxy-4-oxopentanal (**7**) and its diastereomeric hydrates (**8**), see Scheme 3. The ^{1}H and ^{13}C NMR spectra showed **7** in chloroform solution but **8** in aqueous solution, as evidenced by the presence or absence of the aldehyde proton (H-1) and the two carbonyl carbons. The spin–spin coupling between H-1 and the adjacent methylene protons (H-2) was too weak to cause splitting of the H-1 signal but was revealed by sharpening of the H-2 signal on irradiation at the frequency of H-1.



6 7 8 9 10t 11 2t

Scheme 3. Hydrolysis of compound **6**.

On prolonged reaction, **7** gradually cyclized to **2t** and its monomethyl ether **10t**, but no reductic acid (**3**) was detected. The cyclizations of **7** are apparently aldol condensations via cationic analogues (**9** and **11**) of **1**. Owing to rapid tautomerization, the ^{1}H NMR spectrum of **3** in D_2O consists of a single sharp line[7]. The ^{1}H NMR spectrum of **2t** was much more informative and strongly resembled that of its *cis* isomer[8]. However, the two spectra showed different coupling constants (J), especially for coupling between the saturated methine protons (H-4 and H-5). Thus, $J_{4,5}$ 2.7 Hz was observed for **2t** and $J_{4,5}$ 5.3 Hz for the *cis* isomer. The *cis* configuration of the latter isomer followed from its synthesis via the 4,5-di-*O*-isopropylidene derivative[8]. Hence, **2t** is the *trans* isomer. Since the four coupling constants observed for **10t** agreed, within ± 0.1 Hz, with those observed for **2t**, **10t** is also the *trans* isomer. The ^{13}C NMR spectra of **2t** and **10t**, together with the ^{1}H NMR spectra of their acetates, further supported their formulas.

EXPERIMENTAL

General methods.—Solvent mixtures are defined by volume ratios (v/v). The light petroleum used boiled at 60–70°C. Concentration was conducted under diminished pressure below 40°C. The progress of all reactions was monitored by TLC using Silica Gel HF_{254} (Merck) microplates and the following standard spray reagents[9]: *A*, *p*-anisidine · HCl; *B*, resorcinol–aq HCl; and *C*, aq $FeCl_3$. Column chromatography was performed on silica gel (230–400 mesh, Merck). GLC was carried out at 100°C on a Packard 427 instrument fitted with a flame-ionization detector and a DB1 column (30 m × 0.22 mm; linear flow rate, 0.3 m/s). GLC–EIMS was performed at 70 eV. The low-resolution spectra were recorded with a Finnigan 4021 instrument. The high-resolution spectra were recorded with a magnetic sector instrument[10] at 100 μA and 200°C with perfluorotributylamine as a reference. IR spectra were scanned with a Perkin–Elmer 1760X FTIR spectrometer; no solvent was used. NMR spectra were recorded with a Varian VXR-400 instrument at 25°C. The samples were dissolved in $CDCl_3$ or D_2O. ^{1}H NMR spectra were recorded at 400 MHz and referenced to the solvent ($CHCl_3$, δ 7.26) or (in D_2O) to internal $Me_3SiCH_2CH_2CO_2Na$ (Me, δ 0.00). ^{13}C NMR spectra were recorded at 101 MHz and referenced to the solvent ($CDCl_3$, δ 77.1) or (in D_2O) to internal 1,4-dioxane (δ 67.4). For complete assignment of all signals in the di- and tetra-hydrofuran derivatives **5**, **6**, and **8**, H–H COSY, C–H COSY, and long-range C–H COSY experiments were performed, using the standard software from Varian.

Reductic acid (**3**).—This was prepared according to Theander[11].

2-Furaldehyde dimethyl acetal (**4**).—This was prepared from the aldehyde according to a general procedure[12]; bp 55–58°C at 2.0 kPa; lit.[13] 57–58°C at 1.9 kPa.

2,5-Dihydro-2,5-dimethoxy-2-furaldehyde dimethyl acetal (**5**).—2-Furaldehyde dimethyl acetal (**4**; 7.1 g, 50 mmol) and NaOAc (10 g) were dissolved in MeOH (15

mL) and Et_2O (15 mL). NBS (*N*-bromosuccinimide, 8.9 g, 50 mmol) was added in small portions to the stirred solution (which was cooled in an ice bath) kept below 5°C. After 30 min, the mixture was concentrated, aq KOH (50 mL, 7 g, 0.12 mol) added, and the mixture extracted with CH_2Cl_2 (4 × 50 mL). The extract was dried (K_2CO_3) overnight and filtered, the solvent evaporated, and the residue distilled to give a colourless liquid (5.49 g, 58% yield); bp 100–105°C at 2.0 kPa. This liquid was fractionated on a silica gel column (80 × 5 cm) with 5:1 light petroleum –EtOAc. Two chromatographically pure compounds (**5c** and **5t**) were obtained, giving a violet colour with spray *B*, and having the same mass spectrum, *m/z* (*rel* int.): 173 (M − MeO˙, 2) 129 (10), 101 (10), 75 (100). Their ^1H NMR spectra were in accordance with those reported[6].

The *cis* isomer **5c** (yield 14%) had R_f 0.24; GLC retention time, 9.0 min.

The *trans* isomer **5t** (yield 13%) had R_f 0.16; GLC retention time, 9.3 min.

Tetrahydro-2,5-dimethoxy-2-furaldehyde dimethyl acetal (**6**).—A mixture (27.35 g, 0.14 mol) of **5c** and **5t** in dry MeOH (400 mL) was shaken with Raney nickel under H_2 gas overnight under ambient conditions. The solvent was evaporated and a colourless liquid isolated by distillation (25 g, 91% yield); bp 100–110°C at 2.0 kPa. This liquid was fractionated on a silica gel column with 5 : 1 light petroleum–EtOAc. Two chromatographically pure compounds (**6c** and **6t**) were obtained, giving a greyish-red colour with spray *B* and having the same mass spectrum, *m/z* (*rel* int.): 206 (M, 0.5), 175 (3), 144 (5), 131 (42), 115 (12), 99 (18), 75 (100), 71 (88). Their configurations were established by hydrogenation of **5c** and **5t** separately on a smaller scale.

The *cis* isomer **6c** had R_f 0.35; GLC retention time, 9.3 min; ^1H NMR ($CDCl_3$): δ 1.88–2.18 (m, 4 H, H-3,4), 3.36 (s, 3 H, OMe-2), 3.43 (s, 3 H, OMe-5), 3.49 and 3.52 (2 s, each 3 H, OMe-α), 4.22 (s, 1 H, H-α), 5.05 (dd, 1 H, *J* 1.9 and 4.9 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 27.0 (C-3), 32.4 (C-4), 49.6 (OMe-2), 55.4 (OMe-5), 56.4 and 58.1 (OMe-α), 106.3 (C-α), 106.5 (C-5), 111.2 (C-2).

The *trans* isomer **6t** had R_f 0.19; GLC retention time, 8.9 min; ^1H NMR ($CDCl_3$): δ 1.82–2.28 (m, 4 H, H-3,4), 3.30 (s, 3 H, OMe-2), 3.39 (s, 3 H, OMe-5), 3.52 and 3.53 (2 s, each 3 H, OMe-α), 4.27 (s, 1 H, H-α), 5.17 (dd, 1 H, *J* 1.0 and 5.3 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ 26.0 (C-3), 31.6 (C-4), 49.7 (OMe-2), 53.3 (OMe-5), 54.8 and 55.2 (OMe-α), 106.25 (C-α), 106.3 (C-5), 110.0 (C-2).

5,5-Dimethoxy-4-oxopentanal (**7**).—A mixture (5 g, 24.27 mmol) of **6c** and **6t** was heated with water (50 mL) in a water bath at 96°C for 3 h, cooled, and extracted with $CHCl_3$. The extract was evaporated. The syrupy residue was fractionated on a column of silica gel with 10:1 CH_2Cl_2–Me_2CO to give **7** in 38% yield; R_f 0.16 (10:1 CH_2Cl_2–Me_2CO). It gave a yellow colour with spray *A* and a red colour with spray *B*; GLC retention time, 5.3 min; ν_{max} 1730 (C=O); ^1H NMR ($CDCl_3$): δ 2.78 (t, 2 H, H-2), 2.88 (t, 2 H, H-3), 3.42 (s, 6 H, Me), 4.54 (s, 1 H, H-5), 9.8 (s, 1 H, H-1); ^{13}C NMR ($CDCl_3$): δ 29.9 (C-2), 36.9 (C-3), 54.8 (Me), 103.7 (C-5), 200.2 (C-4), 203.9 (C-1); MS, *m/z* (*rel* int.): 159 (M − H˙, 0.1), 129 (M − MeO˙, 2), 97 (2), 85 (3), 75 (100); Calcd for $C_7H_{11}O_4$ (M − H˙): 159.066. Found: 159.061.

Tetrahydro-2,5-dihydroxy-2-furaldehyde dimethyl acetal (**8**).—Compound **7** was dissolved in water.

Major isomer. ^{1}H NMR (D_2O): δ 1.79–2.30 (m, 4 H, H-3,4), 3.558 and 3.561 (2 s, each 3 H, Me), 4.34 (s, 1 H, H-α), 5.60 (m, 1 H, H-5); ^{13}C NMR (D_2O): δ 30.9 (C-3), 31.8 (C-4), 58.3 and 58.5 (Me), 99.6 (C-5), 106.9 (C-2), 107.9 (C-α).

Minor isomer. ^{1}H NMR (D_2O): δ 1.94–2.25 (m, 4 H, H-3,4), 3.54 and 3.55 (2 s, each 3 H, Me), 4.30 (s, 1 H, H-α), 5.52 (m, 1 H, H-5); ^{13}C NMR (D_2O): δ 31.8 (C-3), 32.8 (C-4), 58.3 and 58.5 (Me), 100.4 (C-5), 107.0 (C-2), 107.5 (C-α).

Preparation of compounds **2t** *and* **10t**.—Compound **7** (450 mg, 2.8 mmol) was heated at 80°C in a water bath with Me_2CO (25 mL) and 2% H_2SO_4 (500 μL) for 6 h. The Me_2CO was evaporated. The residue was neutralized with aq Na_2CO_3 and extracted with $CHCl_3$. The extract was evaporated. The resulting syrup was fractionated on a column of silica gel (20 × 5 cm) and three main fractions were collected by elution with 3:2 CH_2Cl_2–Me_2CO. The first fraction gave **2t** in 12% yield; R_f 0.46 (3:2 CH_2Cl_2–Me_2CO), brown colour with spray *A* and red with *B*; GLC retention time, 3.6 min; ν_{max} 1730 (C=O), 1100 (C–OH), and 3400 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$): δ 3.2 and 3.5 (2 bs, each 1 H, OH), 4.21 (d, 1 H, *J* 2.7 Hz, H-5), 4.82 (m, 1 H, *J* 1.4, 1.9, and 2.7 Hz, H-4), 6.28 (dd, 1 H, *J* 1.4 and 6.1 Hz, H-2), 7.47 (dd, 1 H, *J* 1.9 and 6.1 H, H-3); ^{13}C NMR (D_2O): δ 78.7 (C-4), 83.1 (C-5), 134.6 (C-3), 164.9 (C-2), 209.7 (C-1); MS, *m/z* (*rel* int.): 114 (2, M), 113 (3, M − H$^·$), 96 (80), 68 (100); Calcd for $C_5H_5O_3$ (M − H$^·$): 113.024. Found: 113.019.

Compound **2t** (10 mg) was acetylated with dry pyridine (1 mL) and Ac_2O (1 mL) overnight at room temperature. The solution was poured into ice–water and the resulting mixture extracted with $CHCl_3$. The extract was washed with 0.1 M HCl (2 × 25 mL), 0.1 M $NaHCO_3$ (2 × 5 mL), and water (2 × 2 mL), dried (Na_2SO_4), filtered, and evaporated. The diacetate was obtained in 90% yield; GLC retention time, 7.8 min; R_f 0.28 (3:1 light petroleum –EtOAc), red colour with spray *B*; ^{1}H NMR ($CDCl_3$): δ 2.10 and 2.17 (2 s, each 3 H, Ac), 5.18 (d, 1 H, *J* 3.0 Hz, H-5), 5.90 (m, 1 H, *J* 1.4, 2.2, and 3.0 Hz, H-4), 6.41 (dd, 1 H, *J* 1.4 and 6.1 Hz, H-2), 7.45 (dd, 1 H, *J* 2.2 and 6.1 Hz, H-3); MS, *m/z* (*rel* int.): 198 (M, 0.1), 156 (2), 138 (M − AcOH, 2), 96 (25), 68 (22), 43 (100); Calcd for $C_9H_{10}O_5$ (M): 198.053. Found: 198.048.

The second fraction above gave **10t** in 10% yield; R_f 0.76 (3:2 CH_2Cl_2–Me_2CO), no colour with spray *A*, red colour with spray *B*; GLC retention time, 4.3 min; ^{1}H NMR ($CDCl_3$): δ 3.4 (bs, 1 H, OH), 3.65 (s, 3 H, Me), 3.85 (d, 1 H, *J* 2.7 Hz, H-5), 4.82 (m, 1 H, *J* 1.3, 2.0, and 2.7 Hz, H-4), 6.20 (dd, 1 H, *J* 1.3 and 6.2 Hz, H-2), 7.40 (dd, 1 H, *J* 2.0 and 6.2 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 57.5 (Me), 75.6 (C-4), 88.4 (C-5), 133.2 (C-3), 159.0 (C-2), 199.0 (C-1); MS, *m/z* (*rel* int.): 128 (M, 54), 127 (13), 111 (7), 100 (39), 85 (57), 71 (75), 57 (100), 43 (71); Calcd for $C_6H_8O_3$ (M): 128.047. Found: 128.046.

Compound **10t** was acetylated as described for **2t**. The yield of the acetate was 90%; R_f 0.35 (3:1 light petroleum–EtOAc), red colour with spray *B*; GLC retention time, 6.5 min; ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3 H, Ac), 3.65 (s, 3 H, OMe),

3.96 (d, 1 H, *J* 2.7 Hz, H-5), 5.76 (m, 1 H, *J* 1.4, 2.1, and 2.7 Hz, H-4), 6.30 (dd, 1 H, *J* 1.4 and 6.2 Hz, H-2), 7.40 (dd, 1 H, *J* 2.1 and 6.2 Hz, H-3); MS, *m/z* (*rel* int.): 128 (M – CH_2CO, 19), 111 (M – AcO˙, 18), 110 (M – AcOH, 13), 96 (34), 68 (28), 55 (15), 43 (100); Calcd for $C_8H_{10}O_4$ (M): 170.058. Found: 170.058.

The third fraction above mainly contained unreacted **7**, which was recovered in 7% yield.

Hydrolysis and isomerization experiments.—(*a*) Compound **6** was heated in 0.1 M DCl (in D_2O) at 90°C in a water bath. The ^1H NMR spectrum was recorded after 1, 2, and 4 h, and showed increasing amounts of **7** and **8** at the expense of **6**. The last spectrum also showed traces of **2t**. No reductic acid (**3**) was detected on comparison with an authentic sample.

(*b*) Compound **7** was treated as for **6** in (**a**). Compounds **2t** and **10t** formed gradually at the expense of **7**. Again, no **3** was detected.

(*c*) Compound **2t** (100 mg) was heated at 50, 80, or 90°C in a water bath with 1 mL of 0.1 M H_2SO_4, glacial AcOH, 3.5 M HCl, or 0.5 M $NaHCO_3$. Each mixture was analyzed by TLC (3:2 CH_2Cl_2–Me_2CO) after 0.5, 1, 2, 3, and 4 h, using sprays *A*, *B*, and *C*. No **3** was detected, but the amount of **2t** decreased with time.

(*d*) Reductic acid (**3**) was treated as in (*c*). Its amount decreased with time, but no **2t** was formed.

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